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ARTICLE

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Acid–base metabolism: implications for kidney stone formation

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Abstract The physiology and pathophysiology of renal H^+ ion excretion and urinary buffer systems are reviewed. The main focus is on the two major conditions related to acid–base metabolism that cause kidney stone formation, i.e., distal renal tubular acidosis (dRTA) and abnormally low urine pH with subsequent uric acid stone formation. Both the entities can be seen on the background of disturbances of the major urinary buffer system, $NH_3 + H^+ \leftrightarrow NH_4^+$. On the one hand, reduced distal tubular secretion of H^+ ions results in an abnormally high urinary pH and either incomplete or complete dRTA. On the other hand, reduced production/availability of NH_4^+ is the cause of an abnormally low urinary pH, which predisposes to uric acid stone formation. Most recent research indicates that the latter abnormality may be a renal manifestation of the increasingly prevalent metabolic syndrome. Despite opposite deviations from normal urinary pH values, both the dRTA and uric acid stone formation due to low urinary pH require the same treatment, i.e., alkali. In the dRTA, alkali is needed for improving the body's buffer capacity, whereas the goal of alkali treatment in uric acid stone formers is to increase the urinary pH to 6.2–6.8 in order to minimize uric acid crystallization.

Keywords Urolithiasis · Stone formation · Acid–base metabolism · Distal renal tubular acidosis · Low urine pH and uric acid stones · Metabolic syndrome and uric acid stones

Introduction

Like the concentrations of other components of the extracellular fluid, the concentration of free hydrogen (H^+) ions has to be maintained within very narrow limits, at approximately 40 nmol/l (40×10^{-6} mmol/l) [1]. Because the degradation of carbohydrates alone can generate as much as 20,000,000,000 nmol of free H^+ ions per day, the body continuously faces two problems: (1) minimizing the increase in plasma H^+ generated from metabolism and (2) eliminating a huge excess of H^+ ions from the body [2]. This requires powerful buffer systems as well as mechanisms for excreting the excess acid. In an integrated fashion, the body's buffer systems, the lungs and the kidneys, act together in order to minimize any changes in the free H^+ ion concentration [1–3].

Among the various buffers present in the body, the HCO_3^-/CO_2 buffer system is the most important one [1]:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2. \quad (1)$$

This buffer system is essential for the maintenance of acid–base balance, as the HCO_3^- concentration and the partial pressure of CO_2 in arterial blood ($P_{art}CO_2$) can be regulated independently, the former by changes in the renal H^+ ion excretion and the latter by changes in the rate of alveolar ventilation [1, 2]. For instance, an increase in the rate of alveolar ventilation in metabolic acidosis reduces the $P_{art}CO_2$, whereby the equilibrium of Eq. 1 is shifted to the right with a subsequent fall in free H^+ ion concentration.

The purpose of this paper is to briefly review the physiology of renal H^+ ion excretion/ HCO_3^- regeneration and also urinary buffering. Within this context, the two clinically most important disturbances leading to the stone formation which are related to acid–base metabolism, i.e., distal renal tubular acidosis (dRTA) and low urine pH with uric acid stone formation, will be discussed.

Renal hydrogen ion excretion and urinary buffering

Net acid production by the body is the sum of dietary acid intake and endogenous acid production [3]. The

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latter is mainly due to lactic acid production and loss of organic anions in the stool [3]. The net acid production mostly results from the oxidation of sulfur-containing and cationic amino acids [1]. The result is that the body generates at least 50–100 mmol of H^+ per day or even more in situations where acid production is increased [1]. In order to maintain acid–base balance, the kidney must eliminate an equal amount of acid [3] as well as reabsorb the filtered bicarbonate [1].

Renal acid excretion is achieved either by a Na^+–H^+ exchange (cells of proximal tubule and thick ascending limb of Henle's loop) or by an active H^+-ATPase pump (intercalated cells of collecting tubule) [1–3]. Renal tubular H^+ excretion is always coupled with the reabsorption of filtered HCO_3^- [1–3]. Within the tubular lumen, the enzyme carbonic anhydrase accelerates the dissociation of H_2CO_3, generated by the combination of secreted H^+ and filtered HCO_3^-, into H_2O and CO_2 which are then reabsorbed by the tubular cells. Intracelluar H_2O breaks down to H^+ and OH^-, and the latter—catalyzed by intracellular carbonic anhydrase—combines with CO_2 to form HCO_3^- [1]. At the basolateral membrane of tubular cells, HCO_3^- is returned to the systemic circulation [1]. The net effect is a virtually complete reabsorption of filtered HCO_3^- whereby acid–base balance is maintained.

Urinary pH is simply a measure of free H^+ ions in urine, but does not directly reflect renal net acid excretion [3]. For example, the excretion of 100 mmol of H^+ ions in 1 l of urine per day, if all the H^+ ions were unbuffered, would result in a H^+ concentration of 100 mmol/l or 10^{-1} M; this means that the urinary pH would drop to 1.0! The capacity to excrete free H^+ ions in urine, however, is minimal, and the lowest pH that can be achieved in human urine is 4.5 [1]. Thus, powerful buffers must be present in urine in order to keep the concentration of free H^+ ions low. As summarized in Table 1, two systems are responsible for buffering H^+ ions in urine: the NH_3/ NH_4^+ system, which is the most powerful urinary buffer system, and titratable acidity which has only a limited buffering capacity.

The cells of the proximal tubule generate NH_4^+ from the metabolism of amino acids, mainly from glutamine [1,2]. The majority of secreted NH_4^+ is reabsorbed by the thick ascending limb of Henle's loop and recycled within the medulla. In the medullary interstitium, the accumulation of NH_4^+ drives the equilibrium $NH_3 + H^+ \leftrightarrow NH_4^+$ to the left, i.e., more NH_3 and H^+ ions are formed [1]. Whereas H^+ ions are resecreted into the tubular lumen, the luminal membrane of the thick ascending limb of Henle's loop is impermeable to NH_3, which then diffuses across the basolateral membrane into the medullary interstitium. In contrast, the membranes in the collecting tubules are highly permeable to NH_3 but almost impermeable to NH_4^+ [1]. Thus, the interstitial NH_3 passively diffuses into the lumen of the collecting tubules where it combines with H^+ ions to form NH_4^+ [1]. These processes are regulated, and acid loading increases renal excretion of NH_4^+ by two mechanisms: (1) acid loading promotes proximal tubular NH_4^+ generation from glutamine, and (2) at lower urinary pH, there is a rise in NH_3 diffusion into the lumen of medullary collecting tubules [1]. In fact, during severe metabolic acidosis, NH_4^+ production can increase from its normal value of 30–40 meq/day to over 300 meq/day [1].

Subsequently, the two most important disorders related to acid–base metabolism that promote the kidney stone formation will be discussed on the background of alterations of this major urinary buffer system:

$$NH_3 + H^+ \leftrightarrow NH_4^+. \quad (2)$$

Disturbances of this system occur as a consequence either of reduced renal secretion of H^+ ions, inducing dRTA, or of insufficient NH_4^+ generation with abnormally low urine pH, promoting uric acid stone formation.

Table 1 Buffer systems present in human urine

Urinary buffer systems
Ammonia/Ammonium-buffer system
PT generates NH_3 from glutamine; $NH_3 + H^+ \leftrightarrow NH_4^+$
NH_4^+ secreted and reabsorbed by TAL of Henle's loop → secreted by intercalated cells of the collecting duct
Major tubular buffer system: capacity up to 300 mmol H^+/day
Regulation: dietary acid load, metabolic acidosis → ↑ urinary excretion of NH_4^+
Titratable acidity: HPO_4^{2-}, creatinine
Weak acids, freely filtered at the glomerulus
Limited capacity: buffer only 10–40 mmol H^+/day

Adapted from [1–3]
PT proximal tubule, *TAL* thick ascending limb (of Henle's loop)

Distal renal tubular acidosis

Distal or type 1 RTA is characterized by a decrease in net H^+ excretion by the collecting tubules, where acidification is primarily achieved via H^+ secretion by a luminal H^+-ATPase present in the intercalated cells [4]. In the cortical collecting tubule, net H^+ secretion is additionally influenced by Na^+ reabsorption in adjacent principal cells, because the removal of cationic Na^+ from the tubular fluid makes the lumen more electronegative, thereby promoting the secretion of H^+ ions into the tubular lumen [1]. Thus, in the case of a reduced Na^+ reabsorption by principal cells, there is a diminished electrical gradient for H^+ and K^+ secretion, resulting in the voltage-dependent hyperkalemic form of dRTA [4]. Finally, tubular toxins such as amphotericin B can increase membrane permeability which allows for backdiffusion of H^+ ions out of the tubular lumen [4]. Table 2 gives an overview of the three pathogenetic mechanisms and the key features of dRTA, and Table 3 summarizes the major causes of this disorder.

Kidney stone formation is linked to dRTA at least twofold: on the one hand, acidemia both increases calcium phosphate release from bone and reduces the

Table 2 Pathogenetic mechanisms and key features of distal RTA

Type 1 (distal) renal tubular acidosis
Basic defect: ↓ acidification in collecting tubules
Three pathogenetic mechanisms → ↓ H^+ secretion
1. Defect in H^+-ATPase pumps in intercalated cells
2. Voltage-dependent defect: ↓ Na^+ reabsorption by principal cells → ↓ electrical gradient for secretion of H^+ and K^+ → hyperkalemic form of dRTA
3. Gradient defect (toxins): ↑ membrane permeability → backdiffusion of H^+ ions
Key features
Continued H^+ retention → metabolic acidosis
Urine pH constantly > 5.5

Adapted from [4]

tubular reabsorption of these ions. As a consequence, hypercalciuria and hyperphosphaturia, two well-known risk factors of calcium stone formation, develop, and the precipitation of calcium phosphate is greatly favored due to the persistently elevated urine pH [4]. On the other hand, dRTA reduces urinary excretion of citrate, because acid loads or acid retention (such as in dRTA) induce intracellular acidosis in proximal tubular cells which favors reabsorption of citrate [5]. Sufficient citrate in urine is important because citrate retards the crystallization of stone-forming calcium salts [6] and mediates inhibitory effects of macromolecular modulators of calcium oxalate crystallization [7, 8].

Low urinary citrate (hypocitraturia) is a pathogenetically important risk factor for calcium nephrolithiasis, which occurs in 20–60% of calcium stone formers [9]. Interestingly, the incomplete form of RTA (no systemic acidosis, but persistently high urine pH even after acid loading) has been found in 90% of "idiopathic" calcium stone formers with low urinary citrate [10]. Table 4 depicts the differences between complete and incomplete dRTA. Of note is the fact that proximal tubular NH_4^+ production, inappropriately low in all

Table 3 Major causes of distal RTA

Type 1 (distal) RTA—major causes
Primary: idiopathic, sporadic
Hereditary
Familial (incl. Hypercalciuria), Marfan's syndrome, Wilson's disease
Disorders of calcium metabolism / nephrocalcinosis
Idiopathic hypercalciuria
Primary hyperparathyroidism
Hypervitaminosis D
Medullary sponge kidney
Autoimmune diseases
Sjögren, rheumatoid arthritis, SLE, chronic active hepatitis, primary biliary cirrhosis
Drugs and toxins → gradient defect:
Amphotericin B, Lithium, Analgesic abuse, light chain disease, Ifosfamide
Associated with voltage defect → hyperkalemia
Urinary tract obstruction, SLE, renal transplant rejection

Modified from [4]
SLE systemic lupus erythematosus

Table 4 Complete and incomplete distal RTA and hypocitraturia

Complete and incomplete type 1 (distal) renal tubular acidosis—hypocitraturi
COMPLETE type 1 RTA
Patients constantly acidemic = systemic metabolic acidosis
↓pH in prox. tubular cells → ↑citrate reabsorption/utilization
INCOMPLETE type 1 RTA
Patients NOT acidemic = NO systemic metabolic acidosis
↓pH in prox. tubular cells → ↑citrate reabsorption/utilization

BOTH forms: ↑tubular citrate reabsorption → hypocitraturia
Adapted from [4]

forms of RTA [11], appears to be increased in incomplete dRTA, so that the NH_4^+ excretion is normal despite a high urine pH [4]. Finally, Table 5 summarizes all potential mechanisms/conditions besides complete or incomplete dRTA that can provoke hypocitraturia with subsequent kidney stone formation or nephrocalcinosis. They all are related to acid–base metabolism, as the common denominator is always intracellular acidosis in proximal tubular cells [3, 4].

The treatment of dRTA consists of alkali in order to neutralize retained H^+ ions. In adults, the goal is to minimize kidney stone formation, nephrocalcinosis and possibly osteopenia/osteoporosis due to calcium losses from bone [4]. Alkali can be provided either as alkali citrate (reviewed in [12]) or as sodium bicarbonate. Usually, 1–2 meq alkali per kg of bodyweight are necessary [4], but the dose should be up-titrated based on the 24-h urine excretion of citrate; the lower threshold of normal ranges for men and women are 1.70 and 1.90 mmol/day, respectively [10]. In clinical practice, it appears to be important to emphasize that sufficient alkali must be provided on a chronic (lifelong) basis in order to permanently neutralize retained H^+ ions, although this apparently seems to be "paradoxical" to many patients (and some physicians as well) on the background of an already elevated urine pH.

Low urine pH and uric acid stone formation

Uric acid is a weak acid with a pK value of 5.35 in urine [13]. At the lower end of pH range in human urine, uric

Table 5 Mechanisms/causes of intracellular acidosis in proximal tubular cells inducing hypocitraturia

Intracellular acidosis in proximal tubules with subsequent hypocitraturia—causes
Systemic metabolic acidosis (incl. complete dRTA)
Incomplete distal RTA
Dietary acid loads (exaggerated meat protein consumption)
Dietary salt loading (→ ↓ renin → ↓ angiotensin II → ↓ activity of luminal Na^+–H^+-antiporter → ↑ intracellular $[H^+]$)
Carboanhydrase inhibitors: acetazolamide, topiramate (anticonvulsant)
Malabsorption syndromes/chronic diarrhea (HCO_3^- loss)
Potassium depletion (thiazide diuretics!)

Modified from [3]

acid is primarily present in the form of the poorly soluble undissociated uric acid (solubility 0.54 mmol/l, [13]). Thus, at low urinary pH values, abundant uric acid crystallization and subsequent stone formation can occur even if the uric acid excretion rate is completely normal. Indeed, the clinical experience tells that the majority of pure uric acid stone formers exhibit a low urinary pH rather than hyperuricosuria as their main cause of stone formation. This was confirmed in a study by Pak et al. [14] who found that in comparison with controls (patients with absorptive hypercalciuria and healthy volunteers), pure uric acid stone formers had significantly lower values of urinary pH and fractional urate excretion, whereas their serum uric acid levels were elevated. Since such defects of urinary acidification and urate excretion are believed to be associated with primary gout, it was concluded that the idiopathic uric acid nephrolithiasis might be a stone manifestation of primary gout [14].

In two independent studies, the reason for low urine pH in most normouricosuric uric acid stone formers was found to be reduced renal ammonium excretion [15, 16]. In addition, Sakhaee et al. [16] found that the rise in urinary ammonium excretion following the acid loading in uric acid stone formers was from fivefold to sevenfold lower than in calcium stone formers or healthy controls. Furthermore, one-third of pure uric acid stone formers, but none of the calcium stone formers or healthy controls, were diabetic [16]. The conclusion at that stage was that the defective urinary ammonium excretion in the uric acid stone formers could be linked to the insulin-resistant state [16].

In a most recent study, Abate et al. [17] assessed insulin sensitivity by measuring glucose disposal rate during an euglycemic hyperinsulinemic clamp procedure, as originally described by DeFronzo et al. [18], in 55 healthy controls and 13 selected pure uric acid stone formers. As depicted in Fig. 1a, insulin sensitivity was significantly higher in the healthy controls than in the uric acid stone formers, i.e. the latter ones exhibited increased insulin resistance. Furthermore, uric acid stone formers had a significantly lower ratio of urinary ammonium to net acid excretion and a lower urinary pH. A plot of urinary pH values against insulin sensitivity showed a positive correlation in healthy controls, i.e., higher urinary pH was associated with higher insulin sensitivity. Most likely due to the relatively low number of patients studied, this correlation could not be demonstrated in uric acid stone formers whose lower urinary pH values nevertheless tended to cluster in the area of lower insulin sensitivity (i.e., higher insulin resistance) [17].

Furthermore, Abate et al. [17] investigated the various components of the metabolic syndrome [19] which are depicted in Table 6. In comparison with healthy controls, uric acid stone formers had significantly higher values for waist circumferences and blood pressures, the clinical key features of metabolic syndrome [19]. In addition, uric acid stone formers exhibited higher values for fasting blood glucose and triglycerides as well as lower values for HDL cholesterol, as depicted in Fig. 1b. Thus, uric acid stone formers fulfilled the criteria for the diagnosis of metabolic syndrome and, in addition, were more insulin-resistant with lower urinary ammonium and pH values than healthy controls.

Table 7 depicts important findings from animal studies [summarized in 17] which have demonstrated that insulin is critical for ammoniagenesis as well as ammonium secretion in the proximal tubule. Based on this knowledge, the results of Abate et al. [17] could indicate that low urinary pH due to reduced urinary ammonium excretion may be a novel renal manifestation of insulin resistance. The consequence of this metabolic abnormality is the uric acid stone formation, which could be envisioned as an ''innocent renal bystander'' in patients with the metabolic syndrome.

Summary: acid–base metabolism and kidney stones

This review emphasizes on the two major conditions related to acid–base metabolism that can cause kidney

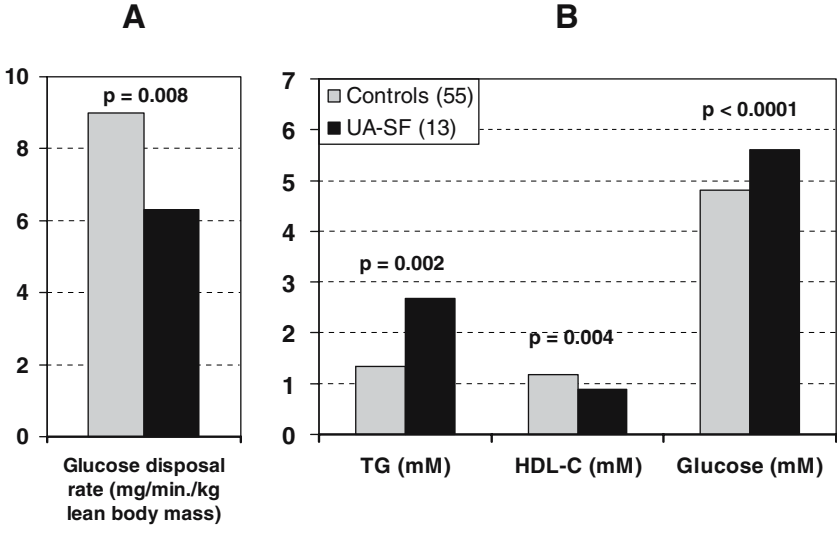

Fig. 1 **a** Glucose disposal rate as a measure of insulin sensitivity in healthy controls and uric acid stone formers. Values are means. Legend as in (**b**). **b** Fasting serum triglyceride and HDL cholesterol levels and fasting blood glucose in healthy controls and uric acid stone formers. Values are means. Adapted from the results by Abate et al. [17]

Table 6 Definition of the metabolic syndrome according to ATP III

Metabolic syndrome—definition Adult Treatment Panel (ATP III) 2001≥3 of the following characteristics must be present	
Clinical symptoms	Laboratory parameters
Hypertension BP≥130/85 mmHg	↑Triglycerides≥1.7 mmol/l
Abdominal Obesity ⇒ Waist circumference	↓HDL-cholesterol
>88 cm (Women) >102 cm (Men)	<1.30 mmol/l (Women)
	<1.05 mmol/l (Men)
	↑Fasting blood glucose
	≥6.1 mmol/l

Adapted from [19]

Table 7 Insulin actions in the proximal tubule and potential consequences in subjects with insulin resistance. Data from animal studies (summarized in [17])

Insulin and urinary NH_4^+ excretion—hypothesis based on in vitro studies
Insulin effects in proximal tubules
Insulin stimulates renal genesis of ammonia from the substrate L-Glutamine
Insulin stimulates Na^+–H^+-antiporter → critical for transport of NH_4^+ (substitutes for H^+) into tubules
Insulin resistance at renal level
↓ Ammoniagenesis
↓ Ammonium transport into the tubular lumen
⇒ Low urine pH

stone formation such as dRTA and abnormally low urine pH with subsequent uric acid stone formation. Both the entities can be seen on the background of disturbance of the major urinary buffer system, as outlined in Eq. 2. On the one hand, reduced distal tubular secretion of H^+ ions results in an abnormally high urinary pH and either incomplete (no acidemia) or complete (permanent acidemia) dRTA. Common to both the forms is intracellular acidosis which increases uptake of citrate by proximal tubular cells, thus resulting in hypocitraturia and subsequent calcium stone formation. On the other hand, reduced production/availability of NH_4^+ is the cause of abnormally low urinary pH which predisposes to uric acid stone formation. Most recent research indicates that this abnormality may be a renal manifestation of the increasingly prevalent metabolic syndrome.

Despite opposite deviations from normal urinary pH values, both distal RTA and uric acid stone formation due to low urinary pH require the same treatment, i.e., alkali. In dRTA, alkali is needed for improving the body's buffer capacity, and increases in 24-h urinary citrate excretion can be used for monitoring the therapeutic effect. In uric acid stone formers with low urine pH, the goal of alkali treatment is to increase the urinary pH to 6.2–6.8 in order to minimize uric acid crystallization. This fits the emerging concept that the alkali treatment (especially, alkali citrate) may become a sort of "panacea" for almost any kind of kidney stone disease [12].

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