Internal Medicine Grand Rounds

Kidney Stones 2019:
Epidemiology, Clinical Pathophysiology and Treatment

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This is to acknowledge that Khashayar Sakhaee, M.D. has disclosed that he does not have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Sakhaee will not be discussing off-label uses in his presentation

Biographic Information

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Interest: Teaching patient care, patient-oriented research with a particular interest in the pathophysiologic mechanisms and treatment of kidney stones and metabolic bone disease.

Purpose & Overview: Unraveling the underlying pathophysiologic mechanisms of hyperoxaluria and low urinary pH in the pathogenesis of calcium oxalate and uric acid kidney stone disease. Exploring novel countermeasures to reduce the risk of kidney stones.

Educational Objectives:

1. To understand the prevalence of kidney stone disease.
2. To unravel the underlying pathophysiologic mechanisms of calcium oxalate and uric acid kidney stone disease.
3. To define novel therapeutic approaches for the treatment of calcium oxalate and uric acid stones.

Grand Rounds Outline

- Introduction
- Global Prevalence of Kidney Stone Disease
- Underlying Pathophysiologic Mechanism(s) of Calcium Stones
- Epidemiology of Uric Acid Kidney Stones
- Physicochemical Properties of Uric Acid Stone Formation
- Clinical Pathophysiology of Uric Acid Kidney Stones
- Future Directions

Introduction

The prevalence of kidney stones has increased globally in recent decades[1-3]. Kidney stones have become increasingly known to be a systemic disorder linked to obesity/metabolic syndrome (MS)[4]. Calcium oxalate stones (CaOx) and uric acid (UA) stones are the most prevalent type of kidney stone disease in the United States and abroad[5] . In recent years, major advances have been made in exploring the underlying pathophysiologic mechanisms and potential treatment in both calcium and uric acid stone forming populations[6,7].

Global Prevalence of Kidney Stone Disease

In a recent NHANES study, the overall prevalence of kidney stones was reported to be 10.6% in males and 7.1% in females[2] (Figure 1). Thus, 1 in 11 individuals in the U.S. had a history of kidney stones in contrast to 1 in 20 in the U.S. population in previous estimates[2]. Moreover, conditions linked with MS were shown to be more predictive of urolithiasis **(Figure 1)**.

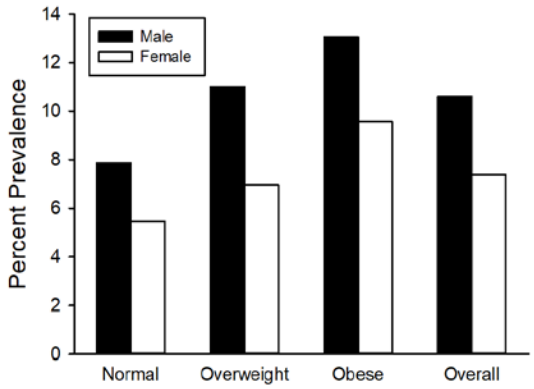


Figure 1: Weighted prevalence of stone disease by gender and body mass index (BMI) category.

In a more recent study[3], it was shown that the prevalence of kidney stone disease in adults increased globally and is higher in the Western world than in the Far East. The highest prevalence was reported in Saudi Arabia and in a few other ancient countries. Besides obesity/MS, global warming has been attributed to significantly increase the prevalence kidney stones in the northern U.S. In a recent retrospective study in Dallas of 1,516 patients over 35 years of age, it was shown that both the proportion of stone formers presenting with uric acid stones has increased significantly and the proportion of females with calcium stones has increased over time[8].

Underlying Pathophysiologic Mechanism(s) of Calcium Stones

CaOx stones are the most prevalent type of kidney stone and have been shown to occur in 60-70% of the kidney stone population **(Figure 2)**. The pathophysiologic mechanisms for CaOx in kidney stone formation are complex and diverse, however hypercalciuria and hyperoxaluria are the most significant etiologic factors for the development of CaOx stone disease[5]. Physiochemically, urinary oxalate was shown to be equally effective as urinary calcium at increasing the urinary saturation of

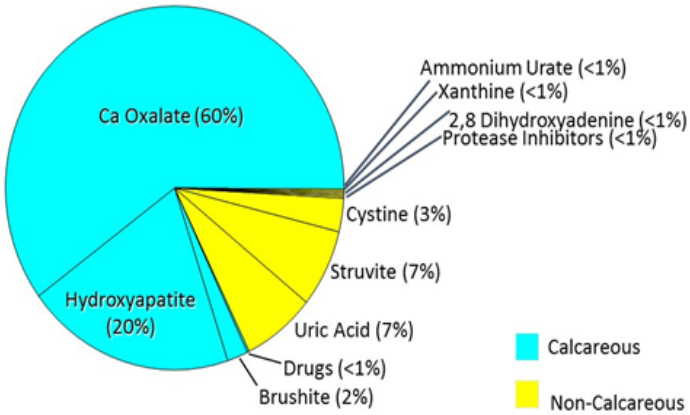


Figure 2: Stone composition and relative

CaOx[9]. The concentration of oxalate (Ox) is 100 times higher in urine than in serum due to water reabsorption in the kidneys. Physiochemically, CaOx is barely soluble in a urinary environment at approximately 57 µmol/l at a pH of 7.0. Therefore, a normal urine with one to two liters per day and a normal urinary excretion of <450 µmol Ox/day is often supersaturated with CaOx.

With an increasing prevalence of obesity/MS, urinary Ox has increased significantly[8]. However, the exact underlying pathophysiologic mechanisms between obesity/MS and increased urinary Ox excretion have not been fully explored. The principal causes of hyperoxaluria can be classified to: (1) increased dietary intake of Ox; (2) increased intestinal Ox absorption and metabolism; and (3) enhanced hepatic Ox production which has been generally attributed to inborn error in metabolism of Ox production **(Figure 3)**. Our recent retrospective study showed a positive correlation between BMI and urinary oxalate among calcium stone formers under a fixed metabolic diet. This result suggests the contribution of potentially increased enhanced intestinal Ox absorption and/or increased endogenous hepatic Ox production[10]. However, the validity of these mechanisms have yet to be explored in a prospective metabolic study.

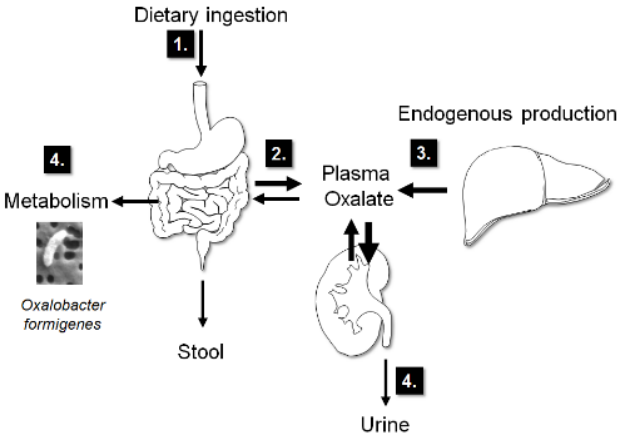


Figure 3: Mechanisms of normal oxalate homeostasis

A recent preclinical study tested the potential underlying mechanisms of obesity-associated hyperoxaluria using *ob/ob* mice[11]. To eliminate the role of dietary oxalate, the *ob* mice were pair-fed with control animals. Despite the dietary control, urinary Ox remained significantly higher in *ob* mice. Moreover, under an Ox free diet for four days, the urinary Ox remained significantly higher in *ob* mice than in the control littermates. The possibility of increased hepatic Ox production was excluded by the measurement of surrogate marker of hepatic Ox synthesis, which was found to be similar in *ob* and control mice.

From the above observations, it has been suggested that increasing the amount of Ox absorbed by the intestine may play a key role in obesity, associated with hyperoxaluria in the *ob* mice model. This notion was supported by an *in vitro* study of jejunal tissue using a Ussing chamber, showing diminished Ox secretion in *ob* mice compared with the controls. The diminished Ox secretion was further supported by the finding of decreased jejunal levels of the putative anion exchange transporter *Slc26a6* (A6) mRNA and protein expression in *ob* mice than with controls. Given that A6 is expressed in apical portions of small intestine and the large bowel, it was concluded that this transporter plays a principal role in defective intestinal Ox secretion in *ob* mice[11]. From the presence of the jejunal wall inflammation the authors concluded that hyperoxaluria in obesity depends on a complex network of inflammatory responses linked to metabolic outcome.

The contribution of altered gut microbiota colonization with *Oxalobactor formigenes* (OF) has also been previously demonstrated in obese subjects. This possibility could not be tested in

mice because they were usually found to be *O formigenes* negative. In one human study, intestinal Ox absorption was found to be similar in *O. formigenes*-positive and *O. formigenes*-negative kidney stone formers, however, plasma Ox concentrations were significantly higher in *O. formigenes*-negative population. These findings exposed the role of decreased intestinal Ox secretion in *O. formigenes*-negative CaOx kidney stone formers[12].

Since there is a strong association between CaOx kidney stones and obesity/MS, it is expected that bench studies will lead to clinical studies that unravel the link between obesity and urinary Ox excretion in humans with CaOx kidney stones. The future mechanistic and clinical studies are crucial in elucidating the pathogenetic role of obesity-induced inflammation and its relationship to altered intestinal microbiota in this population.

Epidemiology of Uric Acid Kidney Stones

Similar to calcium stones, there is global heterogeneity in the prevalence of UA stones. In the United States, the prevalence of uric acid stones has increased steadily with an increasing BMI **(Figure 4)**. In certain areas of the world, including the Middle East, the prevalence of uric acid stones have been reported to be higher and approaching 22-28%[13]. Observational and epidemiologic studies have shown that a there is a higher prevalence of UA stones among diabetic and obese stone formers[14]. The association features of metabolic syndrome in UA stone formers in the Western societies has also been demonstrated in the Hmong population born in the U.S. The increased prevalence of UA stones among this population is much higher than in neighboring regions adjacent to Hmong native land suggesting that the acquisition of Western dietary habits play an important role in the incident of UA stones in this population[15].

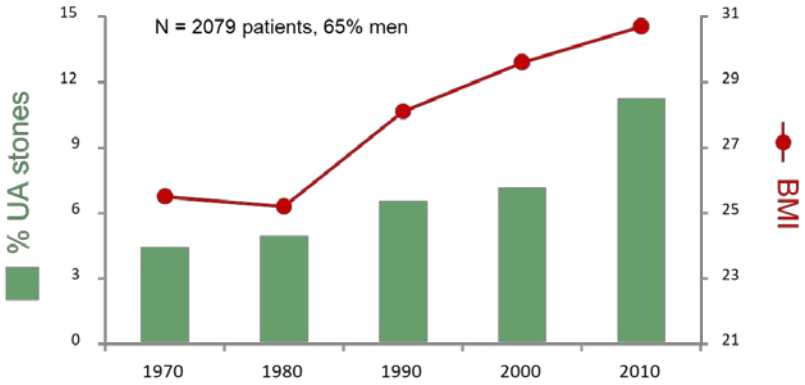
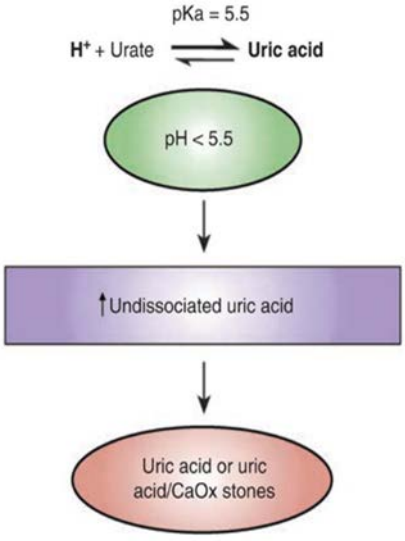


Figure 4 Proportion of Uric Acid Stones and BMI by Decade

Physicochemical Properties of Uric Acid Stone Formation

UA is an end product of purine metabolism which is metabolized by the hepatic enzyme uricase to the soluble allantoin, and consequently excreted into the urine[16]. However, since humans lack the uricase enzyme, they attain higher serum and urinary UA concentrations than other mammals. UA is a weak organic acid (pKa 5.35 at 37° C) with constant ionization in the acidic urinary environment commonly



development of uric acid stones[1]

encountered in UA stone formers (urinary pH ≤5.5). This results in the urine becoming supersaturated with respect to the sparingly soluble UA, thus increasing the risk for UA stone formation[17] **(Figure 5)**. Given that UA excretion under normal circumstances exceeds 600-800 mg/day with a limited UA solubility of 100mg/L the urinary environment is at a great risk for UA precipitation. Therefore, urinary pH plays a key role in the inhibition of UA precipitation.

Clinical Pathophysiology of Uric Acid Kidney Stones

The three most important factors for the development of UA stones are low urinary pH, hyperuricosuria and low urinary volume, with the most significant factor being the low urinary pH, which directly increases undissociated uric acid[18]. We have previously shown under inpatient controlled diets that the two principal factors contributing to low urinary pH in this population are: reduced renal ammonium (NH_4^+) excretion and increased net acid excretion (NAE)[18] **(Figure 6A & 6B)**.

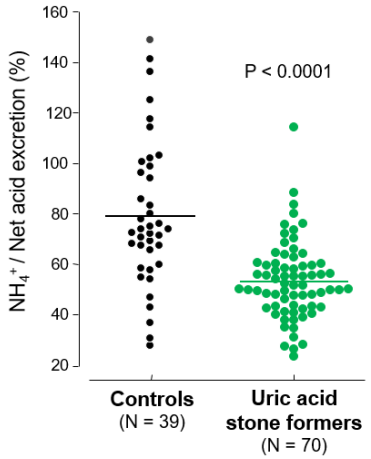


Figure 6A: Urinary Ammonium Excretion under inpatient controlled diet

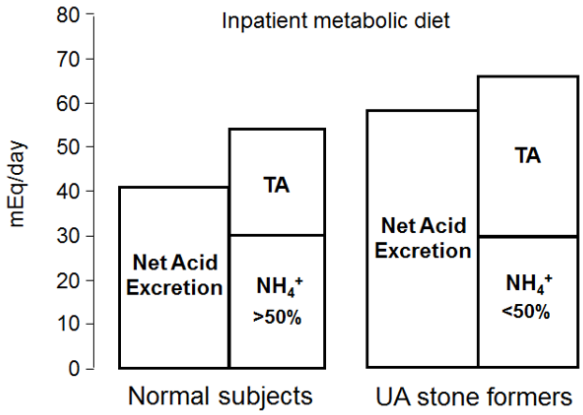


Figure 6B: Urinary Net Acid Excretion under inpatient controlled diet

Under normal circumstances, an acid-base balance is maintained with a high capacity buffer, ammonia (pKa 9.2), which efficiently buffers most of the protons secreted while the remaining protons are buffered by other anions collectively called titratable acids and maintains a normal urinary pH. However, with the defective NH_4^+ excretion in UA kidney stone formers, the proton would be buffered mainly by titratable acids to maintain acid base equilibrium, promoting the formation of undissociated uric acid[1]. The defective urinary NH_4^+ excretion was shown in Zucher Diabetic Fatty (ZDF) rats, an established animal model of obesity and metabolic syndrome[19]. In this animal model, compared to the lean litter mates, a higher renal triglyceride content was accompanied with low urinary NH_4^+ and pH. Moreover, treatment of ZDF with thiazoladinediones (TZD), which are known to reduce ectopic tissue steatosis, restored urinary profiles to that of the lean control animals[19].

A study performed under a constant metabolic diet using urinary metabolomics has shown that excess organic acids presented to the kidney in UA stone formers involved 26 organic anions with acid dissociation constants that allowed them to titrate protons within the pH range of the urine[20]. This study, for the first time demonstrated that higher acid load presented to the

kidney resulted in an increased NAE excretion and plays a key role in the pathogenesis of UA stone formation.

To test the effects of TZD in patients with uric acid stones, a proof-of-concept study demonstrated that treatment with TZD increased urinary pH, reduced NAE and increased the proportion of NAE as NH_4^+[7].

Future Directions

Since the development of potassium citrate in the 1980s here at UT Southwestern, no new pharmacological agents have been developed for the treatment of calcium oxalate or uric acid stones.

A preclinical study in *ob/ob* mice suggests inflammation as a contributor to the pathogenetic mechanism of hyperoxaluria in obesity-associated hyperoxaluria[11]. The contribution of inflammatory pathways in the pathogenesis of hyperoxaluria has not yet been investigated in calcium oxalate kidney stone formers. If the result of the clinical investigations support the preclinical data, one may infer that agents that inhibit inflammatory signals and consequently improve insulin resistance should be tested.

Moreover, the importance of the role of the *OF* could not be examined in mice because they were usually found to be *OF* negative. The contribution of *OF* is important given that a case control study of 274 patients with recurrent calcium oxalate stones and 259 normal subjects have shown that prevalence of *OF* was significantly lower in stone formers than in controls. In this study, although the case and control subjects were matched with respect to age, gender, race, ethnic background, region and antibiotic use, no attempts were made to differentiate the obese and non-obese subjects[21]. In a previous study, the use of *OF,* as an orally administrated probiotic in frozen paste or as enteric-coated capsule, showed a transient, beneficial effect in lowering urinary oxalate excretion in patients with primary hyperoxaluria type 1[22]. However, this effect was not confirmed in a randomized placebo controlled study which lasted over 24 weeks[23].

The use of oral recombinant oxalate decarboxylase enzyme has shown a successful response in a phase I trial in normal subjects with diet-induced hyperoxaluria[6] and also in a phase II trial in patients with enteric hyperoxaluria.

The results of the short-term proof-of-concept study using TZD in patients with uric acid stones is promising given that this targeted therapy not only improves the urinary biochemical profiles but also unravels the underlying pathophysiologic mechanism of obesity/metabolic syndrome in the pathogenesis of uric acid stones.

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