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Nephrolithiasis: A Paleolithic Perspective and Physiological Approach to Prevention

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Keywords

Paleolithic, diet, nephrolithiasis, urinary stone, thiazide, alkali

Abstract

We take a Paleolithic perspective to account for why nephrolithiasis afflicts so many people and review evidence suggesting that the rapid shift in the human diet 10,000 years ago was a key event that increased stone risk in the modern era. For the past 2 million years, the diet of the hominid family was high in potassium, low in sodium, and high in alkali precursors. A series of technological advances in agriculture, animal husbandry, and industrial-scale food production transformed the human diet to contain more sodium, less potassium, and more acid precursors. This dietary shift was abrupt enough that the kidney was forced to maintain homeostasis at the expense of increasing stone risk. In theory, dietary patterns that resemble the Paleolithic diet should reduce stone risk. Medications like thiazides, alkali, and empagliflozin may improve urinary parameters associated with stone risk, but more clinical trials are needed to test their efficacy for reducing stone recurrence.

INTRODUCTION

Nephrolithiasis is common, painful, and recurrent. Urinary stones can obstruct urine flow, which may cause pain, urinary tract infection, or kidney injury. The lifetime prevalence has been estimated to be 13% for men and 7% for women in the United States (1). Moreover, the lifetime prevalence of nephrolithiasis appears to be increasing, roughly twice as high as it was only three decades ago (2). Nephrolithiasis is troublesome because it often recurs, with one in four patients experiencing three or more stone events (3, 4).

The recurrent nature of nephrolithiasis motivates the development of medical approaches that aim to prevent recurrence so that patients develop fewer complications, emergency department visits, and surgical procedures. Although urinary stones can be prevented through generic approaches, a more personalized approach incorporating knowledge of stone composition and 24-h urine excretion of relevant electrolytes and minerals may clarify the underlying reasons a patient develops recurrent disease and provide specific information about how to reduce stone risk. Most patients will have a calcium oxalate stone; less often, patients will develop a calcium phosphate or uric acid stone (5, 6). Uric acid stones are less common than calcium stones, but the prevalence appears to be increasing (6).

In this review, we first discuss why nephrolithiasis has become more common by taking a Paleolithic perspective that considers the dramatic shift in the human diet at the dawn of the modern era as being a watershed moment for placing more people at risk for nephrolithiasis. We then highlight dietary patterns that incorporate aspects of the Paleolithic diet and review current medications that may reduce stone recurrence.

A PALEOLITHIC PERSPECTIVE OF MODERN DIETARY HABITS

A useful approach to understand why nephrolithiasis afflicts so many people is to consider how the human species evolved over the course of several million years to maintain homeostasis. Sebastian and colleagues have proposed that the transformation of the human diet that occurred in the past 10,000 years—with the advent of agriculture, animal husbandry, and, more recently, industrial-scale food production and urbanization—was abrupt enough that natural selection had insufficient time for human biology to optimally adapt and process dietary minerals and electrolytes (7). This dietary shift represents less than 1% of evolutionary time if we assume that the span of humanity has lasted 2 million years.

Before the end of the Late Stone Age, the diet of the hominid family is presumed to reflect a hunter-gatherer diet consisting of wild animals and uncultivated fruits and plants (8). The composition of potassium (K^+) in the Paleolithic diet has been estimated to be high, more than 280 mEq per day, and the composition of sodium (Na^+) to be low, approximately 30 mEq per day (7). Elements of the Paleolithic diet have been hypothesized to comprise between 20% and 50% meat by weight (with the remainder, plant), depending on geography and prehistoric time period (8). More recent evidence from stable isotope studies of hominid bone suggests that hunter-gatherers in the Paleolithic era might have relied less on a diet of meat from wild game and more on a diet of plants, such as wild cereals, fruits, or tubers, for sources of protein (9–12). If this is the case, the Paleolithic diet might have contained an even higher proportion of fruits and vegetables relative to meat than was originally hypothesized (8), signifying that our ancestral diet was quite enriched with alkali precursors.

As the hominid species evolved while consuming this Paleolithic diet, one adaptation that was critical for survival was the need to maintain an apatite-based skeleton while living in a terrestrial environment (13). From a renal physiology standpoint, this was not a trivial endeavor. The

skeleton maintains structural integrity through continuous remodeling and renewal while supplying calcium (Ca^{2+}) in the extracellular fluid for cellular function (14). As a result, turnover of skeletal Ca^{2+} ranges between 200 and 500 mg per day (13, 15). To support this dynamic exchange of Ca^{2+} between bone and the extracellular fluid, the gut absorbs between 150 and 250 mg per day from the diet, and the kidney must excrete a similar amount to maintain Ca^{2+} balance (16).

The physiological challenge for our hominid ancestors, and for *Homo sapiens* today, is to excrete this daily amount of Ca^{2+} while avoiding Ca^{2+} precipitation. Ca^{2+} is excreted into urine with a variety of phosphate species, all of which have relatively low solubility (13). For terrestrial species, excretion of Ca^{2+} with phosphate must be accomplished with low urine volumes to conserve water, which further increases risk of Ca^{2+} precipitation in kidney tissue or urine. Moe & Preisig (13) have postulated that citrate in the urine serves to sequester Ca^{2+} from phosphate or oxalate to keep Ca^{2+} soluble. Such adaptations were successful while our hominid ancestors consumed a Paleolithic diet, which enabled the kidney to keep Ca^{2+} more soluble in the urine even as it faced the challenge of conserving water.

But this delicate balance was disrupted when the human diet changed in the modern era. With the introduction of agriculture and livestock, the modern diet shifted to cereal grains and eventually energy-dense but nutrient-poor foods, neither of which produce net alkali (7) compared with plant foods (17). As industrial food production developed, the modern diet accumulated more Na^+ and less K^+ (18), with the Na^+/K^+ ratio of food content reversing from 1:10 to 3:1 (7). This implies that the corresponding anion pair chloride (for Na^+) and bicarbonate (for K^+) also switched, indicating that the modern diet has lower quantities of HCO_3^- and organic anions. The lower proportion of fruits and vegetables relative to animal meat in the modern diet introduced a higher net acid load, from an estimated acid load of -88 mEq/day for a Paleolithic diet to $+48$ mEq/day for a modern diet (17). **Table 1** summarizes the daily estimated nutrients in the Paleolithic and the modern diets that are relevant for risk of nephrolithiasis.

In the latter part of the twentieth century, greater food availability from industrial food production and urbanization provided people with more food. Food became more affordable, convenient, and palatable, but less nutritious. It thus became easier for people to eat more food, leading to the rising prevalence of obesity and diseases associated with insulin resistance such as metabolic syndrome or diabetes (19).

In the modern era, a mismatch emerged whereby the kidney had evolved to adapt to the Paleolithic diet but now faced a modern diet with more Na^+ (less K^+), more acidogenic precursors, and more calories. Without sufficient time for natural selection to operate, the kidney was forced to adapt to maintain homeostasis—at the cost of increasing stone risk. Below, we highlight the consequences related to nephrolithiasis risk when the kidney attempts to adapt to a modern diet (**Figure 1**).

Table 1 Daily estimated nutrient composition of Paleolithic and modern diets

Dietary composition	Paleolithic era	Modern era
Potassium	280 mEq (7, 8)	67 mEq (13)
Sodium	30 mEq (8)	147 mEq (13)
Potassium:sodium	10:1 (7)	1:3 (7)
Calcium	1,580 mg (8)	740 mg (8)
Net acid load	-88 mEq (12)	$+48$ mEq (12)
Protein	251 g (8)	80 g (20)

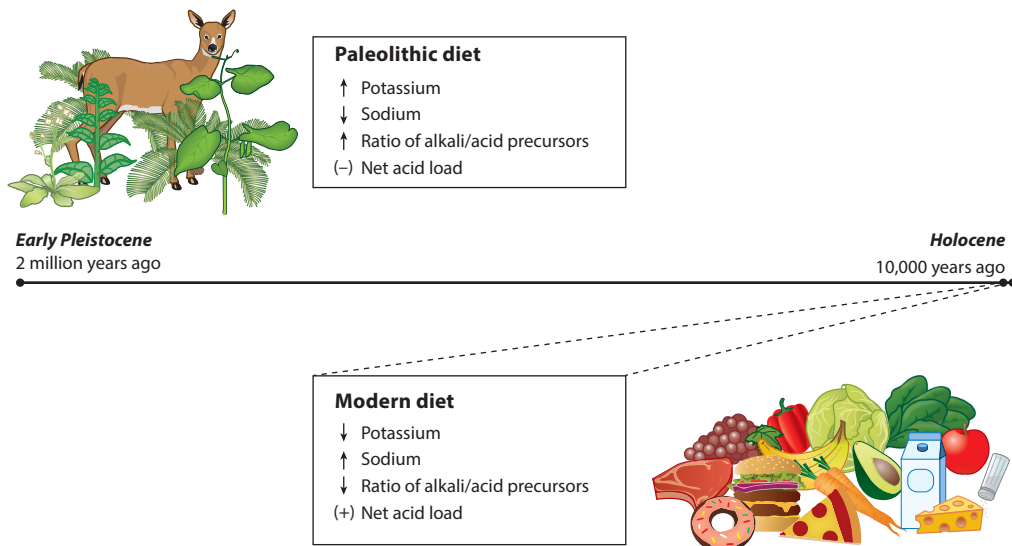


Figure 1

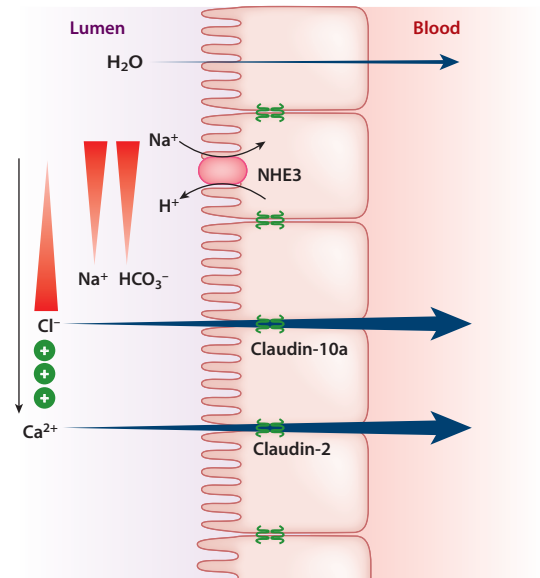
Rapid transformation of the human diet from the Paleolithic to modern era. The mismatch of the time scale between hominid evolution and shift from the Paleolithic to modern diet did not give sufficient time for human physiology to adapt, forcing the kidney to maintain homeostasis at the expense of increasing risk of nephrolithiasis. The human diet shifted to less potassium, more sodium, and a lower proportion of alkali to acid precursors, imposing a higher net acid load. Higher dietary sodium and net acid load increase urinary calcium. Higher net acid load also decreases urinary citrate and urine pH.

Consequence 1: Hypercalciuria and Calcium Stones

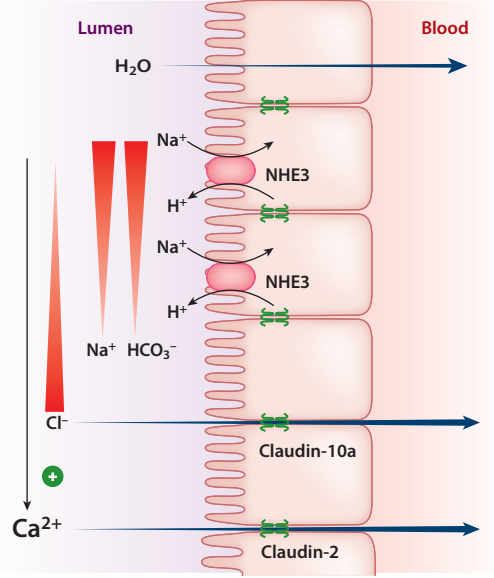
The modern diet contains more Na^+ and a higher net acid load, both of which can increase urinary Ca^{2+} excretion. Hypercalciuria is the most common urinary abnormality for patients with calcium stones (20), and the risk of calcium stones increases when urinary Ca^{2+} excretion exceeds 150 mg/day (21). The association between dietary Na^+ and urinary Ca^{2+} can be explained by the mechanisms by which the kidney couples Ca^{2+} with Na^+ reabsorption in the proximal tubule (Figure 2). Floyd Rector constructed a model of the compositional changes of the luminal fluid across the length of the proximal tubule to characterize Na^+ and chloride (Cl^-) reabsorption (22), and this model explains how the proximal tubule reabsorbs Ca^{2+} . In the early proximal tubule, Na^+ is reabsorbed more avidly in exchange for a hydrogen ion (H^+) via action of the Na^+/H^+ exchanger 3 (NHE3). As a result, more Cl^- remains in the tubular fluid after the early segment. Transcellular water flux maintains isotonic solute reabsorption. The ensuing Cl^- concentration in the tubular fluid is higher in later segments of the proximal tubule, providing a driving force for more Cl^- to be reabsorbed paracellularly through claudin-10a (23). A lumen-positive transepithelial potential (generated by Cl^- reabsorption) and higher luminal Ca^{2+} concentration (generated by isotonic NaCl reabsorption) drive paracellular Ca^{2+} transport across the proximal tubule through claudin-2 (23). In the thick ascending limb (TALH), Na^+ reabsorption (with K^+ and 2Cl^-) through NKCC2, along with recycling of K^+ back to the tubular lumen through ROMK, establishes a lumen-positive diffusion potential that powers paracellular Ca^{2+} reabsorption through claudin-16/19 (23). The high capacity of the proximal tubule and TALH for Ca^{2+} reabsorption then allows the distal convoluted tubule (DCT) to fine-tune the final amount of Ca^{2+} to be excreted in the urine.

The coupling of reabsorption of Ca^{2+} with Na^+ in the proximal tubule and TALH means that more Ca^{2+} will be excreted in the urine when more Na^+ is consumed with the modern diet

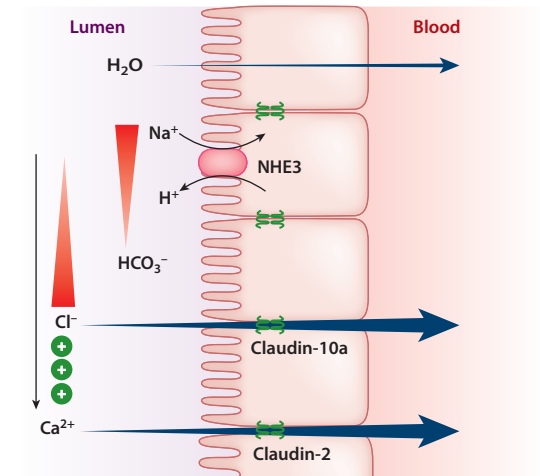
a Lower dietary sodium



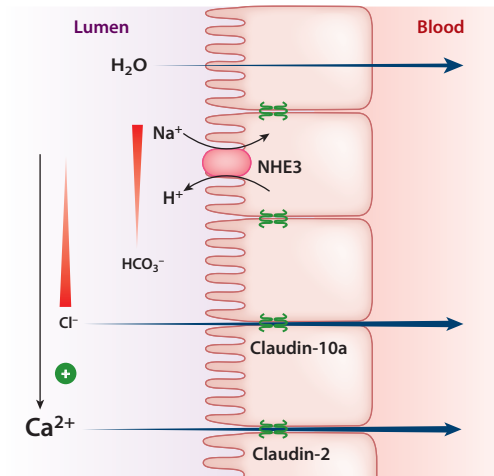
b Higher dietary sodium



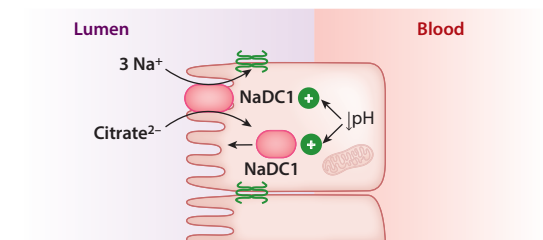
c Lower dietary protein



d Higher dietary protein



e Higher dietary protein



(Caption for Figure 2 appears on following page)

Figure 2 (Figure appears on preceding page)

Calcium and citrate reabsorption in the proximal tubule. (a) Lower dietary sodium: Reabsorption of Ca^{2+} in the proximal tubule is coupled with reabsorption of Na^+ . In the early proximal tubule, Na^+ is reabsorbed more avidly in exchange for a hydrogen ion (H^+) via action of the Na^+/H^+ exchanger 3 (NHE3). As a result, more Cl^- remains in the tubular fluid after the early segment. Transcellular water flux maintains isotonic solute reabsorption. The ensuing Cl^- concentration in the tubular fluid is higher in later segments of the proximal tubule, providing a driving force for more Cl^- to be reabsorbed paracellularly through claudin-10a. A lumen-positive transepithelial potential (generated by Cl^- reabsorption) and higher luminal Ca^{2+} concentration (generated by isotonic NaCl reabsorption) drive paracellular Ca^{2+} transport across the proximal tubule through claudin-2. (b) Higher dietary sodium: High dietary Na^+ will induce less Na^+ and Ca^{2+} reabsorption across the proximal tubule. High dietary Na^+ will increase delivery of more Na^+ and HCO_3^- to later segments of the proximal tubule, which will attenuate the reciprocal rise in luminal Cl^- concentration along the proximal tubule. As a result, the ensuing positive potential difference and luminal Ca^{2+} concentration will be lower, which will reduce paracellular Ca^{2+} transport and net Ca^{2+} reabsorption across the proximal tubule. In turn, more Ca^{2+} will eventually be excreted in the urine. (c) Lower dietary protein: Reabsorption of Ca^{2+} in the proximal tubule depends on dissipation of the HCO_3^- concentration gradient through action of NHE3. Exchange of Na^+ with H^+ will titrate filtered HCO_3^- , which will set up the Cl^- concentration gradient for paracellular Cl^- transport through claudin-10a. The ensuing positive potential difference drives paracellular Ca^{2+} transport across the proximal tubule through claudin-2. (d) Higher dietary protein: Dietary acid load will reduce Ca^{2+} reabsorption by the proximal tubule. Dietary acid load will reduce luminal HCO_3^- concentration in the early segments of the proximal tubule by titration of filtered HCO_3^- from higher NHE3 activity. As a result, the HCO_3^- concentration gradient across the proximal tubule is blunted, as is the Cl^- concentration gradient for paracellular Cl^- transport. Paracellular Ca^{2+} transport and net Ca^{2+} reabsorption across the proximal tubule will be attenuated, and more Ca^{2+} will eventually be excreted in the urine. (e) Higher dietary protein: Dietary acid load will increase citrate reabsorption across the proximal tubule. Citrate is freely filtered into the renal tubular fluid, and typically three-quarters of filtered citrate is reabsorbed from the filtrate into the proximal tubule via NaDC1 . Acid loading will reduce intracellular pH in the proximal tubule, which stimulates expression and activity of NaDC1 to increase proximal tubular citrate reabsorption and decrease urinary citrate excretion.

(24). When dietary Na^+ is low, little or no Ca^{2+} reaches the DCT because the proximal tubule reabsorbs virtually all the filtered Ca^{2+} (**Figure 2a**). As dietary Na^+ increases, the proximal tubule will reabsorb less Na^+ and Ca^{2+} (**Figure 2b**). High dietary Na^+ will increase delivery of more Na^+ and HCO_3^- to later segments of the proximal tubule, which will attenuate the reciprocal rise in luminal Cl^- concentration along the proximal tubule. As a result, the ensuing positive potential difference and luminal Ca^{2+} concentration will be lower, which will reduce paracellular Ca^{2+} transport and net Ca^{2+} reabsorption across the proximal tubule. In turn, more Ca^{2+} arrives at the DCT, where the reabsorptive capacity for Ca^{2+} is limited. As a result, more Ca^{2+} is excreted in the urine. When dietary Na^+ is high, the drive to maintain Na^+ balance obligates the kidney to excrete more Na^+ (and thus Ca^{2+}) in the urine.

The modern diet also introduces higher net acid load since the proportion of alkali precursors from fruits and vegetables is less than the acid precursors from all other foods, including protein (17, 25). Foods enriched with sulfur-containing amino acids produce acid with oxidative metabolism, and consumption of a diet rich in animal protein (meat, fish, poultry, eggs, and milk products) increases urinary Ca^{2+} excretion (26, 27) and risk for calcium stones (28, 29).

The effect of acid loading on Ca^{2+} reabsorption reflects how reabsorption of Ca^{2+} in the proximal tubule depends on dissipation of the HCO_3^- concentration gradient through action of NHE3 (30) (**Figure 2c**). Exchange of Na^+ with H^+ will titrate filtered HCO_3^- , which will set up the Cl^- concentration gradient for paracellular Cl^- transport through claudin-10a. The ensuing positive potential difference drives paracellular Ca^{2+} transport across the proximal tubule through claudin-2. A dietary acid load will reduce luminal HCO_3^- concentration in the early segments of the proximal tubule by titrating filtered HCO_3^- from higher NHE3 activity (**Figure 2d**). As a result, the HCO_3^- concentration gradient across the proximal tubule is blunted, as is the Cl^- concentration gradient for paracellular Cl^- transport. Since the luminal Cl^- concentration gradient establishes the lumen-positive transepithelial potential across the proximal tubule, the driving force for paracellular Ca^{2+} reabsorption similarly decreases, and more Ca^{2+} is delivered

downstream in the tubular fluid (30). In the distal tubule, a lower extracellular or intracellular pH will inhibit activity of the TRPV5 (transient receptor potential-vanilloid type-isoform 5 channel) (31, 32), which mediates apical entry of Ca^{2+} into the DCT cell where transcellular Ca^{2+} reabsorption takes place.

In summary, the modern diet tends to increase urinary Ca^{2+} excretion because it contains more Na^+ and presents a higher net acid load, both of which will reduce reabsorption of Ca^{2+} in the proximal tubule. More Ca^{2+} will thus be delivered to the distal tubule where the reabsorptive capacity for Ca^{2+} is limited. As a result, more Ca^{2+} is excreted in the urine and risk for calcium stone disease increases.

Consequence 2: Hypocitraturia and Calcium Stones

The modern diet, with higher net acid load and lower K^+ content, may also decrease urinary citrate excretion. Hypocitraturia is generally defined as <320 mg/day and is an established risk factor for calcium stone disease (33). Citrate is a key inhibitor of calcium stones because it forms a soluble complex with Ca^{2+} so that urine becomes less saturated with calcium oxalate or calcium phosphate salts. Alpern & Sakhaee (34) have hypothesized that the kidney makes a trade-off in response to a chronic acid load, whereby the proximal tubule will reabsorb more citrate at the expense of lowering urinary citrate excretion. The kidney conserves citrate, which yields alkali when it is oxidized, to help maintain acid-base balance, but the ensuing hypocitraturia increases risk for calcium stone disease (35). The molecular basis for proximal tubular citrate reabsorption is mediated by the sodium dicarboxylate cotransporter-1 (NaDC1). Citrate is freely filtered into the renal tubular fluid, and typically three-quarters of filtered citrate is reabsorbed from the filtrate into the proximal tubule (36, 37) via NaDC1 (38–40). Acid loading stimulates expression and activity of NaDC1 to increase proximal tubular citrate reabsorption (41, 42), which lowers urinary citrate excretion (35, 37) (**Figure 2e**).

The low K^+ content of the modern diet may also lower urinary citrate excretion because proximal tubular citrate reabsorption is also affected by hypokalemia. Low dietary K^+ may predispose persons to hypokalemia, which will induce shifting of more K^+ from the intracellular to the extracellular compartment, in exchange for H^+ , to limit the fall in serum K^+ concentration. The resulting intracellular acidosis increases expression and apical localization of NaDC1 in proximal tubule cells (42) and increases renal citrate reabsorption (43–45). As a result, urinary citrate excretion may fall with sustained dietary K^+ deficiency. Since citrate is a key inhibitor of calcium stones, low urinary citrate excretion from the higher net acid load and/or lower K^+ content of the modern diet will increase risk for calcium stone disease.

Consequence 3: Acidic Urine and Uric Acid Stones

With the advent of the modern diet, chronic diseases associated with caloric excess emerged, such as obesity, the insulin resistance (metabolic) syndrome, and diabetes, predisposing more persons to excrete unduly acidic urine. Low urine pH, defined as a urine pH < 5.5 , increases risk for uric acid stone disease (46–48). The reason can be explained by principles of chemistry. Uric acid is a weak acid with an estimated pKa in urine of 5.35 for the first dissociable H^+ (49). When urine pH nears 5.35, half of uric acid exists as the undissociated form and half in the dissociated (charged) form at equilibrium. The undissociated form of uric acid is poorly soluble, with a solubility limit of 100 mg/L, and contributes to uric acid formation (49). Thus, urinary solubility of uric acid is largely determined by the urine pH and urine volume (49, 50). For example, the urine will be undersaturated with uric acid when the urine pH is 6.5—even if total uric acid excretion were as high as 1,200 mg/day and the urine volume were as low as 1.2 L—because the undissociated uric

EQUATIONS RELATED TO MAINTENANCE OF ACID-BASE BALANCE

Endogenous acid production

= urinary SO_4^{2-} + urinary HPO_4^{2-} + urinary nonmetabolized anions

Net gastrointestinal alkali absorption (NGIA)

= urinary Na^+ + urinary K^+ + urinary Ca^{2+} + urinary Mg^{2+} - (urinary Cl^- + 1.8 urinary P)

Net Acid Excretion (NAE)

= urinary NH_4^+ + urinary titratable acids - urinary HCO_3^-

acid concentration would still be under the solubility limit of 100 mg/L. Conversely, the urine will be oversaturated with uric acid when the urine pH is 5.3—even if total uric acid excretion were as low as 400 mg/day and the urine volume were as high as 2 L—because the undissociated uric acid concentration would still be above the solubility limit. The urine pH, rather than the total uric acid concentration, dictates risk for uric acid stone formation.

Why do uric acid stone formers excrete an acidic urine? To answer this question, we must review how the kidney maintains acid-base balance to understand the determinants of urine pH. The sidebar titled Equations Related to Maintenance of Acid-Base Balance defines the inputs and outputs that relate to whole-body acid-base balance. Endogenous acid production estimates the production of H^+ through oxidation of organic sulfur and inorganic divalent phosphate and urinary excretion of nonmetabolized organic anions in the steady state (51). Net gastrointestinal alkali absorption (NGIA) estimates the net absorption of organic anions, which represents potential alkali when these anions are metabolized (52, 53). NGIA offsets endogenous acid production, and so the kidney ultimately maintains acid-base balance by excreting any remaining acid into the urine in the form of urinary ammonium (NH_4^+) and titratable acid (defined as net acid excretion).

When a person eats a prime ribeye steak (an acid load), organic sulfur is oxidized, which generates H^+ that must be excreted from the body. Yet very little acid is excreted as free H^+ in the urine because the maximum urine H^+ concentration the kidney can excrete is 0.03 mEq/L (54). If a person were to excrete a daily urine volume of 4 L and rely solely on urinary acidification (without action of urinary buffers), only 0.12 mEq of HCO_3^- would be regenerated each day. Since consumption of a modern diet produces approximately 1 mEq/kg body weight of inorganic acid, the amount of HCO_3^- regenerated by urinary acidification alone would be insufficient to replete total body stores of HCO_3^- . Thus, the kidney relies on urinary excretion of NH_4^+ and titratable acids to replete HCO_3^- buffer. Indeed, the kidney is able to excrete urinary NH_4^+ almost fourfold to compensate for a sustained acid load (55). Buffering of H^+ with NH_3 in the urine enables more H^+ to be eliminated as NH_4^+ compared with free H^+ alone, and this buffering enables excretion of H^+ without forcing the urine pH to drop below 5.7—even with chronic acidosis, renal NH_3 production will exceed H^+ secretion (56) (**Figure 3a**).

Uric acid stone formers excrete an acidic urine for two reasons. First, persons with uric acid stone disease may accumulate a higher acid load compared with healthy counterparts; the higher acid load in uric acid stone formers occurs even when they ingest a fixed diet, suggesting that they may have greater endogenous acid production or organic acid absorption from the gut (57, 58). Second, uric acid stone formers excrete proportionally less net acid as NH_4^+ . Thus, while they can excrete sufficient net acid to match endogenous acid production, the lower proportion of net acid excretion attributable to urinary NH_4^+ excretion translates to less urinary buffer and more H^+ in urine (lower pH) (**Figure 3b**). Moe and colleagues have hypothesized that persons with

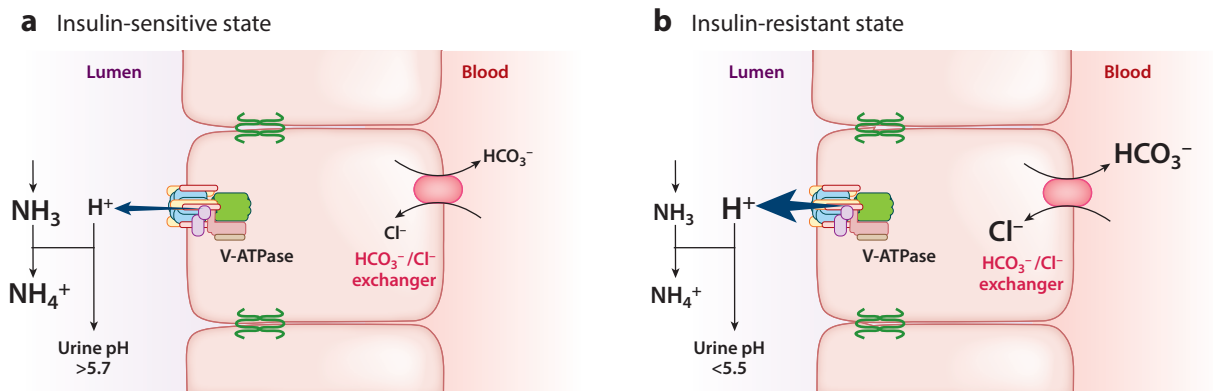


Figure 3

Acid excretion by the alpha-intercalated cell in the distal tubule. (a) Insulin-sensitive (normal) state: Urinary ammonium (NH_4^+) excretion enables more H^+ equivalents to be excreted without forcing the urine pH to drop below 5.7. Alpha-intercalated cells in the collecting duct secrete H^+ via vacuolar ATPase (V-ATPase). Ammonia (NH_3) titrates secreted H^+ to form NH_4^+ and ensuing NH_4^+ excretion keeps urine pH above 5.7. (b) Insulin-resistant state: Diseases associated with caloric excess, such as obesity, the insulin resistance (metabolic) syndrome, and diabetes, can induce excretion of unduly acidic urine and increase risk of uric acid stones. Uric acid stone formers may face a higher acid load from greater endogenous acid production or organic acid absorption from the gut, which would stimulate H^+ secretion via V-ATPase. Concomitant insulin resistance may impair renal ammoniogenesis, which in turn forces excretion of net acid in urine with proportionately less urinary NH_4^+ and more H^+ . Urine pH thus falls below 5.5.

obesity or insulin resistance develop steatosis of proximal tubule cells, which produce NH_3 , and the ensuing lipotoxicity lowers renal NH_3 production and urinary NH_4^+ excretion (59, 60).

In summary, the modern diet presents a higher net acid load, which tends to lower urine pH. If patients develop concomitant insulin resistance, renal ammoniogenesis becomes impaired, forcing excretion of net acid in urine with proportionately less urinary NH_4^+ and more H^+ . In these circumstances, urine pH will fall below 5.5, further increasing risk for uric acid stone disease.

TREATMENT

The Paleolithic perspective can inform clinical practice by focusing on the dietary approach to stone prevention. In theory, a diet containing less Na^+ , more K^+ , and less net acid load may help reduce stone risk in the modern age. If patients fall short of their dietary goals, then medications can be used to correct urinary parameters associated with stone risk. Biochemical stone analysis and 24-h urine testing, which reflects the composition of the steady state diet, provide critical information for identifying risk for stone recurrence. For a more detailed review on the nuances of interpretation of 24-h urine samples, the reader is directed to three outstanding reviews (20, 61, 62). Below, we highlight select treatment options that focus on either restoring elements of the Paleolithic diet or improving individual parameters associated with urinary stone risk.

Fluid

High fluid intake is the cornerstone of an effective stone prevention strategy (63). High fluid intake increases urine volume and decreases supersaturation of calcium oxalate, calcium phosphate, and monosodium urate, thus reducing the propensity for crystallization of calcium and urate salts (64). Two randomized trials and at least seven observational studies have established the benefit of high fluid intake for primary or secondary prevention of urinary stones (65–68). Even increasing daily urine volume by 320 to 500 mL is sufficient to reduce stone risk (69, 70). In the future, it will

be more critical for patients to maintain higher urine volumes as surface temperatures rise due to climate change and as urban heat islands expand with rising urbanization across the globe (71, 72).

Diet: Paleolithic and DASH Diets

If the idea that nephrolithiasis might arise from a mismatch between our evolved physiology and the modern diet, then dietary changes that restore elements of our ancestral diet should reduce stone risk. To date, no studies have comprehensively evaluated urinary stone risk parameters for persons consuming a strict Paleolithic diet, but two studies have examined some physiological effects. In a 10-day study of nine healthy volunteers in a metabolically controlled setting, eating a Paleolithic diet consisting of meat, fish, poultry, eggs, fruits, and vegetables (and without dairy, legumes, cereals, grains, or potatoes) increased urinary K^+ by 71 ± 54 mmol/day and decreased urinary Na^+ by 89 ± 73 mmol/day such that the ratio of urinary K^+/Na^+ increased from 0.5 ± 0.1 mmol/mmol to 2.2 ± 0.6 mmol/mmol (73). Urinary Ca^{2+} decreased in all nine participants, but urine pH remained the same (73). In a 14-day study of 14 patients with obesity and type 2 diabetes, eating a similar Paleolithic diet increased the ratio of urinary K^+/Na^+ from 0.5 ± 0.3 mmol/mmol to 2.0 ± 0.8 mmol/mmol (74). Urinary Ca^{2+} decreased, and urine pH increased by 0.8 ± 0.3 units (74). In both studies, measures of glucose control and insulin sensitivity for study participants also improved.

No randomized controlled trials have been conducted to prove the efficacy of a Paleolithic-based diet for secondary prevention of nephrolithiasis. However, diets that incorporate elements of the Paleolithic diet may still provide clues. For example, a low Na^+ diet, combined with a normal Ca^{2+} and moderate protein diet, has been established as effective prevention of recurrent calcium stones in patients with hypercalciuria (75). The DASH (Dietary Approaches to Stop Hypertension) diet also incorporates elements of the Paleolithic diet, as both diets contain a rich supply of fruits and vegetables, with the notable exception that the DASH diet permits cereal grains, dairy products, and legumes. In a longitudinal cohort study, Curhan and colleagues found that persons eating more similarly to a DASH-style diet had lower risk for incident stone disease compared with those eating a typical American diet (76). Furthermore, those eating more similarly to a DASH-style diet excreted more K^+ and citrate, more alkaline urine, and lower relative supersaturations for calcium oxalate and uric acid. The higher intake of fruits and vegetables likely increased NGIA (although not specifically calculated in the study), leading participants to excrete more citrate and/or more alkaline urine.

Thiazide and Thiazide-Type Agents: Targeting Hypercalciuria

Thiazides and thiazide-type agents are prescribed to lower urinary Ca^{2+} excretion with the goal of reducing the risk of calcium stone formation (77–79). Thiazides inhibit the $NaCl$ cotransporter in the DCT and ultimately stimulate the proximal tubule to reclaim a higher fraction of filtered Ca^{2+} from the tubular fluid so that less Ca^{2+} is excreted (80). Ten clinical trials have evaluated the effects of thiazide diuretics on calcium stone recurrence (81). Results have been mixed. Several early randomized controlled trials demonstrated a reduction in urinary Ca^{2+} excretion and stone recurrence (77, 82, 83). Ettinger et al. (83) conducted a double-blind study where patients with a history of recurrent stones and hypercalciuria (urinary $Ca^{2+} >250$ mg/day in women and >300 mg/day in men) were randomized to receive 25 mg or 50 mg daily of chlorthalidone, magnesium hydroxide, or placebo. Chlorthalidone was superior to magnesium hydroxide and placebo, with a 90% decrease in predicted rates of stone formation for participants taking either 25 mg or 50 mg dosages (83). Borghi et al. (78) randomly assigned hypercalciuric stone formers to three groups: (a) diet and fluid alone, (b) 2.5 mg daily of indapamide, or (c) 2.5 mg daily of indapamide

and allopurinol. After three years of treatment, groups treated with indapamide had a 50% reduction in urinary Ca^{2+} and lower stone recurrence. Finally, in a study of 50 recurrent stone formers with urinary $\text{Ca}^{2+} > 240$ mg/day and/or urinary uric acid > 588 mg/day, those prescribed 25 mg of hydrochlorothiazide twice daily had longer stone-free intervals compared with those prescribed placebo, with a probability of being stone-free during the study period of 75% versus 45% in the placebo group (84).

The NOSTONE trial recently demonstrated that recurrent calcium stone formers who were administered 12.5 mg, 25 mg, or 50 mg daily of hydrochlorothiazide for three years derived no benefit in a composite of symptomatic and radiologic stone recurrence compared with those administered placebo (85). If we consider the mechanisms by which thiazides lower urinary Ca^{2+} excretion, the lack of efficacy of hydrochlorothiazide is surprising. The findings from the NOSTONE trial, however, may provide clues for how hydrochlorothiazide and other thiazide-type agents should be prescribed for stone prevention. First, hydrochlorothiazide, a short acting thiazide with an elimination half-life of just 2.5 h (86), likely requires twice daily dosing and higher doses to achieve a therapeutic, hypocalciuric effect. Second, the hypocalciuric effect of thiazide and thiazide-type agents is blunted when dietary Na^+ is concomitantly high, since the mechanism underlying the hypocalciuric effect of thiazides depends on inducing extracellular fluid volume contraction (80). In the NOSTONE trial, the mean 24-h urinary Na^+ excretion after hydrochlorothiazide treatment ranged between 181 and 199 mEq/day, above the target limit of 50 mEq/day established by Borghi et al. (75). Third, the study design of the NOSTONE trial did not allow for titration of hydrochlorothiazide dose to keep 24-h urinary Ca^{2+} below a certain target; as a result, the mean 24-h urinary Ca^{2+} excretion after hydrochlorothiazide treatment ranged between 232 and 237 mg/day (85), at which point many clinicians might increase the dose of hydrochlorothiazide for further lowering of urinary Ca^{2+} . If we consider all the clinical trial evidence with thiazide and thiazide-type agents, it remains possible that these medications reduce stone recurrence if they are prescribed at higher doses for patients who have hypercalciuria or if there is a therapeutic goal for achieving a lower target for urinary Ca^{2+} , preferably < 150 mg/day (21).

Alkali Supplementation: Targeting Hypocitraturia or Acidic Urine

The mainstay for treatment of hypocitraturia is administration of alkali, typically in the prescribed form of sodium bicarbonate or potassium citrate. The required dose of alkali to raise urinary citrate excretion or urine pH depends on the level of kidney function, the degree of NGIA, and overall acid-base status (35, 87–91). Dosing of alkali has not been formally established but typically ranges between 30 mEq and 60 mEq daily (92). Two small clinical trials demonstrated that potassium citrate reduces stone recurrence in patients with calcium stones (92, 93). In the first study, new calculi formed in 12.9% of participants receiving potassium-magnesium citrate compared with 63.6% of those receiving placebo (93). In the second study, stone formation rate with potassium citrate treatment was tenfold lower than with placebo treatment (0.1 ± 0.2 versus 1.1 ± 0.3 per patient year) (92). For patients with uric acid stones, a small clinical trial of 18 patients with uric acid or mixed uric acid/calcium stones and urine pH < 5.5 , the event rate for recurrent stones decreased dramatically from 1.2 stones to 0.01 stones per patient year (94).

Over-the-counter beverages provide an alternative source of alkali that may taste better and cost less than prescribed medications (95). The least expensive option is baking soda (sodium bicarbonate), but other options such as Litholyte, Effer-K, and Moonstone may be more palatable (96–98). For citrus fruits and drinks, it is important to know the proportion of citrate to citric acid because citrate, and not citric acid, is the alkali equivalent that will raise urinary citrate and/or

urine pH. If the citrate concentration in a citrus drink is low, the patient will need to drink more of it to deliver sufficient alkali to the body. For lemon water or juice, two quarts a day is required to raise urinary citrate to an effective range for stone prevention (99). Citrus-containing diet sodas such as Diet 7-Up, Diet Sunkist Orange, Crystal Light Lemonade, or Diet Kroger Orange Juice also contain potential alkali (100, 101), but again the low citrate concentration in these sodas may require unrealistically high daily fluid volumes to raise urinary citrate or urine pH to a therapeutic level.

Empagliflozin: Targeting Hypocitraturia

A major limitation of alkali supplementation is that alkali can increase the risk of calcium phosphate stones because it may force the excretion of an alkaline urine. When the urine pH exceeds 6.8, urinary phosphate shifts toward the divalent form, HPO_4^{2-} , which binds to free Ca^{2+} in urine and increases tendency for calcium phosphate crystal formation. A promising new drug that can increase urinary citrate excretion—without also raising urine pH—is empagliflozin, which is in the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 inhibitors have emerged as a key treatment for patients with the cardiovascular-kidney-metabolic syndrome, and recent studies have suggested that treatment of patients with SGLT2 inhibitors may also lower incidence of nephrolithiasis (102–104). Kristensen et al. (103) examined 24,290 patients with type 2 diabetes who were taking SGLT2 inhibitors and reported a 50% reduction for incident nephrolithiasis and a 68% reduction in recurrent nephrolithiasis. In a pooled analysis, Balasubramanian et al. (102) demonstrated that empagliflozin reduced incident stone events by almost 40% in patients with type 2 diabetes.

An unexpected mechanism by which empagliflozin might reduce stone risk is through increasing urinary citrate excretion (105). This mechanism of action for empagliflozin was confirmed in the SWEETSTONE trial, the first single-center, double-blind, crossover trial of 53 adults without diabetes and either calcium or uric acid nephrolithiasis (106). Participants were randomized to receive a two-week course of 25 mg daily of empagliflozin followed by a two-week course of placebo, or the reverse order. For patients with calcium stones, empagliflozin treatment was associated with a 36% reduction in urinary relative supersaturation ratios (RSRs) for calcium phosphate compared with placebo; for patients with uric acid stones, empagliflozin treatment was associated with a 30% reduction in RSR uric acid. Empagliflozin induced excretion of a urine pH around 5.6 for both groups of stone formers, which helped to reduce RSR for calcium phosphate and uric acid. Empagliflozin also increased 24-h urinary citrate excretion by 60% in calcium stone formers. The 24-h urine profile of higher urinary citrate excretion and lower urine pH is unique and suggests that empagliflozin could represent a novel treatment option for patients with calcium phosphate stone disease. Future studies are needed to determine the mechanisms by which empagliflozin increases urinary citrate and to confirm if empagliflozin reduces stone recurrence.

CONCLUSIONS

Nephrolithiasis is common, and incident disease is increasing. The rapid shift in dietary patterns from the Paleolithic to the modern era generated a mismatch between human physiology and nutritional demand, forcing the kidney to maintain homeostasis at the expense of increasing stone risk. The modern diet contains more Na^+ , less K^+ , and higher net acid, which may increase urinary Ca^{2+} , decrease urinary citrate, or lower urine pH. All these factors may predispose more people to form urinary stones. In theory, dietary patterns that resemble the Paleolithic diet should reduce stone risk by restoring the low Na^+/K^+ ratio of food content and reducing net acid load.

More clinical trials are needed to test the efficacy of thiazide and thiazide-type agents and SGLT2 inhibitors for reducing stone recurrence.

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LITERATURE CITED

1. Stamatelou KK, Francis ME, Jones CA, et al. 2003. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int.* 63:1817–23
2. Scales CD Jr, Smith AC, Hanley JM, et al. 2012. Prevalence of kidney stones in the United States. *Eur. Urol.* 62:160–65
3. Fwu CW, Eggers PW, Kimmel PL, et al. 2013. Emergency department visits, use of imaging, and drugs for urolithiasis have increased in the United States. *Kidney Int.* 83:479–86
4. Hsi RS. 2019. Prediction tool to predict symptomatic kidney stone episodes: a step toward personalizing kidney stone care. *Mayo Clin. Proc.* 94:179–81
5. Kittanamongkolchai W, Vaughan LE, Enders FT, et al. 2018. The changing incidence and presentation of urinary stones over 3 decades. *Mayo Clin. Proc.* 93:291–99
6. Xu LHR, Adams-Huet B, Poindexter JR, et al. 2017. Temporal changes in kidney stone composition and in risk factors predisposing to stone formation. *J. Urol.* 197:1465–71
7. Frassetto L, Morris RC Jr, Sellmeyer DE, et al. 2001. Diet, evolution and aging: the pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. *Eur. J. Nutr.* 40:200–13
8. Eaton SB, Konner M. 1985. Paleolithic nutrition. A consideration of its nature and current implications. *N. Engl. J. Med.* 312:283–89
9. Melamed Y, Kislev ME, Geffen E, et al. 2016. The plant component of an Acheulian diet at Gesher Benot Ya'aqov, Israel. *PNAS* 113:14674–79
10. Chen JC, Aldenderfer MS, Eerkens JW, et al. 2024. Stable isotope chemistry reveals plant-dominant diet among early foragers on the Andean Altiplano, 9.0–6.5 cal. ka. *PLOS ONE* 19:e0296420
11. Moubtahij Z, McCormack J, Bourgon N, et al. 2024. Isotopic evidence of high reliance on plant food among Later Stone Age hunter-gatherers at Taforalta, Morocco. *Nat. Ecol. Evol.* 8:1035–45
12. Lüdecke T, Leichliter JN, Stratford D, et al. 2025. Australopithecus at Sterkfontein did not consume substantial mammalian meat. *Science* 387:309–14
13. Moe OW, Preisig PA. 2006. Dual role of citrate in mammalian urine. *Curr. Opin. Nephrol. Hypertens.* 15:419–24
14. Holt EH, Lupsa B, Lee GS, et al. 2022. Hormonal regulation of calcium balance. In *Goodman's Basic Medical Endocrinology*, ed. EH Holt, B Lupsa, GS Lee, et al. Elsevier. 5th ed.
15. Morgan JL, Skulan JL, Gordon GW, et al. 2012. Rapidly assessing changes in bone mineral balance using natural stable calcium isotopes. *PNAS* 109:9989–94
16. Tebben PJ, Kumar R. 2013. The hormonal regulation of calcium metabolism. In *Seldin and Giebisch's The Kidney*, ed. RJ Alpern, OW Moe, M Caplan. Academic. 5th ed.
17. Sebastian A, Frassetto LA, Sellmeyer DE, et al. 2002. Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors. *Am. J. Clin. Nutr.* 76:1308–16
18. Cogswell ME, Zhang Z, Carriquiry AL, et al. 2012. Sodium and potassium intakes among US adults: NHANES 2003–2008. *Am. J. Clin. Nutr.* 96:647–57

19. Bleich S, Cutler D, Murray C, Adams A. 2008. Why is the developed world obese? *Annu. Rev. Public Health* 29:273–95
20. Moe OW. 2006. Kidney stones: pathophysiology and medical management. *Lancet* 367:333–44
21. Curhan GC, Taylor EN. 2008. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int.* 73:489–96
22. Rector FC Jr. 1983. Sodium, bicarbonate, and chloride absorption by the proximal tubule. *Am. J. Physiol.* 244:F461–71
23. Yu ASL, Curry JN. 2024. Paracellular transport and renal tubule calcium handling: emerging roles in kidney stone disease. *J. Am. Soc. Nephrol.* 35:1758–67
24. Moe OW, Preisig PA. 2005. Hypothesizing on the evolutionary origins of salt-induced hypercalciuria. *Curr. Opin. Nephrol. Hypertens.* 14:368–72
25. Smit E, Nieto FJ, Crespo CJ, Mitchell P. 1999. Estimates of animal and plant protein intake in US adults: results from the Third National Health and Nutrition Examination Survey, 1988–1991. *J. Am. Diet. Assoc.* 99:813–20
26. Breslau NA, Brinkley L, Hill KD, Pak CY. 1988. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J. Clin. Endocrinol. Metab.* 66:140–46
27. Robertson WG, Peacock M, Heyburn PJ, et al. 1979. Should recurrent calcium oxalate stone formers become vegetarians? *Br. J. Urol.* 51:427–31
28. Ferraro PM, Mandel EI, Curhan GC, et al. 2016. Dietary protein and potassium, diet-dependent net acid load, and risk of incident kidney stones. *Clin. J. Am. Soc. Nephrol.* 11:1834–44
29. Robertson WG, Peacock M, Hodgkinson A. 1979. Dietary changes and the incidence of urinary calculi in the U.K. between 1958 and 1976. *J. Chronic Dis.* 32:469–76
30. Moe OW, Huang CL. 2006. Hypercalciuria from acid load: renal mechanisms. *J. Nephrol.* 19(Suppl. 9):S53–61
31. Yeh BI, Kim YK, Jabbar W, Huang CL. 2005. Conformational changes of pore helix coupled to gating of TRPV5 by protons. *EMBO J.* 24:3224–34
32. Yeh BI, Sun TJ, Lee JZ, et al. 2003. Mechanism and molecular determinant for regulation of rabbit transient receptor potential type 5 (TRPV5) channel by extracellular pH. *J. Biol. Chem.* 278:51044–52
33. Zuckerman JM, Assimos DG. 2009. Hypocitraturia: pathophysiology and medical management. *Rev. Urol.* 11:134–44
34. Alpern RJ, Sakhaee K. 1997. The clinical spectrum of chronic metabolic acidosis: Homeostatic mechanisms produce significant morbidity. *Am. J. Kidney Dis.* 29(2):291–302
35. Alpern RJ. 1995. Trade-offs in the adaptation to acidosis. *Kidney Int.* 47:1205–15
36. Hamm LL. 1990. Renal handling of citrate. *Kidney Int.* 38:728–35
37. Simpson DP. 1983. Citrate excretion: a window on renal metabolism. *Am. J. Physiol.* 244:F223–34
38. Chen XZ, Shayakul C, Berger UV, et al. 1998. Characterization of a rat Na⁺-dicarboxylate cotransporter. *J. Biol. Chem.* 273:20972–81
39. Pajor AM. 1995. Sequence and functional characterization of a renal sodium/dicarboxylate cotransporter. *J. Biol. Chem.* 270:5779–85
40. Pajor AM. 1996. Molecular cloning and functional expression of a sodium-dicarboxylate cotransporter from human kidney. *Am. J. Physiol.* 270:F642–48
41. Aruga S, Wehrli S, Kaissling B, et al. 2000. Chronic metabolic acidosis increases NaDC-1 mRNA and protein abundance in rat kidney. *Kidney Int.* 58:206–15
42. Osis G, Webster KL, Harris AN, et al. 2019. Regulation of renal NaDC1 expression and citrate excretion by NBCe1-A. *Am. J. Physiol. Ren. Physiol.* 317:F489–501
43. Adler S, Zett B, Anderson B. 1974. Renal citrate in the potassium-deficient rat: role of potassium and chloride ions. *J. Lab. Clin. Med.* 84:307–16
44. Fourman P, Robinson JR. 1953. Diminished urinary excretion of citrate during deficiencies of potassium in man. *Lancet* 265:656–57
45. Melnick JZ, Srere PA, Elshourbagy NA, et al. 1996. Adenosine triphosphate citrate lyase mediates hypocitraturia in rats. *J. Clin. Invest.* 98:2381–87
46. Maalouf NM, Cameron MA, Moe OW, Sakhaee K. 2010. Metabolic basis for low urine pH in type 2 diabetes. *Clin. J. Am. Soc. Nephrol.* 5:1277–81

47. Maalouf NM, Sakhaee K, Parks JH, et al. 2004. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int.* 65:1422–25
48. Maalouf NM, Cameron MA, Moe OW, et al. 2007. Low urine pH: a novel feature of the metabolic syndrome. *Clin. J. Am. Soc. Nephrol.* 2:883–88
49. Asplin JR. 1996. Uric acid stones. *Semin. Nephrol.* 16:412–24
50. Rimer JD, Sakhaee K, Maalouf NM. 2019. Citrate therapy for calcium phosphate stones. *Curr. Opin. Nephrol. Hypertens.* 28:130–39
51. Relman AS, Lennon EJ, Lemann J Jr. 1961. Endogenous production of fixed acid and the measurement of the net balance of acid in normal subjects. *J. Clin. Invest.* 40:1621–30
52. Lennon EJ, Lemann J Jr., Litzow JR. 1966. The effects of diet and stool composition on the net external acid balance of normal subjects. *J. Clin. Invest.* 45:1601–7
53. Uribarri J, Douyon H, Oh MS. 1995. A re-evaluation of the urinary parameters of acid production and excretion in patients with chronic renal acidosis. *Kidney Int.* 47:624–27
54. Emmett M. 2020. Metabolic alkalosis: a brief pathophysiologic review. *Clin. J. Am. Soc. Nephrol.* 15:1848–56
55. Madison LL, Seldin DW. 1958. Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. *J. Clin. Invest.* 37:1615–27
56. Carlisle EJ, Donnelly SM, Halperin ML. 1991. Renal tubular acidosis (RTA): recognize the ammonium defect and pHorget the urine pH. *Pediatr. Nephrol.* 5:242–48
57. Wiederkehr MR, Moe OW. 2011. Uric acid nephrolithiasis: a systemic metabolic disorder. *Clin. Rev. Bone Miner. Metab.* 9:207–17
58. Bobulescu IA, Park SK, Xu LHR, et al. 2019. Net acid excretion and urinary organic anions in idiopathic uric acid nephrolithiasis. *Clin. J. Am. Soc. Nephrol.* 14:411–20
59. Bobulescu IA, Dubree M, Zhang J, et al. 2009. Reduction of renal triglyceride accumulation: effects on proximal tubule Na⁺/H⁺ exchange and urinary acidification. *Am. J. Physiol. Ren. Physiol.* 297:F1419–26
60. Bobulescu IA, Dubree M, Zhang J, et al. 2008. Effect of renal lipid accumulation on proximal tubule Na⁺/H⁺ exchange and ammonium secretion. *Am. J. Physiol. Ren. Physiol.* 294:F1315–22
61. Ennis JL, Asplin JR. 2016. The role of the 24-h urine collection in the management of nephrolithiasis. *Int. J. Surg.* 36:633–37
62. Asplin JR. 2022. Neglected analytes in the 24-h urine: ammonium and sulfate. *Curr. Opin. Nephrol. Hypertens.* 31:168–74
63. Qaseem A, Dallas P, Forcica MA, et al. 2014. Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med.* 161:659–67
64. Pak CY, Sakhaee K, Crowther C, Brinkley L. 1980. Evidence justifying a high fluid intake in treatment of nephrolithiasis. *Ann. Intern. Med.* 93:36–39
65. Borghi L, Meschi T, Amato F, et al. 1996. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J. Urol.* 155:839–43
66. Curhan GC, Willett WC, Knight EL, Stampfer MJ. 2004. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch. Intern. Med.* 164:885–91
67. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. 1993. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N. Engl. J. Med.* 328:833–38
68. Curhan GC, Willett WC, Speizer FE, et al. 1997. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann. Intern. Med.* 126:497–504
69. Hosking DH, Erickson SB, Van den Berg CJ, et al. 1983. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J. Urol.* 130:1115–18
70. Strauss AL, Coe FL, Deutsch L, Parks JH. 1982. Factors that predict relapse of calcium nephrolithiasis during treatment: a prospective study. *Am. J. Med.* 72:17–24
71. Brikowski TH, Lotan Y, Pearle MS. 2008. Climate-related increase in the prevalence of urolithiasis in the United States. *PNAS* 105:9841–46
72. Maline GE, Goldfarb DS. 2024. Climate change and kidney stones. *Curr. Opin. Nephrol. Hypertens.* 33:89–96

73. Frassetto LA, Schloetter M, Mietus-Synder M, et al. 2009. Metabolic and physiologic improvements from consuming a paleolithic, hunter-gatherer type diet. *Eur. J. Clin. Nutr.* 63:947–55
74. Masharani U, Sherchan P, Schloetter M, et al. 2015. Metabolic and physiologic effects from consuming a hunter-gatherer (Paleolithic)-type diet in type 2 diabetes. *Eur. J. Clin. Nutr.* 69:944–48
75. Borghi L, Schianchi T, Meschi T, et al. 2002. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N. Engl. J. Med.* 346:77–84
76. Taylor EN, Fung TT, Curhan GC. 2009. DASH-style diet associates with reduced risk for kidney stones. *J. Am. Soc. Nephrol.* 20:2253–59
77. Mortensen JT, Schultz A, Ostergaard AH. 1986. Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. *Int. Urol. Nephrol.* 18:265–69
78. Borghi L, Meschi T, Guerra A, Novarini A. 1993. Randomized prospective study of a non-thiazide diuretic, indapamide, in preventing calcium stone recurrences. *J. Cardiovasc. Pharmacol.* 22(Suppl. 6):S78–86
79. Yendt ER, Cohanim M. 1978. Prevention of calcium stones with thiazides. *Kidney Int.* 13:397–409
80. Reilly RF, Huang CL. 2011. The mechanism of hypocalciuria with NaCl cotransporter inhibition. *Nat. Rev. Nephrol.* 7:669–74
81. Reilly RF, Peixoto AJ, Desir GV. 2010. The evidence-based use of thiazide diuretics in hypertension and nephrolithiasis. *Clin. J. Am. Soc. Nephrol.* 5:1893–903
82. Ohkawa M, Tokunaga S, Nakashima T, et al. 1992. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. *Br. J. Urol.* 69:571–76
83. Ettinger B, Citron JT, Livermore B, Dolman LI. 1988. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J. Urol.* 139:679–84
84. Laerum E, Larsen S. 1984. Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. *Acta Med. Scand.* 215:383–89
85. Dhayat NA, Bonny O, Roth B, et al. 2023. Hydrochlorothiazide and prevention of kidney-stone recurrence. *N. Engl. J. Med.* 388:781–91
86. Brater DC. 1998. Diuretic therapy. *N. Engl. J. Med.* 339:387–95
87. Gianella FG, Prado VE, Poindexter JR, et al. 2021. Spot urinary citrate-to-creatinine ratio is a marker for acid-base status in chronic kidney disease. *Kidney Int.* 99:208–17
88. Goldfarb DS. 2012. A woman with recurrent calcium phosphate kidney stones. *Clin. J. Am. Soc. Nephrol.* 7:1172–78
89. Goraya N, Simoni J, Sager LN, et al. 2019. Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. *Kidney Int.* 95:1190–96
90. Goraya N, Simoni J, Sager LN, et al. 2019. Urine citrate excretion identifies changes in acid retention as eGFR declines in patients with chronic kidney disease. *Am. J. Physiol. Ren. Physiol.* 317:F502–11
91. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. 2018. Mechanism for higher urine pH in normal women compared with men. *Am. J. Physiol. Ren. Physiol.* 314:F623–69
92. Barcelo P, Wuhl O, Servitge E, et al. 1993. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J. Urol.* 150:1761–64
93. Ettinger B, Pak CY, Citron JT, et al. 1997. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J. Urol.* 158:2069–73
94. Pak CY, Sakhae K, Fuller C. 1986. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int.* 30:422–28
95. Dai JC, Maalouf NM, Hill K, et al. 2022. Alkali citrate content of common over-the-counter and medical food supplements. *J. Endourol.* 37:112–18
96. Canvasser NE, Rivera M, Bechis SK, et al. 2022. Over-the-counter alkali agents to raise urine pH and citrate excretion: a prospective crossover study in healthy adults. *Urology* 168:72–78
97. Goldfarb DS. 2019. Empiric therapy for kidney stones. *Urolithiasis* 47:107–13
98. Goldfarb DS, Modersitzki F, Asplin JR, Nazzal L. 2023. Effect of a high-citrate beverage on urine chemistry in patients with calcium kidney stones. *Urolithiasis* 51:96
99. Haleblan GE, Leita VA, Pierre SA, et al. 2008. Assessment of citrate concentrations in citrus fruit-based juices and beverages: implications for management of hypocitraturic nephrolithiasis. *J. Endourol.* 22:1359–66

100. Eisner BH, Asplin JR, Goldfarb DS, et al. 2010. Citrate, malate and alkali content in commonly consumed diet sodas: Implications for nephrolithiasis treatment. *J. Urol.* 183:2419–23
101. Large T, Williams J Jr., Asplin JR, Krambeck A. 2020. Using low-calorie orange juice as a dietary alternative to alkali therapy. *J. Endourol.* 34:1082–87
102. Balasubramanian P, Wanner C, Ferreira JP, et al. 2022. Empagliflozin and decreased risk of nephrolithiasis: A potential new role for SGLT2 inhibition? *J. Clin. Endocrinol. Metab.* 107:e3003–7
103. Kristensen KB, Henriksen DP, Hallas J, et al. 2021. Sodium-glucose cotransporter 2 inhibitors and risk of nephrolithiasis. *Diabetologia* 64:1563–71
104. Paik JM, Tesfaye H, Curhan GC, et al. 2024. Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes. *JAMA Intern. Med.* 184:265–74
105. Harmacek D, Pruijm M, Burnier M, et al. 2022. Empagliflozin changes urine supersaturation by decreasing pH and increasing citrate. *J. Am. Soc. Nephrol.* 33:1073–75
106. Anderegg MA, Schietzel S, Bargagli M, et al. 2025. Empagliflozin in nondiabetic individuals with calcium and uric acid kidney stones: a randomized phase 2 trial. *Nat. Med.* 31:286–93