URINARY CALCIUM EXCRETION IN HUMAN BEINGS

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CALCIUM is the most abundant cation in human beings. The total body content averages about 25,000 mmol, or 1 kg, in a 70-kg man — virtually all of it occurring in bone.1 Perhaps the most important biochemical property of calcium is that it forms salts that are barely soluble (Fig. 1).2 The solubility of calcium monohydrogen phosphate (CaHPO₄·2H₂O) appears to determine the precipitation of calcium phosphates from aqueous solutions; this salt then undergoes transformation to apatites [Ca₁₀(PO₄)₆(OH)₂ or Ca₁₀(PO₄)₂CO₃], which are the principal minerals in bone.3 Apatite and calcium oxalate are the predominant constituents of kidney stones.4,5

In healthy adults in the United States, daily dietary calcium intake typically ranges from 5 to 50 mmol6 and averages about 20 mmol, or 800 mg. Since fecal calcium excretion averages 16 mmol and net intestinal calcium absorption and urinary calcium excretion are about 4 mmol, healthy adults are in calcium balance.7

Urinary calcium excretion immediately reflects the relation between the rates of glomerular filtration and tubular reabsorption and ultimately reflects the net rates of either intestinal calcium absorption or bone resorption — processes that are integrated by the parathyroid and vitamin-D endocrine systems and perhaps by other systems. The normal serum calcium concentration averages 2.4 mmol per liter; about 60 per cent is ultrafilterable or diffusible,8 and the remainder binds to serum proteins, chiefly albumin. At a glomerular filtration rate of 150 liters per day, about 215 mmol of calcium is filtered, and, since only 4 mmol is excreted in the urine, about 98 per cent of filtered calcium is reabsorbed.

**Dietary Calcium**

Figure 2, derived from studies of healthy adults,9-20 shows that daily urinary calcium excretion rises from an average of 2 mmol when dietary calcium intake is less than 5 mmol, to 10 or 12 mmol when intake increases to 100 to 150 mmol with calcium carbonate loads. When intake is normal (5 to 50 mmol), excretion varies widely but seldom exceeds 7 mmol.

To evaluate more rigorously the influence of dietary calcium on urinary calcium, we have modified calcium intake in subjects on an otherwise constant diet.19 Figure 3 shows that urinary calcium changes essentially linearly as dietary calcium decreases by as much as 50 mmol per day or increases by as much as 150 mmol per day. For a given change in dietary calcium intake, urinary calcium excretion changes by an average of only 6 per cent. Thus, changes in dietary calcium cause evident but small changes in urinary calcium excretion.

The influence of a given change in dietary calcium on urinary calcium is also determined by the rate of intestinal calcium absorption, which has two components: active transport controlled by the renal hormone 1α,25-dihydroxyvitamin D or 1,25-(OH)₂D and passive diffusion of calcium down a concentration gradient.21 When dietary intake of calcium is normal, calcium absorption, whether measured by the balance technic18 or with isotopic calcium,23 correlates closely with the plasma concentration of 1,25-(OH)₂D. In patients without kidneys, who lack 1,25-(OH)₂D, net intestinal absorption of calcium does not occur at normal levels of dietary calcium.18 However, absorption can occur when 1,25-(OH)₂D is undetectable if dietary calcium is increased to 100 mmol per day both in patients with chronic renal failure23 and in normal subjects who have taken large amounts of calcium.19 Absorption can also occur if the intestine is perfused directly with fluids that contain 15 mmol per liter of calcium.24

![Figure 1. Relative Solubility in Water of Some Common Calcium, Magnesium, Sodium and Potassium Salts.](image-url)
Changes in dietary calcium appear to alter urinary calcium excretion by altering both the filtered load of calcium and secretion of parathyroid hormone (PTH). Since deprivation lowers the serum concentration of calcium and loading raises it, the consequent fall or rise in the filtered load of calcium may account, in part, for the subsequent fall or rise in urinary calcium. However, changes in renal-tubular reabsorption of calcium caused by altered PTH secretion may be more important. In studies on parathyroidectomized dogs, PTH stimulated renal-tubular reabsorption of calcium. This effect, mediated by cyclic adenosine monophosphate (AMP), was later documented in micropuncture studies. These observations suggest that when dietary calcium increases and serum calcium rises the suppression of serum immunoreactive PTH (iPTH) and urinary cyclic AMP and the rise in filtered calcium increase urinary calcium excretion. In contrast, when intake falls and serum calcium declines, an increase in serum iPTH and urinary cyclic AMP and a fall in filtered calcium reduce urinary calcium excretion. In healthy adults, these sequences occur within 24 hours after changes in dietary calcium. In addition, increased intake is accompanied by a fall in plasma 1,25-(OH)₂D, and reduced intake by plasma 1,25-(OH)₂D. These changes occur within 24 to 36 hours after intake is altered — an observation that is consistent with the rapid turnover of this steroid hormone. Changes in plasma 1,25-(OH)₂D are directly related to the preceding changes in serum iPTH (correlation coefficient, r = 0.65) and the ratio of urinary excretion of cyclic AMP to creatinine (r = 0.69). Moreover, they are reciprocally related to changes in the ratio of urinary excretion of calcium to creatinine (r = -0.75); plasma 1,25-(OH)₂D falls as urinary calcium rises and rises as urinary calcium falls. This inverse relation is also found in healthy adults on their usual, self-selected diets and is extended during dietary calcium loading or deprivation. These data suggest that dietary calcium intake, by its influence on the integrated parathyroid and vitamin-D endocrine systems, helps to determine the capacity of the intestinal calcium-transport system to absorb a subsequent meal that contains calcium.

These observations are relevant to a common clinical disorder, calcium nephrolithiasis, and to an unusual one, the milk-alkali syndrome. Patients with stones often have increased intestinal calcium absorption, and consequently many are hypercalciuric at any level of dietary calcium intake (Fig. 4). In addition, many patients with hypercalciuria and stones have elevated plasma 1,25-(OH)₂D, which augments intestinal calcium absorption even when calcium intake is normal. Perhaps stimulation of bone resorption by 1,25-(OH)₂D prevents maximum renal conservation of calcium in these patients, even when calcium intake is very low.

Patients with hypercalciuria and stones have been classified as having either renal hypercalciuria owing to impaired renal-tubular reabsorption of calcium, or absorptive hypercalciuria owing to increased intestinal absorption of calcium. The relative frequency of these syndromes and the extent to which increased plasma 1,25-(OH)₂D results from secondary hyperparathyroidism in renal hypercalciuria, or from defective metabolism of phosphate or some other factor that regulates renal synthesis of 1,25-(OH)₂D in absorptive hypercalciuria remains unsettled.

As described above, normal subjects given large amounts of calcium have low plasma 1,25-(OH)₂D and plasma 1,25-(OH)₂D are suppressed. Hypercalcemia in these subjects might be expected to reduce glomerular filtration rate and cause renal and soft-tissue calcifications — the disorder known as the milk-alkali syndrome.

### Dietary Acid-Base Factors

Recent studies show that at any level of dietary calcium intake urinary calcium excretion rises as dietary protein increases. Increased dietary protein augments fixed acid production by increasing the formation and urinary excretion of organic acids and the oxidation of amino acid sulfur to inorganic sulfate. Increased urinary excretion of calcium accompanies:

$$\Delta U_{CaV} \text{ mmol/day} = -0.9 + 0.06 \Delta \text{ Diet Ca mg/day}$$

\[ r = 0.93 \]

The solid line represents the rise in urinary calcium excretion as dietary calcium is increased (y = 0.06x - 0.9), and r represents the correlation coefficient.
the metabolic acidosis induced by administration of ammonium chloride. In healthy adults, the rise in urinary net acid excretion (ammonium plus titratable acid minus bicarbonate) parallels the rise in fixed acid production. To evaluate the relation between urinary calcium excretion and urinary net acid excretion, we have modified acid production and thus net acid excretion by administration of ammonium chloride, sodium bicarbonate or increased dietary protein.  

Figure 4 shows that as acid excretion increases, urinary calcium excretion rises exponentially, with peak increments of 15 mmol per day at maximum increments of acid excretion of 300 meq per day. Subjects given large amounts of alkali show a far smaller absolute fall in calcium excretion.

During ammonium chloride acidosis in healthy adults, urinary calcium excretion rises even though glomerular filtration of calcium falls. Thus, reduction of net tubular reabsorption of calcium must accompany increased acid production and excretion. Although increased serum iPTH has been reported during ammonium chloride acidosis, we have observed that serum iPTH, the ratio of urinary cyclic AMP to creatinine and plasma 1,25-(OH)₂D do not change when acid production is increased by either ammonium chloride loads or increased dietary protein. Moreover, both ammonium chloride acidosis induced in patients with hypoparathyroidism and hydrochloric acid administration in parathyroidectomized rats increase urinary calcium excretion.

These data suggest that the parathyroid and vitamin-D endocrine systems do not mediate the reabsorption in renal-tubular reabsorption of calcium that occurs when fixed acid production is increased. Acidemia by itself is also not responsible, since increased urinary calcium excretion does not accompany respiratory acidosis. It is uncertain whether a fall in serum bicarbonate during increased acid production mediates this response, since urinary calcium excretion can increase with small increments in fixed acid production that produce neither a detectable fall in serum bicarbonate nor a fall in absolute bicarbonate below 24 meq per liter, the lower limit of normal.

Even these changes in serum bicarbonate, however, may appreciably alter tubular reabsorption of bicarbonate. Recent micropuncture studies in dogs show that acute correction of chronic ammonium chloride acidosis by infusion of sodium bicarbonate augments reabsorption of calcium by the distal renal tubule. Thus, the delivery of sodium bicarbonate to the distal tubule may help to regulate tubular reabsorption of calcium. Studies of patients with either proximal or distal-renal-tubular acidosis support this possibility. Patients with the proximal-tubular abnormality have neither hypercalciuria nor bone disease. Since proximal-tubular reabsorption of bicarbonate is impaired in these patients, delivery of bicarbonate to the distal tubule is normal or even enhanced, and this effect may account for the absence of hypercalciuria. In contrast, patients with distal-tubular acidosis often have hypercalciuria, as do normal subjects given ammonium chloride. In these circumstances, the decline in filtered bicarbonate and enhanced proximal-tubular reabsorption of bicarbonate may reduce delivery of bicarbonate to the distal tubule and thereby reduce reabsorption of calcium and cause hypercalciuria.

To determine the source of additional urinary calcium during ammonium chloride acidosis, we have compared the results of balance studies of 13 healthy adults during control conditions and during stable, chronic ammonium chloride acidosis. Table 1 shows that fecal calcium falls slightly during acidosis, but there is no statistically significant change in net intestinal absorption of calcium. Urinary calcium rises strikingly, and consequently the subjects are in negative calcium balance. Thus, the additional urinary calcium does not represent increased intestinal absorption of calcium — further evidence that the vitamin-D endocrine system is not activated. Instead, the additional calcium must reflect an increase in net bone resorption; however, it is unclear what causes in-

![Figure 5](image_url)
increased bone resorption when acid production increases. PTH is not involved, since acute acid loading in parathyroidectomized, nephrectomized rats elevates serum calcium and osteoclastic bone resorption accompanies chronic ammonium chloride acidosis in parathyroidectomized rats.46

These observations have implications for distal-renal-tubular acidosis, an unusual clinical disorder, and also for calcium nephrolithiasis. Many patients with distal-renal-tubular acidosis have increased urinary calcium excretion in relation to dietary calcium (Lemmann J: Unpublished data). The combination of hypercalciuria and a persistently alkaline urine facilitates precipitation of calcium phosphate and leads to nephrocalcinosis, nephrolithiasis and sometimes bone disease. Low serum bicarbonate must play a part in bone disease because urinary calcium falls and bone disease heals when these patients are treated with alkali alone.55-57 However, phosphate homeostasis may also have a role in the effects of acid-base balance on calcium homeostasis. Most of these patients have osteomalacia, which can be caused by phosphate depletion, and many also have hypophosphatemia, which commonly accompanies ammonium chloride acidosis.44,45

Calcium nephrolithiasis occurs most frequently in affluent Western nations, and its incidence appears to be increasing, perhaps because of increased intake of protein, particularly animal protein. This relation may be explained in part by the rise in urinary calcium that accompanies increased acid production and excretion during high intake of protein.

**Dietary Sodium**

Although acute saline loads in dogs cause parallel increases in urinary excretion of calcium and sodium, apparently by depression of both proximal and distal-tubular reabsorption of calcium, acute saline loads in human beings have only minimal effects on urinary calcium excretion. In clearance studies in healthy adults, infusion of isotonic saline at 12 ml per minute for two hours raised the rate of fractional excretion of sodium from 1.6 ± 0.6 to 2.9 ± 1.3 per cent (P < 0.01, by Student’s paired t-test) but did not change fractional excretion of calcium (control, 2.1 ± 1.0 per cent; saline loading, 2.0 ± 1.2 per cent; not significant).

Although few studies have investigated the effects of chronic changes in dietary sodium on urinary calcium in human beings, some data suggest that urinary calcium increases about 0.6 mmol per 100-meq increment in urinary sodium. Acute administration of aldosterone does not affect urinary calcium excretion in human beings, but urinary calcium increases progressively after chronic administration of mineralocorticoid when dietary sodium chloride is normal, presumably because tubular reabsorption of both sodium and calcium is reduced.

The clinical implications of the relation between sodium and calcium excretion are unclear because dietary sodium intake, within the usual ranges, causes relatively small changes in calcium excretion. Nevertheless, dietary sodium should be controlled in quantitative studies of other factors that alter urinary excretion of calcium.

**Dietary Phosphate**

Figure 6, derived from several of our studies, shows urinary calcium excretion as a function of dietary phosphate intake. When daily dietary phosphate is 10 to over 100 mmol (and dietary calcium is 2 to 50 mmol), urinary calcium varies but does not exceed about 7 mmol; however, when dietary phosphate is only 3 mmol, urinary calcium is 7 to 18 mmol. Thus, urinary calcium appears to rise only with extreme phosphate deprivation. In addition, on the first day of deprivation, urinary calcium rises promptly. In men it plateaus after the fifth or sixth day of deprivation, but in women it rises progressively as long as deprivation continues. The increment in urinary calcium partly results from increased net intestinal absorption, which, in turn, is caused by increased plasma 1,25-(OH)2D. Some extra calcium would be needed to maintain the plateau.

![Figure 6. Urinary Calcium Excretion as a Function of Dietary Phosphate Intake in Healthy Adults.](image-url)

Open circles represent a daily dietary phosphate intake of 3 mmol or less, and closed circles an intake of 10 mmol or more.
must also be derived from bone, since in some women urinary calcium exceeds dietary calcium. Moreover, during more prolonged dietary deprivation of phosphate in animals, bone loss occurs.

Phosphate deprivation, like increased acid production, augments urinary calcium excretion apparently independently of the parathyroid and vitamin-D endocrine systems. Although the decline in serum iPTH during dietary deprivation of phosphate in human beings may mediate the decrease in renal-tubular reabsorption of calcium, it should depress, not increase, bone resorption. Moreover, animal studies show that neither thyroparathyreodectomy nor vitamin-D deficiency prevents the calcuiic response to subsequent dietary phosphate deprivation.

These observations have clinical implications for phosphate depletion syndromes, calcium nephrolithiasis and distal-renal-tubular acidosis. Phosphate depletion is common in patients with chronic alcoholism, inadequate dietary intake or malabsorption, but reductions in calcium intake may blunt the hypercalcucia caused by this depletion. In patients with calcium nephrolithiasis, who have lower serum phosphate concentrations than do healthy human beings, a still undefined defect in phosphate metabolism may underlie the tendency to have increased plasma 1,25-(OH)₂D concentrations and hypercalcucia. Hypophosphatemia may also play a part in the hypercalciuria of patients with distal-renal-tubular acidosis and osteomalacia and of subjects with induced ammonium chloride acidosis.

Other Nutrients

Urinary calcium rises acutely and transiently after administration of glucose and alcohol. This increase, the result of reduced net tubular reabsorption of calcium, appears to depend on insulin. The implications for human disease remain unclear, although we have observed that patients with calcium nephrolithiasis, as well as their asymptomatic, hypercalciuric relatives, have an exaggerated calciuric response to large amounts of glucose.

Glomerular Filtration Rate

The effect of an increased glomerular filtration rate on calcium excretion in human beings has not been studied, but in dogs increments in the glomerular filtration rate induced by infusion of dopamine, acute protein feeding or administration of dexamethasone, increase calcium excretion very little. However, in human beings with advanced renal disease, urinary calcium falls even when the glomerular filtration rate is reduced to only 50 to 80 ml per minute. Fractional urinary excretion of calcium is also depressed in early renal failure, presumably because of augmented renal-tubular reabsorption of calcium, which is caused by the increased serum iPTH that is apparent even in mild renal failure. Stimulated PTH secretion, in turn, appears to result from phosphate retention. Since plasma concentrations of 1,25-(OH)₂D and intestinal absorption of calcium are normal in early renal failure, the early development of secondary hyperparathyroidism is not caused by a defect in vitamin-D metabolism. In fact, secondary hyperparathyroidism may sustain renal synthesis of 1,25-(OH)₂D at this stage. As renal failure progresses and 1,25-(OH)₂D synthesis declines, reduced intestinal absorption of calcium, a well known feature of advanced renal failure, also contributes to the decline in urinary excretion.

Disordered Bone Turnover

Accelerated bone turnover owing to factors other than PTH, such as stimulation by thyroid hormones, osteoclast-activating factor or prostaglandins, should enhance urinary excretion of calcium. The accelerated net bone resorption and consequent tendency to have elevated serum calcium should increase glomerular filtration of calcium, depress serum iPTH and thus depress renal-tubular reabsorption of calcium.

Diuretics

The diuretics furosemide and ethacrynic acid inhibit reabsorption of chloride in the thick, ascending loop of Henle and secondarily inhibit reabsorption of calcium and sodium. The consequent increase in urinary calcium excretion is beneficial in the treatment of severe hypercalcemia. The thiazide diuretics, in contrast, reduce urinary excretion of calcium by enhancing distal-renal-tubular reabsorption and thus are useful in the treatment of calcium nephrolithiasis. In addition, thiazide diuretics may help to maintain more normal serum calcium levels in hypoparathyroid patients.

In summary, urinary calcium excretion rises in human beings when calcium or sodium intake increases, when fixed acid production increases and when dietary phosphate falls to very low levels. The effect of these factors on urinary calcium excretion in health has not been precisely quantified, presumably because no standard experimental diet exists. Hopefully, a standard diet that is nutritionally adequate, simple, widely reproducible and palatable will be agreed upon soon. Such a diet, given per kilogram of body weight or per unit of urinary creatinine to reflect lean body mass, would help to determine the range and regulation of urinary calcium excretion in health and disease.

Discussion

Dr. Richard Belsey: Why is the plasma 1,25-(OH)₂D concentration elevated in patients with idiopathic hypercalciuria?

Dr. Lemann: In some patients, a renal leak of calcium and secondary hyperparathyroidism appear to cause this elevation, whereas in others a primary abnormality in phosphate homeostasis that directly augments renal synthesis of 1,25-(OH)₂D appears to be responsible. In still other patients with hypercalciuria, plasma 1,25-(OH)₂D levels are elevated without any clear abnormality in serum iPTH or phosphate.
concentrations; presumably some undefined abnormality that stimulates renal synthesis of 1,25-(OH)₂D₃ is present. We have begun to investigate the effects of 40 mmol of calcium carbonate per day for two days on plasma 1,25-(OH)₂D₃ concentrations in patients with calcium nephrolithiasis. Most of these patients appear to have the expected normal suppression of plasma 1,25-(OH)₂D₃ at the expense of exaggerated hypercalcciuria, but others may have nonsuppressible 1,25-(OH)₂D₃ levels.

Dr. Robert Brown: What is the role of crystalluria in the formation of urinary stones?

Dr. Lemann: Crystals in the sediment from fresh urine are presumably formed in the urinary tract and indicate that solute concentrations in the urine exceed the formation product for the crystal in question—an event that is necessary for crystal nucleation but not for crystal (stone) growth, which can occur at lesser degrees of supersaturation. Numerous and large calcium oxalate crystals have been observed in the urine of patients with calcium nephrolithiasis. In unpublished studies, we looked for crystals in the sediment from warm, freshly voided urine obtained from both normal subjects and patients with calcium nephrolithiasis. The sediment from normal subjects almost never contained crystals, despite the presence of maximally concentrated urines. The sediment from patients with stones frequently contained calcium oxalate crystals, if the urine had a normal pH of 5.5, or apatite crystals, if the urine had a less acidic pH of 6.0 to 6.6. The calcium concentration averaged about 8 mmol per liter in urines containing crystals but only about 4 mmol per liter in urines without crystals. Thus, the urinary calcium concentration appears to be an important determinant of crystalluria. We also examined the sediment in a second urine specimen collected two hours later from some of the same patients, after administration of glucose or sucrose. Despite further increases in urinary calcium concentration owing to the carbohydrate, patients with calcium oxalate crystalluria did not have more crystals on a qualitative basis. Patients with apatite crystalluria had fewer or no crystals, since acute carbohydrate loads acidify the urine. Precipitation of calcium phosphate is thus probably more dependent on urinary pH and hence monohydrogen phosphate concentration than on urinary calcium concentration.

REFERENCES