Urinary pH as a Risk Factor for Stone Type

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Abstract: A high urinary pH is main risk factor for the calcium phosphate stone formation; however, its pathophysiologic mechanism has not been fully understood. The introduction of Topiramate in the treatment of various neurological disorders has been complicated by metabolic acidosis, significant hypocitraturia, elevated urinary pH, and calcium phosphate stone formation. This model provides a probe to investigate the pathophysiologic mechanism of calcium phosphate stone formation and perhaps to develop appropriate countermeasures in the future. On the other hand an unduly acidic urine predisposes one to uric acid nephrolithiasis. Our recent investigation linking low urinary pH, and defective renal ammoniagenesis to insulin resistance provides new knowledge to unfold the pathophysiology of uric acid nephrolithiasis. The metabolic profile leading to uric acid stone may emerge as one of the components of metabolic syndrome.

Keywords: urinary pH, Topiramate, nephrolithiasis, calcium phosphate stones, uric acid stones, metabolic syndrome
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Physicochemical and Pathophysiologic Bases of Elevated Urine pH

Urinary pH is a major determinant for kidney stone formation. However, the importance of urinary pH as a major risk factor for kidney stone formation has not been well recognized by practicing urologists and nephrologists. Kamel et al. [1] suggested that urine pH approximately near 6.0 reduces the risk of kidney stone formation. However the risk of uric acid and calcium stone formation increases progressively at urinary pH<5.5 and >6.5, respectively [1]. Until recently the prevalence of calcium phosphate stone formation was reported to be low and mainly associated with distal renal tubular acidosis. However, prevalence of calcium phosphate stones has risen for three decades [2]. One potential association for this change is suspected to be overzealous treatment with alkali, and aggressive extracorporeal shock wave lithotripsy (ESWL) treatment [2]. Moreover, recently the widespread and escalating use of Topiramate (TPM) underscores the importance of considering a possible long-term effect of this drug on kidney stone formation [3].
TPM is a novel neuromodulatory agent which is now prescribed for many neurological disorders including migraine headache prophylaxis and treatment of seizure disorders [4-12]. TPM is known to inhibit isoenzymes of carbonic anhydrase (CA) II and IV which are localized in proximal and distal renal tubular cells [4-11]. We recently reported the largest series of biochemical stone risk profile in 32 TPM treated subjects [3]. TPM resulted in mild metabolic acidosis, marked hypocitraturia and increased urinary pH, which increases the propensity to form calcium phosphate stone. These biochemical features are shared with patients with distal renal tubular acidosis (dRTA) [13].

Despite the lack of kidney stone surveillance with this agent, the reported incidence is estimated to be 1.5% with TPM treatment, which is 2-4 times greater than the stone incidence in a similar, untreated population [14]. Thus the treatment with TPM may be used as a probe to investigate the physicochemical and pathophysiologic bases of calcium stone formation. Potassium citrate is a widely-used and effective treatment against calcium stone formation via multiple actions. Potassium citrate raises urinary citrate excretion, increases soluble complexation of calcium and reduces ionized calcium concentration, thereby reducing calcium oxalate and calcium phosphate supersaturation [13,15,16]. In addition, urinary citrate also antagonizes crystallization of calcium salts directly through inhibition of spontaneous nucleation, crystal growth, and crystal agglomeration of calcium phosphate crystals and preformed calcium oxalate [17-21]. However there may be a concern that potassium citrate may raise urine pH further in TPM-treated subjects, which will convert phosphate to its divalent form, promote calcium-phosphate complexation and thereby attenuate the beneficial effects of the rise in urinary citrate (Fig. 1) [22].

![Figure 1](image-url)  
**FIGURE 1.** Crystallization of calcium phosphate.

**Physicochemical Basis of Uric Acid Stone Formation**

Urinary pH is the principal determinant of uric acid crystallization. Uric acid is weak organic acid with a pKₐ of 5.5 [23]. At this unduly low urinary pH, sparingly soluble uric acid precipitates to form uric acid stones (Fig. 2). Moreover, urate solubility is influenced by urinary cations [24,25]. It has been shown that monopotassium urate has higher solubility than monosodium urate [24,25]. The latter physicochemical characteristic is responsible for formation of calcium oxalate stones through heterogeneous nucleation or by binding of inhibitors of calcium oxalate crystallization [26].
Pathophysiology of Uric Acid Nephrolithiasis

The three important factors responsible for development of uric acid nephrolithiasis are low urine volume, hyperuricosuria, and unduly acidic urine pH [27]. The most invariable factor in development of uric acid nephrolithiasis is unduly acidic urinary pH (≤5.5). Low urinary volume may occur from excessive sweating and chronic diarrheal conditions. The low urinary pH that usually accompanies these clinical states further accelerates the formation of uric acid stones. Hyperuricosuria may occur due to genetic and environmental influences. The genetic disorders include hereditary enzymatic disorders of uric acid metabolism and a recently described mutation in urate transporters [28-32]. Urate overproduction has been proposed as one of the mechanisms for uric acid stone formation in patients with idiopathic primary gout, although it has not been found in the recent studies in uric stone formers [33,34].

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\text{H}^+ + \text{Urate} \rightleftharpoons \text{Uric Acid} \quad \text{pKa} = 5.5
\]

\[
\text{pH} < 5.5 \quad \downarrow \quad \text{Undissociated Uric Acid}
\]

\[
\text{Uric Acid or Uric Acid/CaOx Stones}
\]

**FIGURE 2.** Crystallization of uric acid stones.

Pathophysiology of Low Urinary pH

The pathophysiologic mechanisms for low urinary pH in patients with idiopathic uric acid nephrolithiasis are complex. An increase in endogenous acid production and defective urinary ammonium excretion have been implicated in development of unduly acidic urine in this population [33,35]. Defective ammonium excretion was shown in studies of idiopathic uric acid stone formers under controlled metabolic diet (Fig. 3). This defect was further unmasked by administration of an oral acid load (ammonium chloride) to amplify the ammoniagenic defect [35]. This finding was further supported in a study of uric acid stone formers on a random diet, showing lack
of a rise of urinary ammonium in association with greater dietary acid intake (sulfate load) [35]. The lack of rise in urinary ammonium was shown to be compensated in uric acid stone formers by increasing excretion of urinary titratable acids (phosphates) and decreased urinary citrate excretion [33,35]. Furthermore, at any given acid load uric acid stone formers demonstrated higher net acid excretion (Fig. 4) [35]. This study suggests that greater endogenous acid production is in part responsible for unduly acid urine in uric acid stone formers. Mechanisms that are responsible for the increase in net acid production in uric acid stone formers are not yet fully understood.

One study in a large cohort has demonstrated increased incidence of kidney stone disease in patients with type 2 diabetes mellitus [36]. However, the nature of the stones in this study was not disclosed. Lately, several investigators have reported an increased association of uric acid stones with diabetes mellitus [37-41]. Furthermore, a recent metabolic study using a hyperinsulinemic-euglycemic clamp procedure has shown the pathophysiological link between insulin resistance and defective urinary acidification in uric acid stone formers [42]. In this study, urine pH (surrogate marker of renal insulin resistance) was shown to correlate significantly with glucose disposal rate (surrogate marker of peripheral insulin resistance). The result of this metabolic study was further supported in a large cohort of kidney stone formers from two kidney stone registries in the United States [43]. An inverse relationship was shown between body weight and urinary pH in over 3000 patients with kidney stones.

![FIGURE 3. Renal acidification in uric acid stone formers.](image)

Experimental in vitro studies have shown that insulin enhances renal ammoniagenesis in canine renal proximal tubular cells when incubated with glutamine, the main substrate for renal ammonia production [44]. Moreover, insulin has been shown to activate the Na⁺/H⁺ exchanger (NHE-3) in a dose-dependent manner, thus stimulating ammonia secretion [45-47]. Metabolic studies using the hyperinsulinemic-euglycemic clamp have shown that insulin causes a significant rise in urinary ammonium excretion in normal subjects [42]. In contrast, ammonium
excretion was shown to be blunted under the same metabolic conditions in uric acid stone formers [48].

It is plausible to suggest that the underlying mechanism of increased acid production in uric acid stone formers and in patients with type 2 diabetes may be linked to insulin resistance. The exact nature of the organic anion responsible for increased acid production in these patients is unknown. However, plasma lactate has been shown to increase in type 2 diabetes [49]. This increased level of serum lactate may contribute to increased excretion of titratable acid in this population.

More than one billion adults around the world are overweight and 312,000,000 of them are obese [50]. In parallel, the prevalence of nephrolithiasis in the United States is on the rise [51]. Our recent metabolic studies and population-based epidemiologic studies have shown a link between obesity and uric acid stones. It is possible that the mean urinary pH gradually shifts to lower values as well. Thus, unduly low urinary pH values may arise as one of the components of the metabolic syndrome.

CONCLUSION

Urinary pH is one of the most important determinants of both calcium phosphate and uric acid crystallization. The pathophysiologic basis of high urinary pH—except for TPM-induced kidney stones—has not been fully explored. An optimal treatment would be an agent that augments urinary citrate without increasing urinary pH. Low urinary pH in patients with uric acid nephrolithiasis is due to defective ammonium excretion and increased acid production, which may both be linked to renal insulin resistance. The reversal of insulin resistance may ameliorate these defects and increase urine pH.
REFERENCES


