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SYMPOSIUM PAPER

Evidence for altered renal tubule function in idiopathic calcium stone formers

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Abstract Patients who form calcium kidney stones often have metabolic disorders such as idiopathic hypercalciuria (IH) that reflect abnormalities in mineral handling in the kidney. Renal handling of calcium is altered by ingestion of nutrients such as carbohydrates, protein, and sodium, and patients with IH appear to be more sensitive to these stimuli. Studies using probes such as diuretics or lithium clearance have the ability to clarify which nephron segments are involved in the altered renal calcium transport with nutrient seen in IH. Studies in the genetic hypercalciuric rat demonstrate alterations in both proximal tubule and thick ascending limb calcium reabsorption. Similar studies in humans have begun to provide evidence about the corresponding abnormalities in stone formers with IH. A pattern of altered renal tubule transport in calcium stone formers is suggested by the frequency of such findings as decreased tubular maximal reabsorption of phosphate and abnormal urine acidification as well as hypercalciuria in such patients, not explained by monogenic transport abnormalities.

Keywords Calcium absorption · Calcium oxalate · Idiopathic hypercalciuria · Renal calcium transport

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Introduction

The majority of calcium stone formers do not have systemic diseases or monogenic inherited syndromes. Rather, they have metabolic disorders that lead to higher urinary supersaturation with respect to calcium salts [1]. The most common of these is idiopathic hypercalciuria (IH), defined as an increase in renal calcium excretion with normal serum calcium; the usual parameters are excretion of more than 300 mg calcium daily in men, 250 mg in women, or >140 mg/gm creatinine in either sex. IH is famial, probably polygenic, and involves alterations in calcium handling by gut and bone, as well as kidney [2]. Recent work has begun to examine the sites of abnormal renal calcium transport in IH, in order to discern the underlying mechanisms, and understand how altered renal calcium handling is translated into the patterns of renal medullary calcification found in calcium stone formers [3].

Renal calcium reabsorption

Most of the calcium in glomerular filtrate is reabsorbed in the proximal tubule where reabsorption is mainly passive, driven by electrochemical gradients created by Na reabsorption [4]. Another 20–25% of filtered calcium is reabsorbed in the thick ascending limb; here, most reabsorption is paracellular, driven by the transepithelial voltage established by sodium reabsorption, but some active, transcellular calcium transport appears to occur. Unlike passive reabsorption, active calcium transport can occur without changes in sodium transport. Distal tubule and connecting tubules reabsorb about 8–10% of filtered calcium via active transport; PTH acts to increase calcium reabsorption at this site [5]. Decreased overall calcium reabsorption in IH may

involve altered calcium (and possibly sodium) handling at one or more of these sites.

Effect of nutrients of renal calcium excrteion

Altered renal handling of calcium in response to nutrient intake was noted several decades ago by Lindeman et al. [6], who provided evidence that urinary excretion of calcium and magnesium increased in response to an oral load of glucose or galactose in a dose-dependent manner, while xylose and fat had no effect. Protein (as casein) had a similar effect on calcium excretion, while inulin clearance and sodium excretion did not change with nutrient ingestion in these studies. Lemann et al. [7] extended this work by demonstrating that the increase in urine calcium and magnesium after glucose ingestion persisted even under conditions (standing) that decreased the inulin clearance, thus dropping the calcium filtered load, and which also led to a fall in urine sodium excretion. This clearly implied inhibition of renal reabsorption of these cations.

Calcium oxalate stone formers with IH appear to have a greater augmentation of calcium excretion after glucose or sucrose ingestion compared with normals [8]. When Lemann and colleagues gave carbohydrate to patients with IH, peak calcium excretion exceeded that of normal controls while filtered loads did not vary. They noted a similar pattern in the non-stone forming relatives of stone formers. Both stone formers and relatives also exhibited an exaggerated anti-diuresis after sugar compared with controls, leading to much higher urine calcium concentrations after the nutrient exposure.

Inability of the kidney in IH to regulate calcium reabsorption normally is further suggested by studies that show that calcium conservation on low calcium diet is impaired in IH [9], particularly if dietary sodium is not restricted [10], such that calcium excretion may exceed the amount of calcium ingested. Calcium balance studies in patients with IH show that they are often in negative calcium balance even with normal or elevated net intestinal rates of calcium absorption [2].

Methods for studying renal calcium transport in animals and humans

In order to determine the nephron site(s) at which calcium transport is altered in IH, methods to localize transport abnormalities are needed. Studies in whole animals and humans rely on probes that have relative specificity for particular areas of the nephron, such as diuretics that inhibit unique sodium transporters, or ions such as lithium which have restricted transport characteristics. Since calcium reabsorption is linked to sodium transport in most of the nephron, inhibition of specific sodium transporters has predictable effects on calcium absorption, and studies using such agents can suggest which tubule sites may be associated with altered calcium transport in IH.

Diuretics

Acetazolamide and hydrochlorothiazide, inhibitors of sodium reabsorption in proximal tubule and distal tubule, respectively, have been used as probes of tubule transport in human stone formers [11]. Compared with controls, stone formers had a smaller increase in sodium excretion after acetazolamide, but a greater increase in sodium and calcium excretion after hydrochlorothiazide, suggesting proximal tubule sodium transport might be impaired in stone formers, leading to increased sodium and calcium delivery into the distal nephron.

Furosemide, an inhibitor of the NKCC2 sodium transporter in thick ascending limb (TAL), has been used to probe nephron calcium handling in the genetic hypercalciuric (GHS) rat [12], which exhibits increased gut calcium absorption, enhanced bone demineralization, and inability to conserve calcium on a low-calcium diet [13], similar to humans with IH. Furosemide inhibits sodium reabsorption in TAL, which reduces Ca reabsorption at this site. After furosemide blockade of TAL, calcium delivered out of the proximal tubule, which would normally be reabsorbed in the TAL, is quantitatively delivered into the distal nephron, and most is excreted into the urine. The peak excretion of calcium after furosemide is therefore a gauge of delivery of sodium and calcium to TAL from proximal tubule.

In the studies of renal calcium reabsorption done using the GHS rats, serum calcium was fixed by using calcium infusion after parathyroidectomy, and filtered loads of calcium were equal for GHS and controls. Baseline urine calcium excretion was higher in the GHS rats than control rats, and urine calcium rose in both groups after treatment with furosemide (Fig. 1, upper panel). Absolute calcium excretion and urine volume after furosemide were much higher in the GHS rats, suggesting reduced proximal tubule reabsorption of sodium, calcium, and water, with increased delivery to the loop; blockade of TAL with furosemide leads to delivery of most of this excess solute and fluid into the urine. Furosemide blockade can also test the absolute ability of TAL to reabsorb sodium and calcium. If reabsorption of sodium and calcium at this site is impaired, the change from baseline of calcium and sodium excretion after furosemide will be less than normal, reflecting the relatively lower rate of reabsorption at this site. In the rats (Fig. 1, upper panel), the incremental rise in calcium after furosemide was much less in GHS versus control, indicating impaired baseline loop sodium and calcium

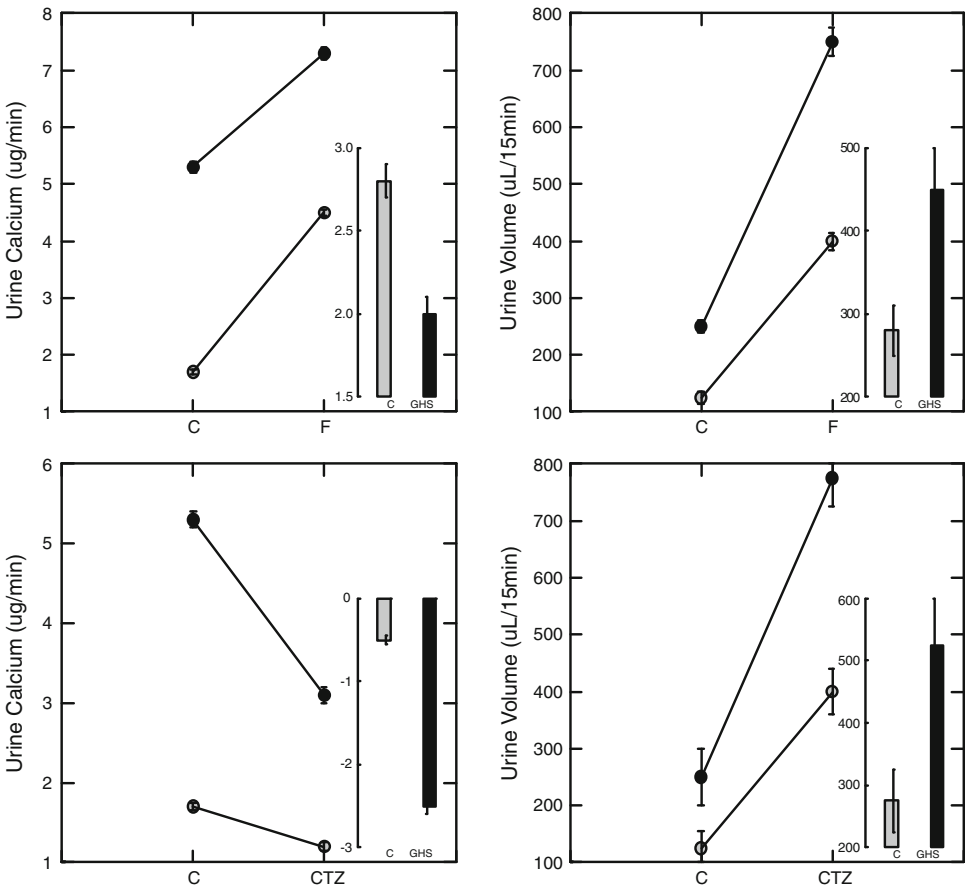

Fig. 1 Effect of furosemide (*F*) (*upper panels*) or chlorothiazide (*CTZ*) (*lower panels*) on urine calcium excretion or volume compared with baseline period (*C*) in genetic hypercalciuric (GHS *black symbols*) or control rats (*gray symbols*) fed a normal calcium diet. Paired studies are connected by *lines*; values are means ± SE. Urine calcium and volume is higher at baseline in the GHS rats. Urine calcium increased after *F* to a lesser extent in GHS rats compared with the controls ($p < 0.05$), while calcium decreased after CTZ to a greater extent in the GHS rats ($p < 0.05$). In contrast, urine volume increased more in the GHS rats with both diuretics. Change in urine calcium (*left panel*) and volume (*right panel*) is shown in the inset of each panel (GHS *black bars*; control rats *gray bars*). Data from Ref. [12]

transport in GHS (the lesser rise means less reabsorption had been occurring prior to furosemide). Response of the GHS rats to hydrochlorothiazide (Fig. 1, lower panel) was augmented, indicating normal or increased function in distal tubule, compatible with increased delivery of sodium and calcium from more proximal nephron sites. Thus, the impaired renal calcium conservation in GHS rats seems to reflect abnormal transport at both proximal tubule and thick ascending limb.

Lithium

Lithium has been used in both animals and humans as another marker of sodium and volume delivery out of proximal tubule [14–17]. Micropuncture studies have shown that reabsorption of lithium occurs primarily in proximal tubule and parallels absorption of sodium [18]. In order to achieve lithium levels measurable by conventional methods exogenous lithium is administered, but it may affect renal sodium handling; this problem is avoided by measurement of endogenous lithium levels, which requires atomic absorption with a graphite furnace or atomic emission spectrometry [19]. Distal nephron absorption of lithium is minimal in the absence of sodium depletion, and under ordinary conditions there is little lithium absorption in tubule segments beyond the loop [20]. A small amount of lithium absorption may occur in the loop, which is inhibited by furosemide [21, 22]. A change in proximal tubule lithium absorption suggests comparable changes in sodium and calcium absorption at that site, as well.

Renal calcium reabsorption in patients with IH after nutrient ingestion

The mechanisms underlying the increase in renal calcium excretion with nutrients have been investigated using mixed nutrient diets, which include a normal calcium and fixed sodium intake [23, 24] during a three-meal day. Patients with IH and normal controls were studied in the General Clinical Research Center (GCRC), and the IH subjects were found to have a marked increase in calcium excretion after eating compared with normal subjects that was not due to changes in filtered load, but was related to a decrease in tubule calcium reabsorption (Fig. 2). While urine magnesium rose significantly with nutrient intake, excretion did not differ between IH subjects and controls until after lunch. The decrease in calcium reabsorption was

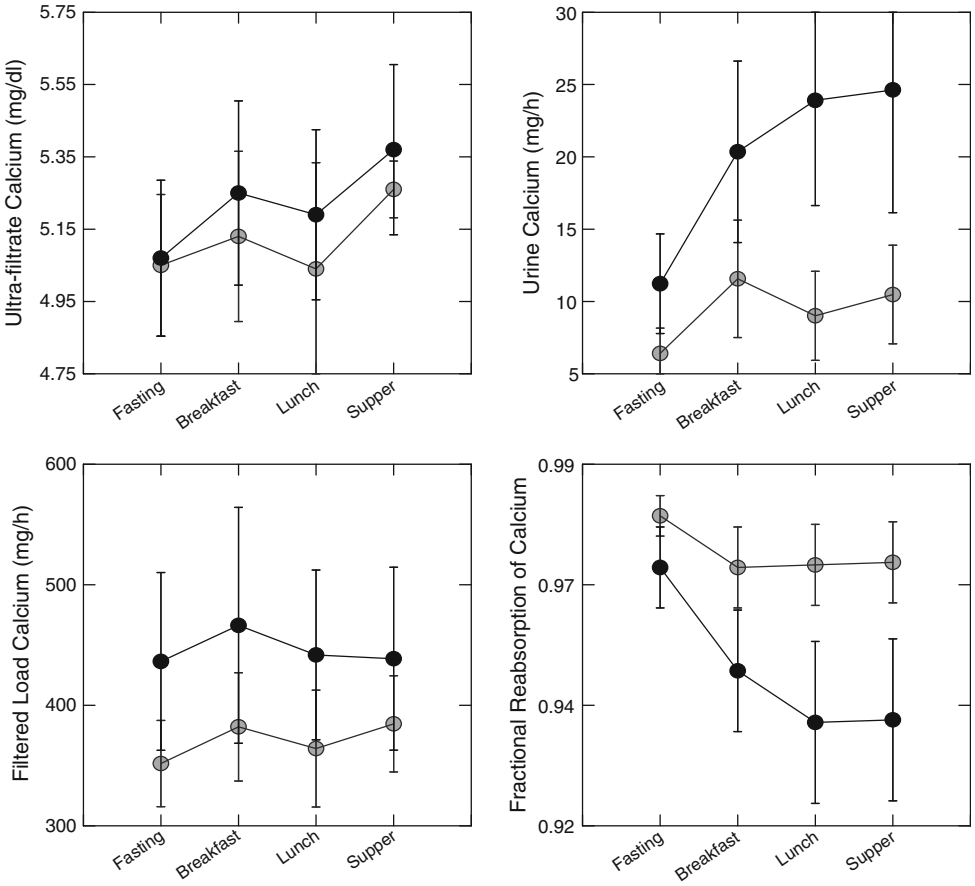

Fig. 2 Effect of nutrient on serum ultrafiltrable calcium (*upper left*), filtered load of calcium (*lower left*), urine calcium excretion (*upper right*) and fractional reabsorption of calcium (*lower right*) in stone formers with idiopathic hypercalciuria (*black symbols*) or controls (*gray symbols*). Periods are fasting, breakfast to lunch (*breakfast*), lunch to supper (*lunch*), and supper to end of protocol (*supper*). Values are means with 1.96 SE on either side. (Used by permission from Ref. [23])

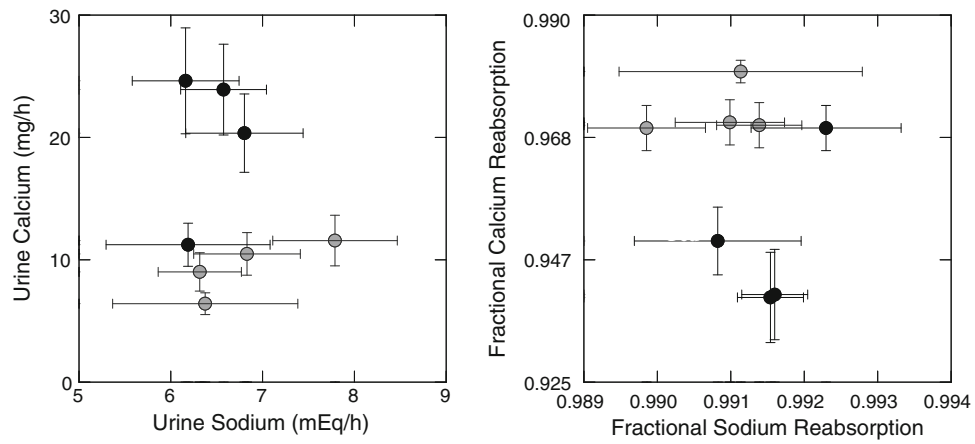

Fig. 3 Urine calcium and sodium excretion (*left panel*) and fractional reabsorption (*right panel*) in stone formers with IH (*black symbols*) and controls (*gray symbols*) during fasting and three post-prandial time periods. Calcium excretion is higher and fractional reabsorption is lower in subjects with IH than controls at overlapping values of sodium excretion. Values are means with 1.96 SE. (Used by permission from Ref. [23])

not related to differences between stone formers and controls in either sodium excretion (Fig. 3) or parathyroid hormone levels (Fig. 4) during either the fasting or fed periods of the study.

Using endogenous lithium measurements, many of the IH patitents were found to have reduced post-prandial proximal nephron sodium and calcium reabsorption compared with normals, with increased delivery of sodium and calcium into the distal nephron (Fig. 5) [25]. The excess sodium is completely reabsorbed distally, so that total sodium excretion is the same in normals and stoneformers with IH. However, despite increased absolute distal nephron calcium reabsorption, excess calcium delivered out of the proximal nephron is not completely reabsorbed, leading to increased fractional (Fig. 5, left panel) and total (right panel) calcium excretion in IH: in other words, leading to hypercalciuria. Caffeine was not permitted during the study, and all subjects were normotensive (actually, blood pressure was slightly but significantly lower in subjects with IH), so that neither pressure-natriuresis [26] nor

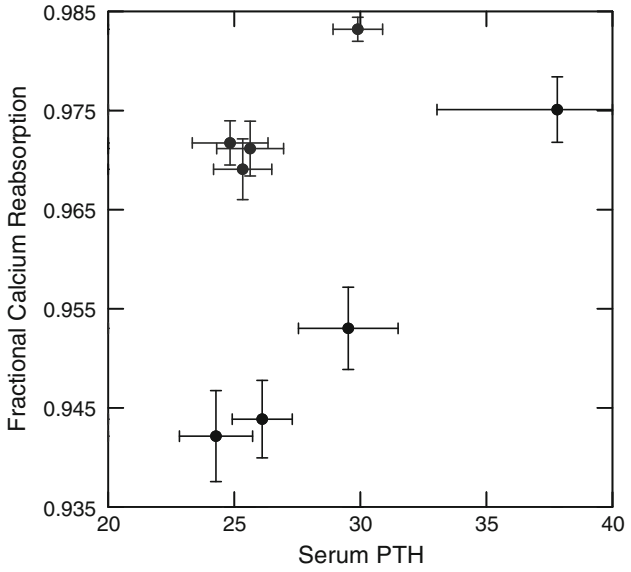

Fig. 4 Relationship between serum PTH and fractional calcium reabsorption in stone formers with IH (*black symbols*) and controls (*gray symbols*) during fasting and three post-prandial time periods. Fractional reabsorption is lower in subjects with IH at overlapping values of PTH. (Used by permission from Ref. [23])

caffeine-induced adenosine A_1 blockade [14, 27] would be expected to play a role in altered proximal tubule function in the subjects with IH.

It appears that many, but not all, subjects with IH have a decrease in proximal tubule calcium reabsorption. Figure 5 illustrates that subjects with IH often have higher calcium excretion at comparable rates of delivery of sodium and calcium out of proximal tubule, suggesting other sites of altered calcium reabsorption must be present. It is not known whether defects in thick ascending limb calcium transport are present in subjects without the proximal transport defect, to explain their hypercalciuria. It is possible that some subjects may have defects at both sites, similar to the GHS rats. Further studies are needed to answer these questions and seek explanations for the altered sodium and calcium transport at these sites.

Renal phosphate transport in idiopathic calcium stone formers

A well-known example of altered proximal tubule transport in stone formers is the hypophosphatemia seen in many patients [9, 28] which is associated with decreased tubule reabsorption of phosphate. Prie et al. [28] compared 207 calcium stone formers with 105 normal subjects of similar age, and found that although the values of renal phosphate threshold (TmPi) were normally distributed in both groups, the stone formers of both sexes were shifted to lower values, such that 19% of stone formers had a TmPi below 0.63 mmol/L, a value lower than that of 95% of the normals. The mean TmPi of the stone formers was 0.72 ± 0.13 mmol/L versus 0.87 ± 0.18 mmol/L in the controls, $p < 0.0001$. The stone formers as a group had higher $1,25(OH)_2D_3$ levels than the non-stone formers ($p < 0.05$), but the levels did not differ between the stone formers with and without low TmPi ($1,25(OH)_2D_3$ levels: 45.4 ± 3.9, 44.7 ± 1.9, and 32 ± 2.7 pg/ml, low TmPi stone formers, normal TmPi stone formers, and controls, respectively). PTH levels did not differ between any of the groups.

Nutrient intake may not affect phosphate reabsorption in the same manner that it alters renal handling of calcium and magnesium. The IH patients studied in the GCRC described above had significantly lower serum phosphorus levels than the normal controls (Fig. 6, upper left panel); in both groups, serum phosphate rose gradually during the fed period. Urine phosphorus excretion rose significantly with meals over the course of the day, but did not differ

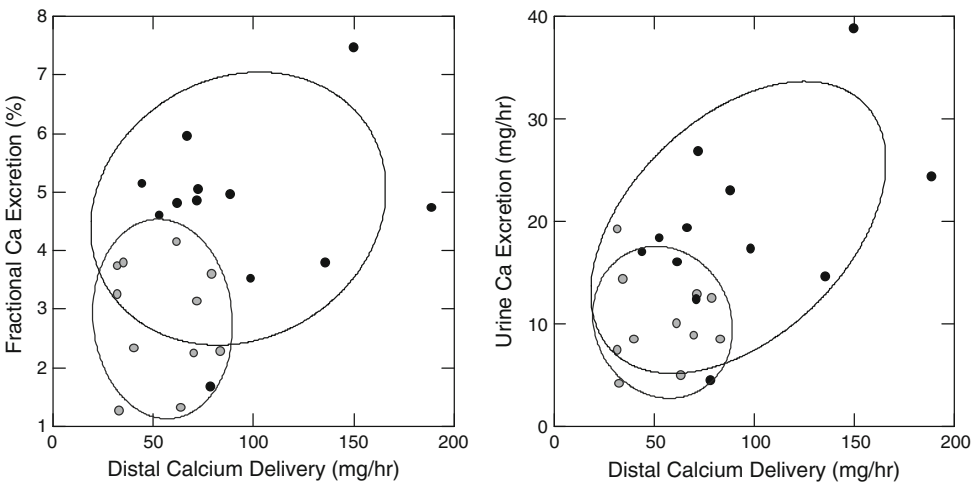

Fig. 5 Relationship between distal calcium delivery and fractional (*left*) and absolute (*right*) urine calcium excretion in stone formers with IH (*black symbols*), and controls (*gray symbols*). Distal delivery is higher in subjects with IH, and calcium excretion rises with distal delivery, but excretion is higher in IH versus controls at comparable deliveries. (Used by permission from Ref. [25])

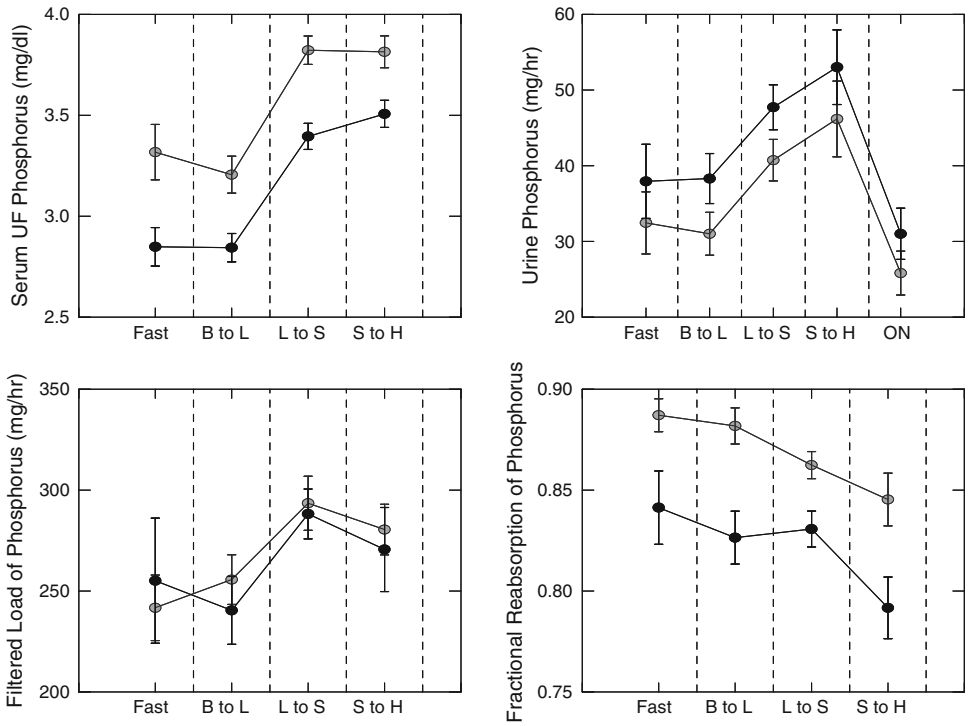

Fig. 6 Effect of nutrient on serum ultrafiltrable phosphate (*upper left*), filtered load of phosphate (*lower left*), urine phosphate excretion (*upper right*) and fractional reabsorption of phosphate (*lower right*) in stone formers with idiopathic hypercalciuria (*black symbols*) or controls (*gray symbols*). Values are means with 1.96 SE on either side. (Used by permission from Ref. [23])

significantly between the two groups of subjects (Fig. 6, upper right panel). Fractional reabsorption of phosphate was significantly lower in the stone formers, but did not vary between fasting and fed (Fig. 6, lower right panel). Overall, the stone formers appear to have an alteration in tubule phosphate handling, which sets serum phosphate at a lower level than in controls, but both groups respond to nutrient in a similar manner, and the stone formers do not appear to be hyperphosphaturic.

The cause for the altered phosphate reabsorption in hypophosphatemic stone formers is not known. Although there are case reports of patients with hypercalciuria or stone formation and hypophosphatemia associated with mutations in one of the sodium-phosphate co-transporters located in the apical membrane of the proximal tubule [29, 30], or in the sodium–hydrogen exchanger regulatory factor 1 (NHERF1) [31] which controls renal phosphate reabsorption, these genetic abnormalities are too rare to be the cause of the common hypophosphatemia of stone formers. Whether phosphatonins, such as FGF23, are responsible for the altered handling of phosphorus is still unclear; one study suggests that this may be true [32].

Renal acidification in idiopathic calcium stone formers

The formation of calcium phosphate stones is favored by alkaline urine pH which decreases the solubility of calcium phosphate [33, 34]; alkaline urine pH and calcium phosphate stones both appear to be more common in women. A number of studies have suggested that stone formers may have alterations in renal acidification mechanisms, such that urine pH is not lowered appropriately in response to provocative tests such as ammonium chloride loading, although metabolic acidosis is not present at baseline [35–38]. The nature of these tubule alterations and their source is not clear, and in the absence of acidosis the alteration appears to be benign except for the tendency toward more alkaline urine and calcium phosphate supersaturation.

Conclusion

The metabolic abnormalities found in idiopathic calcium stone formers often appear to reflect some alterations in renal tubule function. These abnormalities may be genetic; in the case of IH, they are certainly familial and polygenic. Their expression is also influenced by diet, but they remain present even when dietary factors are controlled. They may also be linked to alterations in the physiology of gut or bone; this is clearly the case for IH and may prove to be true in other cases as well.

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References

1. Coe FL, Evan A, Worcester E (2005) Kidney stone disease. J Clin Invest 115:2598–2608
2. Worcester EM, Coe FL (2008) New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol 28:120–132
3. Evan AP, Lingeman JE, Coe FL, Worcester EM (2008) Role of interstitial apatite plaque in the pathogenesis of the common calcium oxalate stone. Semin Nephrol 28:111–119
4. Friedman PA (2008) Renal calcium metabolism. In: Alpern RJ, Hebert SC (eds) Seldin and Giebisch's the kidney. Elsevier Academic Press, Amsterdam, pp 1851–1890
5. Boros S, Bindels RJ, Hoenderop JG (2009) Active Ca(2+) reabsorption in the connecting tubule. Pflugers Arch 458:99–109
6. Lindeman RD, Adler S, Yiengst MJ, Beard ES (1967) Influence of various nutrients on urinary divalent cation excretion. J Lab Clin Med 70:236–245
7. Lemann J Jr, Lennon EJ, Piering WF, Prien EL Jr, Ricanati ES (1970) Evidence that glucose ingestion inhibits net renal tubular reabsorption of calcium and magesium in man. J Lab Clin Med 75:578–585
8. Lemann J Jr, Piering WF, Lennon EJ (1969) Possible role of carbohydrate-induced calciuria in calcium oxalate kidney-stone formation. N Engl J Med 280:232–237
9. Coe FL, Favus MJ, Crockett T, Strauss AL, Parks JH, Porat A, Gantt CL, Sherwood LM (1982) Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1, 25(OH)2D3 levels in patients with idiopathic hypercalciuria and in normal subjects. Am J Med 72:25–32
10. Phillips MJ, Cooke JNC (1967) Relation between urinary calcium and sodium in patients with idiopathic hypercalciuria. Lancet 1:1354–1357
11. Sutton RA, Walker VR (1980) Responses to hydrochlorothiazide and acetazolamide in patients with calcium stones. Evidence suggesting a defect in renal tubular function. N Engl J Med 302:709–713
12. Tsuruoka S, Bushinsky DA, Schwartz GJ (1997) Defective renal calcium reabsorption in genetic hypercalciuric rats. Kidney Int 51:1540–1547
13. Bushinsky DA, Frick KK, Nehrke K (2006) Genetic hypercalciuric stone-forming rats. Curr Opin Nephrol Hypertens 15:403–418
14. Shirley DG, Walter SJ, Noormohamed FH (2002) Natriuretic effect of caffeine: assessment of segmental sodium reabsorption in humans. Clin Sci 103:461–466
15. Seidlerova J, Staessen JA, Maillard M, Nawrot T, Zhang H, Bochud M, Kuznetsova T, Richart T, Van Bortel LM, Struijker-Boudier H, Manunta P, Burnier M, Fagard R, Filipovsky J (2006) Association between arterial properties and renal sodium handling in a general population. Hypertension 48:609–615
16. Thomsen K, Shirley DG (2002) Importance of proximal tubular fluid output in regulating long-term urinary sodium excretion in health and disease. Nephron 90:121–132
17. Thomsen K (1990) Lithium clearance as a measure of sodium and water delivery from the proximal tubules. Kidney Int 37:S10–S16
18. Hayslett JP, Kashgarian M (1979) A micropuncture study of the renal handling of lithium. Pflugers Arch 380:159–163
19. Durr JA, Miller NL, Alfrey AC (1990) Lithium clearance derived from the natural trace blood and urine lithium levels. Kidney Int 37:S58–S62
20. Walter SJ, Sampson B, Shirley DG (1995) A micropuncture study of renal tubular lithium reabsorption in sodium-depleted rats. J Physiol 483:473–479
21. Shirley DG, Walter SJ, Sampson B (1992) A micropuncture study of renal lithium reabsorption: effects of amiloride and furosemide. Am J Physiol Renal Physiol 263:F1128–F1133
22. Boer WH, Koomans HA, Dorhout Mees EJ (1990) Lithium clearance in healthy humans suggesting lithium reabsorption beyond the proximal tubules. Kidney Int 37:S39–S44
23. Worcester EM, Gillen DL, Evan AP, Parks JH, Wright K, Trumbore L, Nakagawa Y, Coe FL (2007) Evidence that postprandial reduction of renal calcium reabsorption mediates hypercalciuria of patients with calcium nephrolithiasis. Am J Physiol Renal Physiol 292:F66–F75
24. Bergsland KJ, Coe FL, Gillen DL, Worcester EM (2009) A test of the hypothesis that the collecting duct calcium-sensing receptor limits rise of urine calcium molarity in hypercalciuric calcium kidney stone formers. Am J Physiol Renal Physiol 297:F1017–F1023
25. Worcester EM, Coe FL, Evan AP, Bergsland KJ, Parks JH, Willis LR, Clark DL, Gillen DL (2008) Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. Am J Physiol Renal Physiol 295:F1286–F1294
26. Johnson RJ, Schreiner GF (1997) Hypothesis: the role of acquired tubulointerstitial disease in the pathogenesis of salt-dependent hypertension. Kidney Int 52:1169–1179
27. Massey LK, Sutton RAL (2004) Acute caffeine effects on urine composition and calcium kidney stone risk in calcium stone formers. J Urol 172:555–558
28. Prie D, Ravery V, Boccon-Gibod L, Friedlander G (2001) Frequency of renal phosphate leak among patients with calcium nephrolithiasis. Kidney Int 60:272–276
29. Prie D, Huart V, Bakouh N, Planelles G, Dellis O, Gerard B, Hulin P, Benque-Blanchet F, Silve C, Grandchamp B, Friedlander G (2002) Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. N Engl J Med 347:983–991
30. Lorenz-Depiereux B, Benet-Pages A, Eckstein G, Tenenbaum-Rakover Y, Wagenstaller J, Tiosano D, Gershoni-Baruch R, Albers N, Lichtner P, Schnabel D, Hochberg Z, Strom TM (2006) Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am J Hum Genet 78:193–201
31. Karim Z, Gerard B, Bakouh N, Alili R, Leroy C, Beck L, Silve C, Planelles G, Urena-Torres P, Grandchamp B, Friedlander G, Prie D (2008) NHERF1 mutations and responsiveness of renal parathyroid hormone. N Engl J Med 359:1128–1135
32. Rendina D, Mossetti G, De Filippo G, Cioffi M, Strazzullo P (2006) Fibroblast growth factor 23 is increased in calcium nephrolithiasis with hypophosphatemia and renal phosphate leak. J Clin Endocrinol Metab 91:959–963
33. Parks JH, Coe FL, Evan AP, Worcester EM (2009) Urine pH in renal calcium stone formers who do and do not increase stone phosphate content with time. Nephrol Dial Transplant 24:130–136
34. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE (2004) Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int 66:777–785
35. Backman U, Danielson BG, Johansson G, Ljunghall S, Wikstrom B (1980) Incidence and clinical importance of renal tubular defects in recurrent renal stone formers. Nephron 25:96–101
36. Tessitore N, Ortalda V, Fabris A, D'Angelo A, Rugiu C, Oldrizzi L, Lupo A, Valvo E, Gammaro L, Loschiavo C (1985) Renal acidification defects in patients with recurrent calcium nephrolithiasis. Nephron 41:325–332
37. Megevand M, Favre H (1984) Distal renal tubular dysfunction: a common feature in calcium stone formers. Eur J Clin Invest 14:456–461
38. Gault MH, Chafe LL, Morgan JM, Parfrey PS, Harnett JD, Walsh EA, Prabhakaran VM, Dow D, Colpitts A (1991) Comparison of patients with idiopathic calcium phosphate and calcium oxalate stones. Medicine 70:345–358