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Epidemiology and Clinical Pathophysiology of Uric Acid Kidney Stones

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Epidemiology of uric acid nephrolithiasis and its association to the metabolic syndrome

There are global diversities in uric acid stone prevalence. Prevalence is highest in the Middle East and a few countries in Europe. In fact, uric acid stone occurrence was reported to be 28 % in Pakistan and 22 % in Israel [1-3], while comprising only 8-10 % of all kidney stones in the United States [4]. The incidence of uric acid stones in Japanese and Chinese descendants in San Francisco was reported to be 15-16 %. Moreover, the prevalence of uric acid nephrolithiasis and gout among the Hmong immigrant population in the U.S. is significantly higher [5, 6].

The exact cause for global diversity in uric acid (UA) nephrolithiasis prevalence has not yet been fully elucidated. However, a high prevalence of obesity, diabetes and hypertension is commonly associated with uric acid nephrolithiasis in Western societies and has been shown to be present in Hmong populations born in the United States [7-9]. This is novel as there is generally a low incidence (approximately 20 %) of UA stones in Northeastern Thailand, a geographic region adjacent to the Hmong homeland of Laos with an ethnically distinct population [10]. Therefore, it appears that both genetic factors and the adoption of Western dietary behaviors play an important role in the high incidence of uric acid stone prevalence.

It has been established that stone formers with type 2 diabetes mellitus (T2DM) have UA stones as the main stone constituent more frequently than non-diabetic stone formers [11] (Fig. 1). This greater prevalence among T2DM stone formers has since been confirmed by other investigators [8, 9, 12]. A higher prevalence of UA stones has also been demonstrated among obese stone formers [13, 14]. Moreover, it was shown that greater body mass index (BMI) and T2DM are independent risk factors for UA nephrolithiasis [15].

Etiologic causes of uric acid stone formation

The etiologic cause(s) of the formation of uric acid nephrolithiasis are complex; they may include genetic and/or acquired factors [16]. However, features of metabolic syndrome (MS) have emerged as the most common cause of uric acid stone formation [7, 9]. In fact, chronic diarrhea has a major impact on stone formation. In inflammatory bowel diseases, including ulcerative colitis and Chron's disease, the majority of stones contain calcium. However, 1/3 of stones are composed of uric acid, an incidence which is higher than the 8-10% incidence reported for general populations with uric acid nephrolithiasis [17-19]. Moreover, in patients following ileostomy, uric acid stones are common and comprise 2/3 of all stones [17]. In these subjects unduly acidic urine pH (< 5.5) is commonly encountered compared to control subjects [20-22]. However, urinary uric acid excretion has been reported to be normal in this population [23]. The underlying pathophysiologic mechanism for undue urine acidity in this population has not yet been fully investigated. However, loss of bicarbonate in the stool and systemic metabolic acidosis may play an important role in lowering urinary pH. The major therapeutic modality in these subjects should involve administration of alkali treatment to combat abnormally acidic urine [23] in conjunction with increased intake of fluids as urine volume is significantly low due to persistent diarrheal fluid loss.

Physiochemical properties of uric acid stone formation

Mammals produce UA as an end product of purine metabolism [4]. UA is then metabolized by the hepatic enzyme uricase to a more soluble allantoin, which is then excreted into the urine. However, humans and higher primates lack uricase and, due to their inability to metabolize uric acid, disclose serum and urinary acid concentrations many folds higher than other mammals [24]. Since urinary UA excretion in humans generally exceeds 600 mg/day, the limited urinary UA solubility of 96 mg/l poses a great risk for UA precipitation [25]. Urine pH plays the most dominant role in UA solubility, as UA is a weak organic acid with an ionization constant (pKa 5.35 at 37° C) [26]. Unduly acidic urine (urine pH 5.5) leads to precipitation of the sparingly soluble UA, increasing the predisposition to UA nephrolithiasis [27].

Normal urine is often metastably supersaturated with respect to UA; thus, the presence of a urinary inhibitor of crystallization also plays some role in UA precipitation. Therefore, acidic urine may be necessary but is not sufficient to cause UA nephrolithiasis. It is plausible that the lack of an *inhibitor* or the presence of a promoter, may account for the difference in the propensity for UA stone formation. In this situation unlike that of calcium oxalate, the roles of inhibitors have not been clearly identified. However, an *in vitro* experiment has identified that the presence of molecules inhibit the adhesion of UA renal epithelial cells which supports the inhibitory role of this micromolecule against UA precipitation [28-30].

Pathophysiology of acidic urine pH in uric acid nephrolithiasis

Three significant urinary abnormalities have been described in patients with uric acid nephrolithiasis: low urinary pH, hyperuricosuria, and low urinary volume [16]. In uric acid stone forming patients, the most important and invariant features are an overly acidic urine

which increases the urinary content of disassociated uric acid, and the propensity for uric acid precipitation [7, 31]. We have previously shown that two major etiologic factors result in unduly low urinary pH of uric acid stone formers: reduced renal ammonium (NH_4^+) excretion and increased net acid excretion (NAE), with the combination resulting in overly acidic urine [7, 9]. These abnormalities have been encountered under both fixed metabolic diets and ad-lib diets. In addition, overly acidic urine, defective NH_4^+ excretion and increased NAE were also demonstrated in diabetic non-stone formers who share some phenotypic features with uric acid stone formers under a fixed metabolic diet (Fig. 2) [32]. Given that the net acid excretion matches net acid production at a steady state, these findings of significant net acid excretion in uric acid stone formers and T2DM patients without kidney stones suggest that net acid production is significantly higher in this population.

Mechanisms of impaired ammonium excretion

NH_4^+ is a high capacity urinary buffer (pKa of 9.2) which efficiently buffers most of the hydrogen secreted by the kidney. In patients with UA stones, the defective NH_4^+ excretion in most of the secreted hydrogen molecules is buffered by titratable acid (TA) to maintain acid-base homeostasis [33]. Therefore, the trade-off will be unduly acidic urine which poses a high risk for UA precipitation. Defective NH_4^+ has been demonstrated at a steady state and also following a single dose of acid load with ammonium chloride [7]. Renal proximal tubular cells are the main segment for the synthesis and secretion of NH_4^+ [34]. Ammonium made in proximal renal tubular cells is transported across the apical membrane either directly as NH_4^+ or as non-ionic diffusion of free ammonia (NH_3). The sodium-hydrogen exchanger NHE3 plays a key role in both of these processes [34, 35]. The underlying cellular mechanism(s) associating MS to the development of UA stones has been extensively studied. In obesity, diabetes and MS, disequilibrium occurs between caloric intake and caloric utilization. Hence, the name of “lipotoxicity” has been adopted for this process [36]. This process involves fat distribution in non adipocyte tissue including cardiac myocytes, pancreatic β cells, skeletal muscle cells and parenchymal liver cells [36-38]. Renal proximal tubal cells are specifically vulnerable to lipotoxicity due to increased filter load of free fatty acids [39]. The supporting role of renal steatosis in the pathogenesis of urinary acidification defects was found in opossum proximal tubular cell cultures and in Zucker Diabetic Fatty (ZDF) rats, and established an animal model of obesity and MS [40]. The comparison of ZDF rats to lean litter mates demonstrated a higher renal triglyceride content, associated with low urinary NH_4^+ and pH, as well as lower levels of brush border membranes NHE3 activity and proteins. Furthermore, treatment of ZDF rats with thiazoladinediones, which is known to reduce non-adipocyte tissue steatosis, was shown to restore urinary profiles to that of the controlled litter mates as well as significantly reduce renal triglyceride accumulation [40]. However, an established link between renal steatosis and defective ammonium excretion in humans with uric acid stone formations has not yet been fully elucidated.

Tissue injury is principally due to the accumulation of non-esterified fatty acid and their toxic metabolites including acyl-CoA, diacylglycerol, and ceramide [33, 41].

Mechanisms of increased acid production

Under a fixed metabolic diet and a steady state when the urine specimens were collected under mineral oil, compared to control subjects patients with UA nephrolithiasis and T2DM patients without kidney stones exhibited significantly higher NAE, approximately 1.5 fold, suggestive of increased acid production in these two populations.

To date, no study has explored the source and nature of these putative acid anions. A plausible mechanism is increased organic production by intestinal and aerobic metabolism [42]. This may occur in diabetics, and potentially in UA stone formers, due to differences in the gut microflora [43, 44]. Consequently, this process will result in greater acid production and/or net gastrointestinal (GI) alkali loss by increased excretion of the base precursors in the stool [7, 9, 32].

Conclusion

With the worldwide problem of obesity of epidemic proportions, it has emerged that uric acid prevalence increases with metabolic syndrome (obesity and T2DM). Fundamental progress has been made in the elucidation of the pathophysiologic mechanisms of uric acid stone formation and its link to metabolic syndrome. The two principal defects examined by careful metabolic studies include defective ammonium excretion and increased net acid production. Previous studies using ZDF and opossum kidney cell culture have shown that renal steatosis may be responsible for reduced ammonium excretion. Future studies are needed to elucidate whether renal fat accumulation will play a similar role in human subjects with uric acid stones and whether metabolic syndrome and diabetes play an important pathogenetic role in increased acid production in this population.

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Figure 1. Prevalence of Uric Acid Stones in Diabetic versus Non-diabetic Stone Formers

Figure 2. Inpatient Controlled Diet: NH_4^+ Excretion in UA Stone Formers and T2DM Non-stone Formers