Acidosis and Urinary Calcium Excretion: Insights from Genetic Disorders

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ABSTRACT

Metabolic acidosis is associated with increased urinary calcium excretion and related sequelae, including nephrocalcinosis and nephrolithiasis. The increased urinary calcium excretion induced by metabolic acidosis predominantly results from increased mobilization of calcium out of bone and inhibition of calcium transport processes within the renal tubule. The mechanisms whereby acid alters the integrity and stability of bone have been examined extensively in the published literature. Here, after briefly reviewing this literature, we consider the effects of acid on calcium transport in the renal tubule and then discuss why not all gene defects that cause renal tubular acidosis are associated with hypercalciuria and nephrocalcinosis.


EFFECT OF ACID-BASE PERTURBATIONS ON BONE

Acute or chronic administration of exogenous acid increases urinary calcium excretion. Initial studies exploring the effects of acid loading on overall calcium handling concluded that intestinal calcium absorption is not affected; however, recent work found increased solvent drag mediated calcium flux and altered expression of tight junction proteins in the duodenum of rats with chronic metabolic acidosis. Given that the vast majority of calcium in the body is stored in bone as part of the hydroxyapatite crystal, it is expected that dissolution of bone during acid loading leads to urinary calcium wasting. Extensive evidence from multiple experimental models is consistent with this. There is an acute physicochemical buffering of hydrogen ions (H+) followed by a more chronic effect on cells mediating bone turnover.

It has been appreciated for nearly a century that metabolic acidosis is associated with increased urinary calcium excretion. Overall, this occurs via at least two mechanisms: release of calcium from bone and changes in calcium transport within the renal tubule. Given that bone is an important reservoir of buffer (with both calcium carbonate and phosphate), there is a myriad of data and a strong rationale to implicate its role in buffering acid. Dissolution of bone releases calcium, either as carbonate or phosphate. The net movement of calcium from bone into blood leads to excess calcium being excreted in urine, in an effort to stabilize systemic calcium concentrations. Metabolic acidosis increases ionized calcium in blood, by decreasing the amount bound to albumin. Furthermore, metabolic acidosis causes alterations in the renal reabsorptive capacity for calcium due to the direct inhibition of calcium transport within the nephron; this is evidenced by classic human studies where metabolic acidosis was induced and urinary calcium wasting observed, despite a fall in the filtered load of calcium. However, genetic diseases causing renal tubular acidosis vary with regard to increased calcium excretion and sequelae resulting from excessive urinary calcium losses, such as nephrocalcinosis and nephrolithiasis.

In this review, we will first briefly summarize over 90 years of experiments examining the relationship between acidosis and urinary calcium excretion. We will then highlight selected genetic disorders of altered acid-base balance, using them to understand why a direct coupling between acidosis and renal calcium losses and their associated sequelae are not consistently observed.

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Acute Acidosis

Studies examining the mechanisms by which bone buffers H⁺ have been eloquently reviewed previously.6,7 In brief, the surface of bone is littered with negatively charged sites that bind both sodium and potassium. During acute metabolic acidosis (<3 hours) there is an exchange of both these monovalent cations with H⁺ thereby increasing plasma pH.13–15 There is also some rapid direct dissolution of calcium carbonate and hydroxyapatite from bone releasing calcium, which is likely part of the rapidly exchangeable pool of calcium.13,14,16 Both of these physicochemical processes occur independently of bone cell activity.

Chronic Acidosis

In contrast to the acute situation, exposure of bone to chronic metabolic acidosis i.e., for 24 hours or more, affects bone cell function. Osteoclast activation is stimulated and osteoblast activity is inhibited by lower pH.17–19 Importantly, the converse is true; metabolic alkalosis increases osteoclastic activity and inhibits osteoclastic activity, favoring bone formation.20 One mechanism whereby acidosis mediates its effect on bone involves the release of PGE₂, which stimulates the expression of receptor activator of nuclear factor κ-B (RANK) ligand altering osteoclast differentiation, maturation and H⁺-ATPase activity thereby increasing resorption.21–23

EFFECTS OF ACID-BASE PERTURBATIONS ON THE RENAL TUBULE

Metabolic acidosis causes renal calcium wasting not only via the liberation of calcium from bone, but also by directly altering calcium handling within the renal tubule. This is evident as an increase in urinary calcium excretion occurs despite a decrease in filtered calcium load.5,24 Furthermore, metabolic acidosis alters renal tubular calcium handling irrespective of changes in parathyroid hormone (as patients with hypoparathyroidism demonstrate this phenomenon), and independent of tubular sodium handling.5,25,26 In order to consider how these alterations occur, we must first review tubular calcium reabsorption along the nephron.

Ionized calcium that is filtered by the glomerulus is reabsorbed via both paracellular and active transcellular pathways. The proximal tubule and thick ascending limb (TAL) of the Henle loop demonstrate predominantly, if not exclusively, passive paracellular transport. In the proximal tubule, water absorption is driven by transcellular sodium movement, which is largely mediated by the apical sodium hydrogen exchanger 3 (NHE3).27 Luminal water removal increases the concentration of different solutes, such as calcium, that are not reabsorbed via secondary active transport processes. Calcium then moves down its concentration gradient or with water through the tight junction.28 In the TAL, removal of water in the relatively calcium impermeable thin descending limb,29 and a lumen positive voltage, provides the driving force for paracellular calcium flux. Activity of the apically expressed sodium potassium chloride cotransporter 2 (NKCC2) in concert with potassium efflux back into the lumen via the renal outer medullary potassium channel (ROMK) is necessary to create the lumen positive potential. Consistent with a role in calcium reabsorption, genetic deletion or pharmacological inhibition of either NKCC2 or NHE3 causes hypercalciuria.30–34

Paracellular calcium transport requires both a driving force, and tight junction permeability. Calcium permeation of the proximal tubule and TAL is conferred by specific tight junction proteins called Claudins.35 Their identity is better delineated in the TAL where Claudins-16 and -19 form a cation permeable pore,36 and Claudin-14, whose expression is directly induced via the calcium-sensing receptor (CaSR) signaling in the presence of increased ionized calcium levels, prevents calcium reabsorption.37 In the proximal tubule, Claudin-2 may form a cation permeable pore.38 However, further work is required to clearly delineate the proteins permitting calcium permeation across this segment.

The link between transcellular sodium flux and paracellular calcium absorption under conditions of metabolic acidosis are yet to be clearly elucidated. NHE3 is essential for proximal tubular bicarbonate reabsorption.27 Consequently, metabolic acidosis increases NHE3 activity,39,40 an effect that should attenuate increased urinary calcium excretion accompanying metabolic acidosis. However, metabolic acidosis dissociates sodium reabsorption from calcium reabsorption distal to the late proximal tubular micropuncture site, causing increased urinary calcium excretion relative to sodium.35,41 The overall contribution of the TAL to changes in calcium transport under conditions of metabolic acidosis remains to be fully elucidated. Given our current understanding of TAL transport, one could envision that increased ionized calcium in blood (both mobilized from bone and due to decreased binding to albumin) would increase Claudin-14 expression by activating the CaSR, thereby altering the permeability of the paracellular pore. This would increase urinary calcium excretion and could contribute to the dissociation between increased NHE3 activity and increased urinary calcium excretion observed with metabolic acidosis. However, direct evidence in support of this hypothesis has not been presented, and one must also consider the reduced sensitivities of the CaSR at acidic pH.42

Although the majority of calcium is reabsorbed by the proximal tubule and TAL, the remaining <10% is reabsorbed by the distal convoluted tubule and connecting tubule. This occurs in an active transcellular fashion and discernable changes in transport within this region have been clearly documented during acidosis.43 Apical calcium influx occurs through the transient receptor potential cation channel subfamily V member 5 (TRPV5) channel.44 The calcium binding protein calbindin-D₂₈K buffers ionized calcium, which is extruded across the basolateral membrane via calcium dependent ATPases (plasma membrane Ca²⁺ ATPase) or a sodium calcium exchanger.45,46 Micropuncture studies demonstrate that calcium reabsorption from the distal nephron is inhibited by
metabolic acidosis, independent of changes in parathyroid hormone (PTH), inferring a direct effect on renal transport processes.\textsuperscript{41,47,48} Consistent with this, renal Trpv5 expression is decreased by systemic acid loads and metabolic alkalosis increases expression.\textsuperscript{49} Moreover, metabolic acidosis does not further augment existing calcium wasting in the Trpv5 knockout mice.\textsuperscript{49} Together, this data suggests that systemic acid-base status, at least in part, alters urinary calcium excretion \textit{via} an effect on the expression and activity of Trpv5 in the distal tubule. Importantly, Trpv5-deficient mice display reduced bone thickness due to increased osteoclast-mediated bone resorption, likely as a consequence of renal calcium wasting.\textsuperscript{50} However, Trpv5 is also expressed in the ruffled border of the osteoclast, where it partakes in vectorial calcium transport from the subosteoclastic resorption zone.\textsuperscript{51} Therefore, the effect of metabolic acidosis on Trpv5-mediated calcium reabsorption in kidney, independent of loss of Trpv5 in osteoclasts, remains to be determined.

\textbf{CONSIDERATION OF TYPE OF ACIDOSIS}

Studies described thus far were limited to very controlled situations where acid-base status was manipulated by strict administration of an acid or alkali. Furthermore, the effect of respiratory perturbations on acid-base status and calcium handling reveals an important role for bicarbonate. Moreover, other than causing metabolic acidosis, additional effects of specific acids and their counter ions on calcium homeostasis and consequently urinary calcium excretion further complicate the situation. However, consideration of these effects aids our understanding of the dynamic physiologic processes occurring simultaneously.

\textbf{Metabolic Versus Respiratory Acidosis}

In different studies respiratory acidosis either does not increase urinary calcium excretion or increases urinary calcium excretion less so than a similar decrease in pH caused by a metabolic acidosis.\textsuperscript{52–54} As noted earlier, prostaglandin (PG) E\textsubscript{2} promotes osteoclast maturation and H\textsuperscript{+} ATPase activity \textit{via} the RANK pathway thereby increasing bone resorption.\textsuperscript{21–23} PGE release is preferentially stimulated by experimental metabolic acidosis rather than respiratory acidosis.\textsuperscript{22} Moreover, elegant \textit{in vitro} studies manipulating bicarbonate levels independent of pH demonstrate that calcium mobilization from bone in response to a metabolic acidosis occurs to a greater extent when bicarbonate concentration is simultaneously reduced.\textsuperscript{55,56} This may explain why respiratory acidosis is less potent than metabolic acidosis in promoting urinary calcium wasting.\textsuperscript{52–54} Consistent with this, \textit{in vitro} models of acidosis with elevated bicarbonate levels can actually increase carbonate incorporation into bone.\textsuperscript{57} Consequently, plasma bicarbonate levels themselves, independent of pH, affect bone formation and dissolution. Thus, when considering the effect of acid-base status on calcium homeostasis, one must also consider bicarbonate, because it appears to have a greater effect on bone than changes in pH. We are unaware of studies directly examining renal tubular calcium handling in the presence of respiratory acidosis. However, the effects of hypercarbia on luminal bicarbonate concentration may increase distal calcium absorption, further attenuating urinary calcium excretion.

\textbf{Different Exogenous Acids}

Hydrochloric acid and ammonium chloride administration have been employed to model disease states such as the acidosis observed in renal failure or that induced by ingestion of a high protein diet. These models simplify complex disease processes and conclusions from them must therefore be carefully considered. In the case of uremic metabolic acidosis, it is typically accompanied by an elevated PTH and suppressed active 1,25-dihydroxyvitamin D levels. These hormones have significant effects on urinary calcium excretion by themselves. Increased PTH enhances bone resorption favoring calcium mobilization into blood. However, considerable evidence exists that the effect of acid on bone, and consequently calcitriol, occurs independently of PTH.\textsuperscript{58–60} Similarly, reduced 1,25-dihydroxyvitamin D levels decrease intestinal calcium uptake, which should reduce urinary calcium excretion. However, many, but not all, studies found that metabolic acidosis increases urinary calcium excretion without altering intestinal calcium absorption,\textsuperscript{4,60,61} and argued against a direct role for 1,25-dihydroxyvitamin D in this process. Indeed, 1,25-dihydroxyvitamin D generation in response to the calcitriol of any metabolic acidosis is indirectly suppressed by bone resorption which elevates plasma calcium.\textsuperscript{62}

The ingestion of protein has many diverse physiologic effects including the production of hormones and nonvolatile acid. A meta-analysis examining dietary interventions to increase acid producing food ingestion found a proportionate increase between urinary acid excretion and urinary calcium excretion.\textsuperscript{63} The calcium was assumed to come from bone. However, this has been called into question because another meta-analysis by the same group found that total calcium balance and markers of bone breakdown were not altered by increased dietary acid consumption.\textsuperscript{64} A high protein diet itself can increase intestinal calcium uptake, growth hormone, and insulin like growth factor 1 levels as well as lower PTH, which are factors that favor bone formation.\textsuperscript{65} Thus, translating models of ammonium chloride induced acidosis into recommendations on protein consumption to promote bone health, one needs to consider confounding factors. Similarly, diabetic ketoacidosis and lactic acidosis are typically associated with volume contraction, which reduces urinary calcium excretion by increasing proximal tubular calcium reabsorption. However, the osmotic diuresis caused by the former would attenuate proximal tubular calcium reabsorption. This and decreased insulin levels partially explain the more severe urinary calcium loss observed in
diabetic ketoacidosis relative to lactic acidosis.66

**INSIGHT FROM HUMAN DISEASES**

**Distal Renal Tubular Acidosis**

Distal renal tubular acidosis (dRTA) is a disease characterized by a failure to acidify urine, i.e., an inappropriately elevated urine pH in the presence of a nonanion gap (or hyperchloremic) metabolic acidosis. The genetic causes of this disease are often, but not always, accompanied by hypercalciuria and nephrocalcinosis and/or nephrolithiasis (Table 1). Given the previous discussion on the effect of metabolic acidosis on bone, one would predict severe osteoporosis in these patients. However, this is rarely observed; instead, a mild reduction in bone density has been reported, which can be ameliorated by the administration of alkali.57,68 The molecular cause of dRTA has been ascribed to mutations in the H⁺-ATPase B1 subunit (ATP6V1B1),69 α 4 subunit (ATP6V0A4), and the anion exchanger 1 (AE1/SLC4A1). We discuss urinary calcium excretion with respect to specific gene defects below.

**ATP6V1B1**

Patients with mutations in ATP6V1B1 typically have dRTA accompanied by deafness, and nearly all reported cases display nephrocalcinosis.69–71 Why some younger children with mutations in ATP6V1B1 do not have hypercalciuria was recently discussed.9 Although many factors are considered, including other polymorphisms, the authors provide a strong argument for decreased intravascular volume and low sodium intake in preventing hypercalciuria. Importantly, ATP6V1B1 has been implicated in sodium absorption, and children with these mutations also have salt-losing nephropathy.72,73 The relationship between sodium ingestion and calcium excretion is well known.74 The molecular details linking the two are less clear. Given that paracellular calcium absorption is driven by sodium reabsorption from the proximal tubule and TAL,75–77 it can be argued that a low sodium diet leads to increased sodium reabsorption and consequently increased driving force for calcium across these nephron segments (Figure 1). Similarly, intravascular volume status strongly affects proximal tubule sodium, water, and consequently calcium reabsorption.78 Consistent with this, Coe et al.57 found that hypercalciuria associated with ammonium chloride-induced metabolic acidosis was prevented by salt restriction and only when subjects became salt replete did hypercalciuria ensue. It is therefore likely that the lower sodium diet ingested by infants who are either breast-fed or fed formulae masks the hypercalciuria induced by metabolic acidosis. Furthermore, when these children start to consume solids more sodium would be ingested and they consequently develop hypercalciuria. Finally, infants have a significant net positive calcium balance in order to mineralize bone, and a reduced ability to concentrate their urine79,80; both these factors would further attenuate the effect of acidosis on hypercalciuria.

Patients with incomplete dRTA due to milder mutations in ATP6V1B1 often display hypercalciuria and a tendency to form kidney stones.81,82 The etiology of nephrocalcinosis in these patients is due to intraluminal precipitation of calcium phosphate in the inner medullary collecting duct, likely resulting from an elevated intraluminal pH.83 However, it raises the intriguing question as to why some hypercalciuric disease states result in frank calcifications throughout specific parts of the kidney, i.e., nephrocalcinosis, whereas others cause discrete calcification as a stone, i.e., nephrolithiasis.

**ATP0V4**

Mutations in the α 4 subunit of the H⁺-ATPase cause dRTA, which is sometimes associated with deafness.84–85 Nephrocalcinosis was observed in all patients for whom data are reported, although nephrolithiasis is rare. As with ATP6V1B1 mutations, a minority presented without hypercalciuria.85–87 Interestingly, the patients without hypercalciuria were aged <6 months. It is therefore likely that a low sodium intake, volume contraction, and/or a net positive calcium balance contributed to their normocalciuria, despite significant metabolic acidosis.

Table 1. RTA gene defects, calciuria, nephrocalcinosis and nephrolithiasis

<table>
<thead>
<tr>
<th>Gene/protein</th>
<th>Hypercalciuria, %</th>
<th>Nephrocalcinosis, %</th>
<th>Nephrolithiasis, %</th>
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<tbody>
<tr>
<td>dRTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP6V1B1/V1-ATPase B1 subunit</td>
<td>89 (25 of 28)</td>
<td>100 (38 of 38)</td>
<td>72 (13 of 18)</td>
</tr>
<tr>
<td>ATP6V0A4/V0-ATPase A4 subunit</td>
<td>78 (7 of 9)</td>
<td>100 (9 of 9)</td>
<td>Not reported</td>
</tr>
<tr>
<td>SLC4A1/AE1, Anion Exchanger isoform 1</td>
<td>89 (8 of 9)</td>
<td>66 (21 of 32)</td>
<td>50 (12 of 24)</td>
</tr>
<tr>
<td>Mixed RTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA2/carbonic anhydrase 2</td>
<td>0 (0 of 12)</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>pRTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC4A4/NBCe1, electrogenic Na⁺/HCO₃⁻ cotransporter</td>
<td>0 (0 of 5)</td>
<td>0 (0 of 6)</td>
<td>0 (0 of 6)</td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTNS/cystinosin</td>
<td>60 (38 of 63)</td>
<td>68 (43 of 63)</td>
<td>17 (11 of 63)</td>
</tr>
<tr>
<td>CLCN5/CLC-5, Dent disease</td>
<td>89</td>
<td>76</td>
<td>41</td>
</tr>
<tr>
<td>ORCL1/ORCL-1, oculocerebrorenal syndrome of Lowe (but mutations can also cause Dent disease)</td>
<td>88 (22 of 25)</td>
<td>48 (12 of 25)</td>
<td>24 (6 of 25)</td>
</tr>
</tbody>
</table>

Patients with dRTA have long been appreciated to also have a disorder of sodium wasting. The molecular details of how the vacuolar H+-ATPase in the collecting duct contributes to sodium reabsorption were recently described. In combination with pendrin and Slc4A8, the H+-ATPase mediates thiazide-sensitive sodium reabsorption through the β-intercalated cell under situations of volume depletion. Mutations in either disease causing subunits would therefore prevent transcellular sodium reabsorption via this mechanism. Consequently, patients with mutations in the H+-ATPase would be prone to volume contraction and, as has been suggested for mutations in NCC, have increased proximal tubular sodium and consequently calcium reabsorption. Thus, if volume contracted, these patients would further attenuate hypercalciuria induced by metabolic acidosis. However, it should also be noted that volume contraction could exacerbate nephrocalcinosis and nephrolithiasis by decreasing urinary flow resulting in increased urine supersaturation of calcium, phosphate, or oxalate.

**SLC4A1**

Mutations in AE1 (SLC4A1) cause dRTA, which can be transmitted in either an autosomal dominant or recessive fashion. Patients present without deafness but commonly have hypercalciuria, nephrolithiasis, and nephrocalcinosis. Interestingly, not all patients with nephrolithiasis have nephrocalcinosis and vice versa. Hypercalciuria and its sequelae appear to be suppressed through the administration of alkali, suggesting that urinary calcium excretion is driven largely by the metabolic acidosis. As with all causes of dRTA, patients are unable to acidify their urine.

**Figure 1.** Effect of metabolic acidosis on calcium homeostasis. Metabolic acidosis via a physicochemical process is acutely buffered by exchange of surface sodium (Na+) and potassium ions (K+) with protons on bone. Chronically, via osteoclast specific mechanisms, CaCO3 and Ca10(PO4)6(OH)2 are liberated. These processes are also significantly affected by serum HCO3- levels. Calcium liberated from bone is filtered by the glomerulus; however, acidosis also directly alters tubular handling. In the distal convoluted tubule (DCT) and connecting tubule (CNT), acidosis effects the expression of TRPV5, but also the luminal H+ concentration has direct effects on TRPV5 activity (H+ inhibits). Consequently, bicarbonaturia, by increasing luminal pH increases TRPV5 activity. There is debate as to whether there is significant calcium reabsorption from the collecting duct. However, α intercalated cells in this segment, when unable to secrete protons such as with dRTA, will fail to acidify the urine altering the solubility of calcium salts. In the proximal tubule, a high pH inhibits citrate reabsorption (as observed in pRTA). Further proximal sodium reabsorption, which significantly increases proximal calcium absorption, such as under conditions of hypovolemia, can effect urinary calcium excretion, but also the water reabsorption and the supersaturation of calcium (Ca2+) salts. C2, claudin-2; calb 28K, calbindin-D28K; NaDC1, Na+ dicarboxylate contranporter 1; NBCe1, sodium bicarbonate exchanger e1; NCX, sodium calcium exchanger; PMCA, plasma membrane calcium ATPase; PO4, phosphate.
Unfortunately, an alkaline pH increases the supersaturation of calcium phosphate in the tubular lumen, thereby augmenting the risk of stone formation (calcium oxalate supersaturation remains relatively independent of urinary pH). Finally, stone risk is further enhanced in dRTA patients due to reduced urinary excretion of citrate.94

Proximal Renal Tubular Acidosis
Isolated metabolic acidosis due to a defect in proximal tubular bicarbonate reabsorption is referred to as type 2 or proximal RTA (pRTA). This disease is most commonly associated with global renal dysfunction, i.e., Fanconi syndrome (see below). pRTA rarely occurs without other types of proximal tubular dysfunction. To date, only mutations in NBCe1 have been found to cause isolated pRTA in humans.8,95,96 Patients with this disorder do not have evidence of altered bone breakdown, hypercalcemia, or nephrocalcinosis; however, they typically display decreased growth, a likely consequence of their metabolic acidosis.8,95,97–99 The lack of hypercalcemia is surprising because loss of proximal bicarbonate reabsorption would result in decreased sodium and consequently calcium reabsorption,100 which might overwhelm distal tubular calcium reabsorption capacity. However, this observation could be explained by an elevated luminal pH of the distal tubule, which would increase the surface expression and activity of the apical channel, TRPV5, and consequently calcium reabsorption,101 Finally, in contrast to dRTA and patients with metabolic acidosis, patients with pRTA have significant citrate in their urine (due to inhibition of proximal citrate reabsorption by an alkaline luminal pH). This would help prevent calcium precipitation and stone formation in patients with pRTA.102,103

Type 3 RTA and Carbonic Anhydrase 2 Deficiency
Renal tubular acidosis of a mixed nature, i.e., both proximal and distal, is called type 3. This is caused by a defect in carbonic anhydrase 2 (CA2).104,105 This enzyme is required for both acid secretion in the α intercalated cell but also for bicarbonate reabsorption from the proximal tubule. Consequently, individuals lacking CA2 activity demonstrate both bicarbonaturia and the inability to acidify their urine in the presence of metabolic acidosis.104,106,107 Given the discussion, one would predict that these patients have severe osteoporosis. However, this is not the case. They demonstrate osteopetrosis resulting from insufficient bone resorption.106,108 This occurs because CA2 is required to generate protons secreted into the subosteoclastic resorption pits by the osteoclasts, so that the mineralized matrix can be dissolved.109 Hence, even with metabolic acidosis there is impairment of calcium dissolution from bone, reinforcing the notion that bone loss during chronic metabolic acidosis is mediated by altered osteoclast activity and is not simply a physicochemical response. Consequently, CA2-deficient mice do not display hypercalcemia (R.T. Alexander, unpublished observation), and patients with CA2 deficiency are not reported to have hypercalcemia.106–108 As with pRTA, the tubular lumen of the distal convoluted tubule would contain significant bicarbonate to increase TRPV5 activity, further preventing the hypercalcemia associated with their metabolic acidosis.

Fanconi Syndrome
The Fanconi syndrome describes the presence of multiple defects in proximal tubular reabsorptive capacity including pRTA, phosphaturia, glucosuria, amino aciduria, and low molecular weight proteinuria. There are many genetic defects that can cause this disorder and discussing them all is beyond the scope of this review. However, a few points are worth considering. Twenty-five-hydroxyvitamin D circulates bound to the vitamin D binding protein. This complex is filtered at the glomerulus and is reabsorbed by the proximal tubule, providing the 1-α hydroxylase enzyme with substrate.110 Failure to endocytose this complex results in decreased conversion to active vitamin D, which reduces intestinal calcium absorption, bone turnover, and consequently affects urinary calcium excretion, as is often seen with Fanconi syndrome.

Defects in CLC5 cause Dent disease.111 This type of Fanconi syndrome is characterized by hypercalciuria and nephrocalcinosis. CLC5 is a proton-chloride exchanger expressed in endocytic vesicles in the proximal tubule, where it colocalizes with the H⁺ATPase.112 Importantly, defects in CLC5 can cause disorders other than Dent disease. It has been suggested that hypercaleuria in these patients is a result of increased vitamin D. This is thought to occur due to reduced 24-hydroxylation of vitamin D in the proximal tubule. Ultimately this would suppress PTH, increasing urinary calcium excretion. However, not all patients with Dent disease display increased vitamin D levels and only one of the two knockout mice strains has increased vitamin D levels.113,114 Calcium is reabsorbed in a paracellular fashion from the proximal tubule; consequently, endocytic defects caused by mutations in CLC5 could alter the permeability to and/or the molecules generating the driving force for calcium across the proximal tubule, thereby resulting in hypercalcemia. Further confusing the situation is that although uncommon, mutations in the OCRL gene can also cause hypercalcemia and nephrocalcinosis without metabolic acidosis.115,116 Understanding the mechanisms causing CLC5 and OCRL mutations to cause calcium and nephrocalcinosis will undoubtedly provide further information on the complex interplay between metabolic acidosis and urinary calcium excretion.

SUMMARY
It is an oversimplification to suggest that urinary calcium excretion occurs merely in response to acidosis-induced bone dissolution. Although bone is a buffer, the concentration of serum bicarbonate, i.e., type of acidosis, has a strong influence on calcium release from bone. Moreover, pH has a strong effect on tubular calcium handling, independent of
PTH and vitamin D. Not only does pH regulate the expression of calcium transporting proteins in the distal nephron, the pH of the luminal fluid is likely to directly affect the activity of calcium transport mechanisms. Finally, when examining urinary calcium excretion, compensatory aspects of tubular physiology must also be considered, i.e., volume status and sodium ingestion, because these control calcium reabsorption from more proximal aspects of the nephron and supersaturation of calcium salts in luminal fluid. Much work remains to be done in order to understand why some transport defects cause hypercalciuria and nephrolithiasis as opposed to nephrocalcinosis. Our emerging understanding of the tight junction and paracellular transport may help provide these answers.

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DISCLOSURES

None.

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BRIEF REVIEW


