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Physiology of Acid-Base Balance: Links With Kidney Stone Prevention

Mitchell L. Halperin, Surinder Cheema Dhadli, and Kamel S. Kamel

Two processes permit the urine pH and the medullary interstitial pH to remain in an "ideal range" to minimize the risk of forming kidney stones. First, a medullary shunt for NH_3 maintains the urine pH near 6.0 to minimize uric acid precipitation when distal H^+ secretion is high. Second, excreting dietary alkali excreting alkali as a family of organic anions—including citrate—rather than as bicarbonate maintains the urine pH near 6.0 while urinary citrate chelates ionized calcium, which minimizes $CaHPO_4$ precipitation. In patients with idiopathic hypercalciuria and recurrent calcium oxalate stones, the initial nidus is a calcium phosphate precipitate on the basolateral membrane of the thin limb of the loop of Henle (Randall's plaque). Formation of this precipitate requires medullary alkalinization; K^+ -depletion and augmented medullary H^+/K^+ -ATPase may be predisposing factors.

KEYWORDS acid-base, citrate, kidney stones, renal medulla pH, urine pH

It is truly an honor to contribute to this issue of *Seminars in Nephrology*, which recognizes the many novel contributions of Neil Kurtzman that have provided insights into the renal regulation of acid-base balance and its broader physiologic impact. In this style, we examined the regulation of acid-base balance from the perspective of how to maintain acid-base balance while the urine pH is close to 6 to minimize the risk of precipitating calcium phosphate and uric acid in the urine (Fig 1).[1] Examining acid-base balance in this way led us to challenge some of the accepted dogmas and to suggest alternative interpretations of the physiology, with possible important clinical implications. We also extend our analysis to the regulation of the pH level in the medullary interstitial compartment because recent evidence suggests that the initial phase of calcium oxalate stone formation is the precipitation of calcium-phosphate ($Ca_3(PO_4)_2$) nidus in the medullary interstitium, a process that requires medullary alkalinization.[2] New insights for the renal regulation of potassium (K^+) homeostasis[3] were very helpful for this analysis.

From the Renal Division, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.
Address reprint requests to Mitchell L. Halperin, MD, St. Michael's Hospital Annex, Lab # 1, 38 Shuter St, Toronto, Ontario, M5B 1A6, Canada. E-mail: mitchell.halperin@utoronto.ca

Acid Balance and Precipitation of Uric Acid Stones

Acid balance has 3 components: the production of H^+ in the liver from the oxidation of dietary proteins, titration of these H^+ by HCO_3^-,[4] and the addition of new HCO_3^- to the body when ammonium ions (NH_4^+) are excreted in the urine.[5] The major acids of dietary origin requiring renal disposal are phosphoric acid and H_2SO_4. Only the H^+ from H_2SO_4, which is derived from the oxidation of sulfur-containing amino acids in the liver, require NH_4^+ excretion to eliminate these protons because of the low affinity of SO_4^{2-} for H^+. Support for this version of acid balance is that the daily urinary excretion of NH_4^+ and SO_4^{2-} are very similar in milliequivalent terms.[6]

Traditional Analysis of the Excretion of NH_4^+

The major renal response to a large chronic acid load is to increase the rate of excretion of NH_4^+.[7] There are 2 sites where NH_4^+ is added to the lumen of the nephron: the proximal convoluted tubule (PCT) and the medullary collecting duct (MCD).[7] Our focus will be on the transfer of NH_4^+ from the lumen of the thick ascending limb of the loop of Henle (LOH) to the MCD, the medullary shunt of ammonia (NH_3).[8] In the traditional view, an increased secretion of H^+ in the distal nephron drives the medullary shunt of NH_4^+ because it de-

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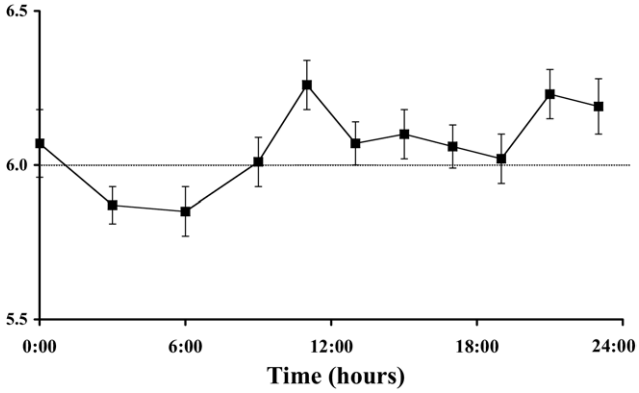

Figure 1 Diurnal variation in the urine pH in normal subjects. The solid line connecting the filled black squares depicts the values in normal volunteers (mean ± SEM). Note that urine pH is approximately 6.0 for most of the 24-hour period.

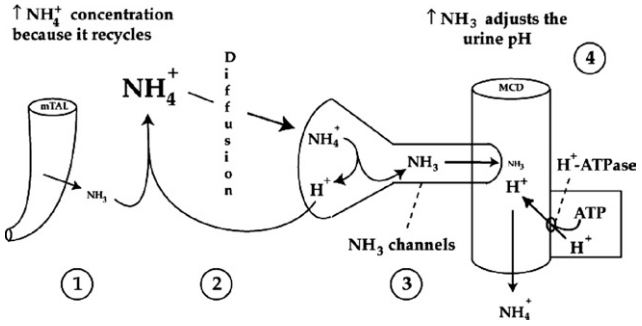

Figure 2 Hypothesis for the function of the medullary shunt pathway for NH_3/NH_4^+. The mTAL of the LOH is shown on the left and the MCD is shown on the right. The funnel-shaped structure in the MCD represents 2 different NH_3 channels, one in the basolateral membrane and the other in the luminal membrane of MCD cells. Reabsorption of NH_4^+ from the mTAL and its diffusion to the MCD permits NH_4^+ to enter the hydrophobic mouth of the NH_3 channel where it is converted to H^+ and NH_3. This increases the local $[NH_3]$, which diffuses into the lumen of the MCD if this channel is open. This entry of NH_3 increases the luminal pH despite continuing H^+ secretion by the H^+-ATPase. The net result is a higher urine pH and a somewhat higher rate of NH_4^+ excretion.

creases the urine pH and thereby the concentration of NH_3 in the lumen of the MCD, which allows for a more rapid rate of diffusion of NH_3 down its concentration difference from the medullary interstitium into the lumen of the MCD. This poses a conundrum because if a low urine pH were required to have high rates of excretion of NH_4^+, there would be an increased risk of precipitation of uric acid in the urine because the negative log of the dissociation constant (pK) of uric acid in the urine is approximately 5.3.[9] This led us to re-examine this traditional view of the physiology of NH_4^+ excretion.

Data in Conflict With the Traditional Interpretation of the Physiology of NH_4^+ Excretion

If a low luminal pH were needed to drive the diffusion of NH_3 into the MCD, one would expect to find a low urine pH when NH_4^+ excretion is increased markedly. Nevertheless, this is not the case because when human subjects were given a large chronic acid load the urine pH was close to 6.0 when the rate of excretion of NH_4^+ was greatly augmented.[10,11] In addition, when human beings were deprived of food for prolonged periods and developed chronic ketoacidosis, the urine pH was again close to 6.0 when the rate of NH_4^+ excretion was at its peak.[12]

Table 1 Concentration Difference of NH_3 in the Renal Medullary Interstitial Compartment

Lumen pH	Interstitial $[NH_3]$	Lumen $[NH_3]$	Difference in $[NH_3]$
7.0	20	10	10
6.7	20	5	15
6.3	20	2	18
6.0	20	1.0	19
5.0	20	0.1	19.9

In this calculation, we assumed that the interstitial fluid pH was 7.3. The concentration of NH_3 in the interstitial compartment is set at 20 in arbitrary units. Decreasing the urine pH toward 6.3 is the only pH range in which there may be a quantitatively important effect on the concentration difference for NH_3 between the interstitial compartment and the lumen of the MCD. In other words, only a large defect in the distal H^+ secretion (a very high urine pH) will have a large negative impact on the rate of diffusion of NH_3 into the MCD.

Another problem with the assumption that a low pH is important for augmenting the diffusion of NH_3 into the lumen of the MCD becomes evident when this process of diffusion is examined in quantitative terms (Table 1). Although diffusion depends on a concentration difference, the magnitude of the concentration difference for NH_4^+/NH_3 is almost exclusively a result of the high concentration of NH_4^+/NH_3 in the medullary interstitial compartment because changes in the concentration of NH_4^+/NH_3 in the luminal fluid of the MCD are very small at luminal pH values lower than 6.3.

There are 2 sets of data that provide insights on the quantitative importance of this medullary NH_3 shunt. The micropuncture data from studies in rats by Jaeger et al[13] and Sajo et al[14] revealed that 100% of the NH_4^+ to be excreted was present in the lumen of the PCT, whereas 33% to 50% of this NH_4^+ remained in fluid samples obtained from the earliest distal convoluted tubule. Hence, there was a large addition of NH_4^+ between this distal site and the final urine. If these were the only data evaluated, one would mistakenly conclude that the medullary NH_3 shunt accounted for the majority of NH_4^+ excreted. This, however, is not the case because in the study by Sajo et al[14] in which fluid also was sampled form the terminal cortical collecting duct, this fluid contained 75% of the NH_4^+ to be excreted in rats with chronic acidosis, and therefore only a small amount of NH_4^+ actually was added via the medullary NH_3 shunt.

To explore this issue further, we examined the rate of excretion of NH_4^+ and the concentration of NH_4^+ in the medullary interstitial compartment before and after inhibition of LOH function with a dose of furosemide that did not lead to

a decrease in the urine pH in a rat model with high rates of excretion of NH_4^+.[15] Although there was a significant decrease in the medullary concentration of NH_4^+, there was actually a small increase, rather than a significant decrease, in the rate of excretion of NH_4^+. These findings provide further evidence to suggest that there are other primary functions of this medullary shunt pathway for NH_3/NH_4^+ than to achieve high rates of excretion of NH_4^+; this raised questions about the traditional view of the physiology of excretion of NH_4^+.

Revised View of the Physiology of the Medullary Shunt of NH_3

The insights gained from our study and the recent findings of Khademii et al,[16] Verlander et al,[17] and Weiner et al[18] provide the basis for suggesting a new function for the medullary shunt pathway for NH_4^+ and NH_3—we surmised that this function is to prevent too large a decrease in the urine pH when distal H^+ secretion is stimulated (Fig 2).[19] Its components require that NH_4^+ (rather than NH_3) be the compound that diffuses through the renal medullary interstitial compartment because of its higher concentration. Because NH_4^+ (and NH_3) cannot cross cell membranes by simple diffusion, an additional component such as an NH_3 channel is needed to aid the diffusion of NH_3 across both the lipid-containing the basolateral and luminal cell membranes of the MCD. This channel has a very critical property, its mouth is extremely hydrophobic and this causes the pK of NH_4^+ to decrease by orders of magnitude. The resultant local increase in the concentration of NH_3 would be enormous in the mouth of the channel, which provides the driving force for rapid rates of diffusion of NH_3 through membranes that contain this channel in its open configuration. The combination of NH_4^+ entry into the mouth of these channels in conjunction with H^+ exit completes the H^+ balance in the renal medullary interstitial compartment when NH_3 enters from the basolateral surface of medullary thick ascending limb (mTAL) cells (Fig 2).

There are no data at present as to how the open probability of these NH_3 channels may be controlled. If they were to open by a sufficient degree, the addition of NH_3 into the lumen of the MCD could force the urine pH upward (toward 6.0) by removing luminal H^+ despite continuing H^+ secretion by the H^+-adenosine triphosphatase (ATPase). The net result is a final urine pH that is approximately 6.0, with a somewhat higher rate of NH_4^+ excretion. Hence, we suggested previously that the major function of this medullary shunt pathway may be to adjust the urine pH when distal H^+ secretion is stimulated and therefore to minimize the risk of precipitation of uric acid rather than to augment the excretion of NH_4^+.[20]

Base Balance and Precipitation of Calcium Phosphate Stones

The ingestion of fruit and vegetables provides an alkali load, which must be eliminated to maintain base balance. Examining the net acid excretion formula (equation 1),[21] which describes the role of the kidney to maintain acid-base balance, would suggest that this alkali load is eliminated by markedly increasing the excretion of HCO_3^-.[22] This notion is supported by the study by Pitts and Lotspeich,[23] which suggested that there was a tubular maximum and a renal threshold for the reabsorption of HCO_3^-.

$$\text{Net acid excretion} = U_{NH_4} + U_{\text{Titrated acid}} - U_{HCO_3} \quad (1)$$

There was a conundrum for base balance if bicarbonaturia were an important way to eliminate dietary alkali because this would increase the urine pH markedly. This high urine pH would create an important risk for $CaHPO_4$ precipitation because of the large increase in the concentration of urinary divalent phosphate (HPO_4^{2-}). In quantitative terms, a urine pH of 6.8 would be sufficient to cause the ion product of ionized calcium (Ca^{2+}) and HPO_4^{2-} to exceed its solubility constant (Table 2). Hence, we doubted that base balance would be maintained by excreting dietary alkali in the form of HCO_3^-.

Table 2 Effect of Increasing the Urine pH Level on the Divalent Phosphate Concentration

Urine pH Level	$H_2PO_4^-$, mmol/L	HPO_4^{2-}, mmol/L
6.1	25	5
6.8	15	15
7.1	10	20
7.3	7.5	22.5
7.4	6	24
7.5	5	25

For this calculation, we used a total 24-hour excretion of inorganic phosphate of 30 mmol/d and a urine volume of 1 L/d. At a urine pH of 7.1, two thirds of the total phosphate is in the divalent form. There is a small increase in HPO_4^{2-} concentration when the urine pH increases from 7.1 to 7.5.

Data in Conflict With the Traditional View of Base Balance

Because the urine pH is close to 6.0 for the majority of the 24-hour period (Fig 1), the urine contains very little HCO_3^-. A second conclusion is that there is no renal threshold or tubular maximum for the reabsorption of HCO_3^- because the plasma HCO_3^- concentration increases each time HCl is secreted in the stomach.[24] If there were a tubular maximum or a renal threshold for HCO_3^- reabsorption as proposed by Pitts and Lotspeich,[23] bicarbonaturia should occur on a regular basis, but frequent measurements of the urine pH did not reveal this high pH (Fig 1). To explain this difference in interpretation, one must examine the associated findings with the gain of HCO_3^-. When HCl is secreted, there is no expansion of the extracellular fluid (ECF) volume (there is a loss of Cl^- and a gain of HCO_3^- in the ECF compartment[24,25]). In contrast, the ECF volume is expanded in the experiments performed by Pitts and Lotspeich[23] because $NaHCO_3$ was infused to add HCO_3^-. As shown by Kurtzman,[26] this led to a depressed tubular maximum for the reabsorption of HCO_3^- during the

alkaline tide in the proximal convoluted tubule and an apparent renal threshold for HCO_3^-.

How base balance is achieved

The dietary alkali load is converted initially to HCO_3^- in the liver. This is followed by the production of organic acids in the H^+ titrate HCO_3^- hence the alkali load is eliminated, base balance is maintained by the excretion of organic anions[22] with dietary K^+ in the urine.[27] This description of base balance removes the less specific, *endogenous acid production*, while revealing that it is a component of the larger integrative physiology of elimination of dietary alkali. Therefore, to describe the role of the kidney in acid-base balance, it is essential to incorporate the excretion of the daily dietary alkali load in the form of organic anions that can metabolized to produce HCO_3^- in the body into the net acid excretion formula as potential HCO_3^- (equation 2).

$$\text{Revised net acid excretion} = U_{NH_4} + U_{\text{Titrated acid}} - U_{HCO_3} - U_{\text{Potential } HCO_3} \quad (2)$$

To eliminate dietary alkali without increasing the likelihood of forming $CaHPO_4$, a family of organic anions, including citrate are excreted. Not only does this achieve base balance while maintaining the urine pH close to 6.0, it has a second advantage in stone-prevention terms because this minimizes the excretion of ionized calcium by increasing the excretion of its chelator, citrate.

Pathophysiology of the Alkaline Urine pH in Patients With $CaHPO_4$ Stones

In our recent publication,[28] we used these concepts of base balance to study the pathophysiology of persistently alkaline urine pH in patients with recurrent $CaHPO_4$ stones. Understanding the pathophysiology in these patients is especially important to design therapy to prevent the recurrence of stones because patients with this type of kidney stone develop progressive parenchymal damage and nephron loss as a result of plugging of the terminal collecting duct with $CaHPO_4$ crystals.[29] Our study illustrated that these patients represent a heterogeneous group with regard to the pathophysiology of their alkaline urine pH. Although dietary factors seemed to be important in many patients, we described 2 possible novel lesions that may cause persistently alkaline urine pH values in a subset of these patients. In 1 patient, the lesion seemed to be an acidified PCT cell pH because this patient had a high NH_4^+/SO_4^{2-} and marked hypocitraturia. The other patient also had a high NH_4^+/SO_4^{2-}, however, the rate of excretion of citrate was not low. We suggested that the lesion may be a NH_3 channel in the MCD with a higher open probability (Fig 2).

Medullary Interstitial pH and the Initiation of Kidney Stone Formation

It is now clear from the exciting studies of Evan et al[2] that in patients with idiopathic hypercalciuria, calcium oxalate stones begin when a nidus of $Ca_3(PO_4)_2$ precipitates on the basolateral aspect of the thin limbs of the LOH (Randall's plaque). Eventually, a calcified mass grows sufficiently to erode into the collecting system, where it provides a site for deposition of calcium oxalate and stone formation. The question we shall now address is, "What factors may lead to high enough concentrations of ionized calcium and trivalent phosphate (PO_4^{3-}) in the inner medullary interstitial compartment so that their ion product exceeds their solubility product constant?"

Although absorption of calcium from the LOH and changes in the ionic strength in the medullary interstitial compartment may modify the concentration of ionized calcium in this location, our emphasis will be on PO_4^{3-}. A high pH in this location is critical to increase the concentration of PO_4^{3-}. Although it is possible that the activity coefficient for HPO_4^{2-} will be altered, there is a paucity of experimental evidence on which to base this.[30] Hence, we focus on ways to alter the pH of the renal medullary interstitial compartment.

The most important sites where alkali may be added to the interstitial compartment are the LOH and the MCD. In the LOH, this occurs when $NaHCO_3$ is reabsorbed in this nephron segment, but this is not known to be a major variable. In contrast, there can be a large addition of HCO_3^- to this interstitial compartment when K^+ is absorbed in the MCD by the H^+/K^+-ATPase—hence, we focus on this cation exchanger.

To understand the role of H^+/K^+-ATPase in K^+ homeostasis, it is important to examine the regulation of the renal excretion of K^+ from a Paleolithic perspective because control mechanisms developed in response to major stimuli that were present at that time. It is very likely that these regulatory systems should persist because pressures of modern times do not have enough control strength to replace them.

The Paleolithic diet provided a large episodic K^+ load with HCO_3^- precursors (organic anions), and little NaCl. This large intake of K^+ should be excreted promptly to avoid the development of a cardiac arrhythmia, but K^+ excretion must diminish quickly when food (K^+) intake stops. To achieve this aim, a mechanism is needed to increase the distal delivery of Na^+ to augment the excretion of K^+ only while the K^+ load is present, and natriuresis must be avoided. In rats fed a diet that simulated the Paleolithic intake, the reabsorption of NaCl in the LOH was inhibited in response to a K^+ load.[3] This seemed to be mediated by an increase in concentration of K^+ in the renal medullary interstitial compartment in response to the K^+ load. We speculated that H^+/K-ATPase was involved in the reabsorption of K^+. Thus, the initial stimulus to upregulate the excretion of K^+ was, paradoxically, to reabsorb more K^+ in the inner MCD. Having this reabsorption of K^+ coupled with the secretion of H^+ seemed appropriate because the diet provided a large alkali load. There is an obvious problem, however, with our proposal—the H^+/K-ATPase in the MCD has an increased activity during K^+-depletion,[31,32] whereas our hypothesis requires an increased flux via H^+/K-ATPase in response to a K^+ load. To resolve this problem, we added another component to the hypothesis.[33] When the K^+ load is absorbed, the plasma K^+ (P_K)

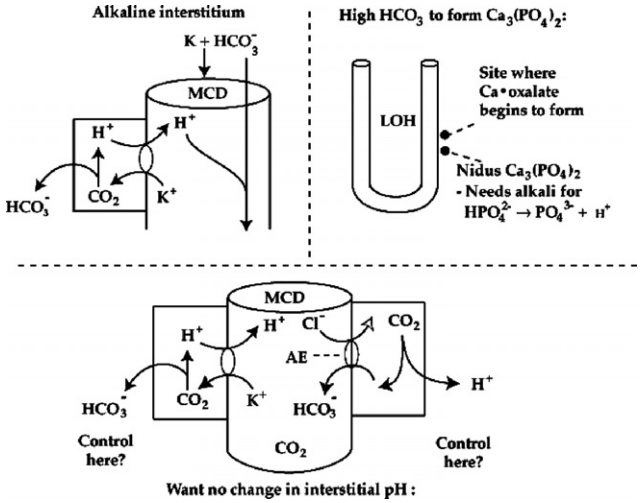

Figure 3 Increased H^+/K^+-ATPase flux on H^+ balance in the renal medullary interstitium. The larger structure in the upper left represents the MCD whereas the smaller one in the upper right is the thin limb of the LOH. As shown in the top left, when more K^+ is reabsorbed by the H^+/K^+-ATPase in the MCD, HCO_3^- ions are added to the interstitial compartment. As shown in the top right, this alkalinization increases the concentration of PO_4^{3-}, which can lead to local precipitation of $Ca_3(PO4)_2$ on the basolateral aspect of the thin ascending limb of the LOH. This nidus can lead to deposition of calcium oxalate precipitates. As shown in the bottom section, the pH in this interstitial compartment might be regulated by interactions between the H^+/K^+-ATPase and the Cl^-/HCO_3^- anion exchanger (AE-1).

concentration increases, but the H^+/K-ATPase is still active because of the prior period of diminished K^+ intake. Therefore, there can be an increased delivery of K^+ to the inner MCD, which can increase the medullary interstitial $[K^+]$ sufficiently to have a temporary but appreciably higher $[K^+]$. This in turn will lead to a modest degree of inhibition of mTAL function.[3] With time, as the increase in the P_K is sustained, there will be fewer luminal H^+/K-ATPase units in the inner MCD, so the rate of K^+ reabsorption decreases somewhat and the interstitial $[K^+]$ is less increased and hence the inhibition of reabsorption in the mTAL is not as marked. As a result, there could be enough distal delivery of Na^+ and Cl^- to maintain high rates of K^+ secretion in the cortical collecting duct, but not induce a large natriuresis.

Because modern diets provide much less K^+, this transporter now has a different major function because it is needed to prevent K^+ depletion.[31,32] This adaptive change, however, comes with a price to pay. Increased reabsorption of K^+ via the H^+/K^+-ATPase adds HCO_3^- to the interstitial compartment (Fig 3, lower left portion). This alkalinization could lead to the conversion of some HPO_4^{2-} to PO_4^{3-} and thereby lead to the deposition of $Ca_3(PO_4)_2$.

This hypothesis raises the issue of the role of dietary K^+ intake in the pathophysiology of calcium oxalate stone formation. In this regard, it also is important to consider processes that might add H^+ to the medullary interstitial compartment. One candidate is the Cl^-/HCO_3^- anion exchanger in β-intercalated cells of the inner MCD (Fig 3, lower right portion), the activity of which might be modulated by the interstitial fluid pH. Lesions affecting this transporter or the H^+/K^+-ATPase might be potential candidates for the development of medullary alkalinization and subsequent precipitation of calcium oxalate kidney stones.

Conclusions

Although the excretion of NH_4^+ generates new HCO_3^- to eliminate a H^+ load,[5] this function should be achieved while maintaining a urine pH of approximately 6.0 to minimize the risk of precipitating uric acid.[9] We suggest that the medullary shunt process for NH_3 might not be quantitatively important for NH_4^+ excretion—rather, its primary function could be to prevent a large decrease in the urine pH consequent to distal H^+ secretion and thereby minimize the risk of forming uric acid precipitates. Base balance must be maintained while avoiding bicarbonaturia to prevent precipitation of $CaHPO_4$. Excreting dietary alkali as a family of organic anions—including citrate—achieves base balance while ensuring that the urine pH remains close to 6.0 and also minimizes the excretion of ionized calcium by increasing the excretion of its chelator, citrate. In patients with idiopathic hypercalciuria and recurrent calcium oxalate stones, the initial precipitate is $Ca_3(PO_4)_2$, which deposits on the basolateral aspect of the thin limbs of the LOH (Randall's plaque). Precipitation of $Ca_3(PO_4)_2$ requires medullary alkalinization. A role of K^+-depletion and activation of medullary H^+/K^+-ATPase is suggested.[21]

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