

Milk Alkali Syndrome and the Dynamics of Calcium Homeostasis

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Intensive treatment with calcium-containing antacids and milk first was used in the early 20th century for the treatment of peptic ulcer disease and sometimes was associated with toxicity, eventually known as the milk alkali syndrome. Despite the introduction of H₂ blockers and proton pump inhibitors for the treatment of peptic ulcer disease, the milk alkali syndrome continues to occur but is seen more frequently in older women who are receiving treatment for osteoporosis. The milk alkali syndrome provides a unique opportunity to discuss calcium homeostasis in a setting in which the primary calcium regulatory hormones, parathyroid hormone (PTH) and calcitriol, are not overtly abnormal. A thorough understanding of the pathophysiology of the milk alkali syndrome, including its generation and maintenance, requires knowledge of intestinal calcium absorption, bone influx and efflux of calcium, and renal calcium excretion and also how these processes change with age. In this review, the pathophysiology of the milk alkali syndrome is discussed in light of recent advances in our understanding of calcium homeostasis, particularly the role of the calcium-sensing receptor (CaSR) and epithelial calcium channels that are present in various tissues such as the parathyroid gland, kidney, and intestine. The contributions of alkalosis, *per se*, to the generation and maintenance of hypercalcemia are discussed in detail.

History of the Milk Alkali Syndrome

Almost 100 years ago, Sippy (1) developed a calcium-laden milk and antacid regimen for the treatment of peptic ulcer disease. His rationale was to neutralize the hyperacidity that was deemed responsible for peptic ulcer disease. The Sippy regimen was used for the treatment of peptic ulcer disease, a disorder that was most common in middle-aged men, until the 1970s, when nonantacid treatment first was introduced (2–4). The original recommendation by Sippy consisted of the hourly administration of milk and cream together with what became known as Sippy powders, which were 10 grains (1 grain = 65 mg) each of heavily calcinated magnesia and sodium bicarbon-

ate, alternating with a powder that contained 10 grains of bismuth subcarbonate and 20 to 30 grains of sodium bicarbonate (1). Subsequently, many variants of this regimen were used, but each contained large quantities of calcium, milk, and alkali.

In 1923, Hardt and Rivers provided a detailed description of the toxicity that was associated with the antacid and milk regimen (5). It consisted of headache, nausea, vomiting, dizziness, musculoskeletal pains, and weakness followed by prostration. Abnormal laboratory findings included an elevated blood urea nitrogen (BUN) and serum creatinine, alkalosis, and albuminuria. In 1936, Cope (6) first recognized that hypercalcemia was a major feature of toxicity. He also showed that after treatment was stopped, resolution of the alkalosis and hypercalcemia was relatively rapid, but the recovery of renal function was much slower, sometimes taking weeks. Moreover, the milk alkali syndrome could be differentiated from primary hyperparathyroidism because of the absence of hypophosphatemia and the resolution of the hypercalcemia once treatment with antacids was stopped. In 1949, Burnett *et al.* (7) described a chronic variant of the milk alkali syndrome in which renal failure was persistent and soft tissue calcifications were extensive.

In the 1950s, Palmer and associates (3) reported their experience in 3300 patients who were treated for peptic ulcer disease between 1947 and 1956. Thirty-five patients had unequivocal evidence of the milk alkali syndrome. Between 1947 and 1953, only one to three patients per year were found to have hypercalcemia. In the subsequent three years, eight or more patients per year had hypercalcemia even though lesser amounts of calcium-containing antacids were used for treatment. It was concluded that the increased incidence of hypercalcemia in the later years was because serum calcium was measured more frequently.

In the 1960s, Punsar and Somer (8) provided a classification of the milk alkali syndrome, which divided the disorder into three different types: Acute, subacute (Cope's syndrome), and chronic (Burnett's syndrome) toxicity. Shortly thereafter, McMillan and Freeman (9) used this information to generate a comprehensive table that compared the clinical presentation, biochemical findings, and resolution of the three different types of the milk alkali syndrome (Table 1). In actuality, the three types represent a continuum with considerable overlap. The acute form was seen a few days to weeks after starting treat-

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Table 1. Different forms of the milk alkali syndrome^a

Acute	Subacute or Intermediate	Chronic
Other names		
toxemia	Cope's syndrome	Burnett's syndrome
alkalosis	alkalosis	
Blood chemistry		
elevated calcium, BUN, and creatinine	same as acute	same as acute
normal or elevated phosphorus and CO ₂ content	same as acute	same as acute
Symptoms		
frequent nausea, vomiting, anorexia, weakness, lethargy, mental changes (psychosis or encephalitis-like symptoms), headache, dizziness	frequent nausea, vomiting, anorexia, mental changes, asthenia, muscle aching, polydipsia and polyuria, occasional conjunctivitis	infrequent nausea, vomiting, anorexia, occasional mental changes, asthenia, muscle aching, pruritus, polydipsia and polyuria
Other findings		
no band keratopathy or abnormal calcifications	occasional band keratopathy; soft tissue calcifications absent	band keratopathy and other abnormal calcifications, including nephrocalcinosis (histologic but not necessarily radiographic)
Response to withdrawal of milk and alkali		
rapid relief of symptoms, return of renal function to normal status	rapid relief of some symptoms, others clear gradually; gradual but marked improvement in renal function; normocalcemia but less rapid than in acute cases	muscle aching and pruritus clear slowly; little or no improvement in renal function; gradual normalization of blood calcium; some reduction of abnormal calcification
Circumstance in which the type is seen		
complication of treatment with milk and alkali, usually after approximately one week of such treatment	usually seen during therapy with milk and alkali used intermittently for years	occurs after long history of high milk or alkali intake or both

^aReprinted from reference (9), with permission. BUN, blood urea nitrogen.

ment with calcium and alkali. Symptoms and laboratory abnormalities rapidly normalized after treatment was stopped. The subacute form (Cope's syndrome) was seen during therapy with calcium and alkali that had been used intermittently for years. In contrast to the acute form, there was less rapid improvement in symptoms, and recovery of renal function was slower. The chronic form (Burnett's syndrome) occurred after a long history of ingestion of large amounts of calcium and alkali. Patients often complained of pruritus and diffuse musculoskeletal symptoms. Nephrocalcinosis and band keratopathy were observed frequently, as were large soft tissue calcium deposits (7,10). Although symptoms usually improved with discontinu-

ation of calcium antacids, resolution of hypercalcemia was slow, especially in patients with large soft tissue deposits of calcium. Renal insufficiency often improved but did not resolve completely.

The Only Prospective Study of the Milk Alkali Syndrome

The only study to evaluate prospectively the development of the milk alkali syndrome was reported in 1965 (9). Forty male patients with peptic ulcer disease (mean age 47 ± 10 yr) and normal serum creatinine values were divided into two equal

groups and treated for 7 d with milk and either calcium carbonate or aluminum hydroxide. Both groups received 6 oz (180 ml) of milk every 2 h, alternating in in-between hours with either 5 ml of calcium carbonate or 15 ml of aluminum hydroxide. In the calcium carbonate group, the total daily dose was 28 g, a value at the lower end of the recommended treatment regimen for peptic ulcer disease. In the calcium carbonate group, (1) serum calcium values increased and exceeded 12 mg/dl in 25% of the patients; (2) urinary calcium excretion increased by more than two-fold; (3) serum phosphorus increased from 3.5 to 4.5 mg/dl; and (4) serum creatinine increased from 1.2 to 1.4 mg/dl, whereas creatinine clearance fell by 20 ml/min. After 7 d, one patient had serum calcium, creatinine, and bicarbonate values of 18 mg/dl, 3 mg/dl, and 40 mM, respectively, but even if alkalosis did not develop, patients who received calcium carbonate had a reduction in renal function. In contrast, the group that was given milk and aluminum hydroxide did not have any biochemical changes. Therefore, the frequency of hypercalcemia in this prospective study supports the impression by Palmer and associates (3) that the finding of hypercalcemia depends on how frequently serum calcium values are measured.

Milk Alkali Syndrome after Introduction of Nonantacid Treatment of Peptic Ulcer Disease

In the 1970s, the use of antacids to treat peptic ulcer disease declined dramatically with the introduction of H₂ blockers. More recently, the milk alkali syndrome has been recognized in patients with decreased renal function even though these patients ingest lesser amounts of calcium-containing antacids than were given to patients with peptic ulcer disease (4). In 1986, hypercalcemia was reported to develop in 65 of 297 heart transplant recipients who were given 8 to 12 g of calcium carbonate daily in an attempt to reduce steroid-induced bone loss (11). Of 65 patients who developed hypercalcemia, 31 also had alkalosis. Serum creatinine was >1.5 mg/dl in more than half of the patients before treatment. Therefore, reduced renal function likely contributed to the development of the milk alkali syndrome.

A retrospective chart review of hypercalcemia at a single institution showed that from 1985 to 1989, only one of 51 cases of hypercalcemia was due to the milk alkali syndrome (12), but from 1990 to 1993, six of 49 cases of hypercalcemia were due to the milk alkali syndrome. In cases of the milk alkali syndrome, six were in women, and all seven were taking oral calcium carbonate. The results of a more recent study with a surveillance period from 1998 to 2003 confirmed that the milk alkali syndrome is a common cause of hypercalcemia today (13). In 125 patients who presented to the hospital with hypercalcemia, the milk alkali syndrome was the third most common cause of hypercalcemia (8.8%) and the second most common cause of severe hypercalcemia (>14 mg/dl). Again, there was a female predominance (eight of 11 patients). Therefore, with the increased use of calcium carbonate for treatment of osteoporosis, an increased awareness of the milk alkali syndrome is neces-

sary. Also, as the two cases presented next show, even today, when antacid therapy is not routinely used for the treatment of peptic ulcer, there continue to be reports of the milk alkali syndrome from calcium antacids that are used for the self-treatment of dyspepsia (14–24).

Case Presentations

Our interest in the milk alkali syndrome was stimulated because we have seen two cases of the milk alkali syndrome in middle-aged men who were admitted to the West Los Angeles Veterans Administration Medical Center. Despite the presence of renal failure and metabolic alkalosis in both patients, the milk alkali syndrome was not even considered as a possible diagnosis on admission. In one case, part of the diagnostic failure may have been because serum calcium and phosphorus are no longer measured routinely in general medical admissions at our hospital, but this information was available in the second patient who was admitted to the medical intensive care unit. Both cases are summarized here because we believe that they serve to heighten the awareness of this disorder and to show potential differences in patient presentation.

Patient 1

A 55-yr-old white man with a medical history that was significant for reflux esophagitis and dyspepsia presented to the outpatient clinic with complaints of polydipsia, polyuria, nausea, frequent emesis, and generalized fatigue for 2 wk. During the previous 4 mo, he had lost approximately 10 lb (4.5 kg), and nocturia had increased from one to five times per night. On presentation, physical examination was significant for a BP of 150/90 mmHg and trace pretibial edema. Laboratory tests showed a serum sodium of 137 mEq/L, potassium 4.7 mEq/L, chloride 92 mEq/L, bicarbonate 34 mM, BUN 63 mg/dl, and creatinine 5.0 mg/dl. The serum creatinine had been 0.9 mg/dl two years earlier. Hemoglobin and hematocrit were 13.2 g/dl and 37%, respectively. Urinalysis showed a pH of 7.5 but was otherwise unremarkable. Renal ultrasound showed a right kidney of 14 cm and a left kidney of 13.5 cm with a minimal increase in echogenicity. The patient was admitted to the general medicine ward, and a renal consult was requested. Because of azotemia with an elevated serum bicarbonate, the renal consultant requested measurement of total serum calcium, ionized calcium, and serum phosphorus, which were 12.3 mg/dl, 1.66 mM, and 4.3 mg/dl, respectively. The pH of arterial blood that was drawn 1 d after admission and after treatment with normal saline reduced serum bicarbonate from 34 to 29 mM was 7.48. Two days after admission, PTH was 15 pg/ml (normal 10 to 65) and 25-hydroxyvitamin D was 18 ng/ml (normal 9 to 38 ng/ml). When asked, the patient freely admitted that he took large amounts of Tums (calcium carbonate) for dyspepsia and reflux esophagitis. Before reporting to the medical ward, he had even retrieved a bottle of Tums from his car so that he could take them in the hospital. A diagnosis of the milk alkali syndrome was made. Calcium carbonate was stopped, and intravenous hydration with normal saline was started. By 48 h, his symptoms had resolved completely. The serum calcium concentration decreased to 10.1 mg/dl in 3 d and decreased further to 9.0 mg/dl at day 10, when he was seen as an outpatient. Serum creatinine decreased to 2.1 mg/dl in 3 d and was 1.2 mg/dl at day 10. Six months after admission, the serum creatinine value was 1.0 mg/dl and serum calcium was normal.

Patient 2

A 65-yr-old white man with a medical history that was significant for coronary artery disease, hypertension, and esophageal reflux was seen in the emergency department because of a severe frontal headache and vomiting. He denied any other problems. Outpatient medications that were taken on a daily basis included fosinopril 20 mg, aspirin 81 mg, simvastatin 10 mg, and atenolol 50 mg, but these medications had not been taken for 2 wk. Physical examination was notable for a BP of 202/112 mmHg. The remainder of the examination was unremarkable. Laboratory tests showed a serum sodium of 143 mEq/L, potassium 3.3 mEq/L, chloride 101 mEq/L, bicarbonate 42 mM, BUN 20 mg/dl, and creatinine 2.4 mg/dl. Arterial blood gas was remarkable for a pH of 7.49, P_{CO_2} of 53, and P_{CO_2} of 64. Urine pH was 8.5, but the urinalysis was otherwise unremarkable. One day after admission, PTH was 15 pg/ml (normal 10 to 65 pg/ml), and 3 d after admission, serum calcitriol was 6 pg/ml (normal 16 to 55 pg/ml). The chest x-ray showed cardiomegaly with mild pulmonary vascular congestion, and a computed tomography scan of the head was negative. A renal ultrasound showed normal-size kidneys without increased echogenicity. The patient was admitted to the medical intensive care unit for hypertensive urgency, and an intravenous nitroprusside infusion was started. Because his vomiting and headache became worse, the nitroprusside was stopped and the elevated BP was treated with clonidine. Without a stated rationale, this hypertensive patient was started on normal saline at 125 ml/h. Because the patient had been admitted to the medical intensive care unit, serum calcium and phosphorus measurements were performed, and these values were 11.3 mg/dl and 4.1 mg/dl, respectively; the ionized calcium value was 1.45 mM. When a renal consult was requested 3 d after admission, the hypercalcemia and metabolic alkalosis had almost resolved. Because of the association of hypercalcemia, renal insufficiency, and metabolic alkalosis, the diagnosis of milk alkali syndrome was considered likely. When the patient was asked whether he took antacids, he stated that for the past several months he had been taking a large number of Roloids (calcium carbonate) during the day and baking soda at night for his reflux esophagitis. Three days after admission, his serum calcium was normal and his serum creatinine and bicarbonate values were 1.7 mg/dl and 27 mM, respectively. At an outpatient visit 1 wk later, serum creatinine was 1.4 mg/dl and 5 mo afterward was 1.2 mg/dl. Hypercalcemia did not recur.

These two cases show that even today, milk alkali syndrome is seen as a consequence of the excessive ingestion of calcium-containing antacids that are taken for gastrointestinal disorders. Both patients presented with hypercalcemia, renal insufficiency, and metabolic alkalosis as a result of taking large amounts of calcium carbonate for dyspepsia and esophageal reflux. Both patients had a rapid resolution of hypercalcemia, metabolic alkalosis, and renal insufficiency when calcium carbonate was stopped and intravenous normal saline was given. Neither patient had detectable soft tissue calcifications. On presentation, both patients had hypertension, but it was more severe in patient 2, who had a history of hypertension and had recently stopped his antihypertensive medications. In both cases, vomiting probably contributed to the decreased renal function and the magnitude of hypercalcemia and alkalosis. In patient 1, the diagnosis of the milk alkali syndrome was made after renal consultation because of the combination of renal insufficiency and metabolic alkalosis. In patient 2, even though hypercalcemia was known to be present on admission along with the new onset of renal insufficiency and metabolic alka-

losis, the milk alkali syndrome was not considered as a potential diagnosis by the primary care physicians.

Pathogenesis of the Milk Alkali Syndrome

Pathogenesis of the milk alkali syndrome should be divided into the generation and maintenance phases. Factors that are involved in the generation of hypercalcemia include increased intestinal absorption, saturation of bone buffering of calcium, and decreased renal excretion. Once hypercalcemia is generated, factors that promote (1) volume depletion from the natriuresis and diuresis that are induced by activation of the CaSR by hypercalcemia; (2) a decrease in the GFR, which reduces the filtration of calcium; and (3) an increase in renal reabsorption of calcium, which occurs as a result of metabolic alkalosis and volume depletion, contribute to the maintenance of hypercalcemia. The development of hypercalcemia in the milk alkali syndrome also is important to evaluate for several reasons: (1) It develops even when the primary calcium regulatory hormones PTH and calcitriol are suppressed appropriately; and (2) it provides a distinct opportunity to discuss and evaluate the dynamics of intestinal, skeletal, and renal factors that drive the development of hypercalcemia and how this balance changes with age. An overview of calcium balance is shown in Figure 1.

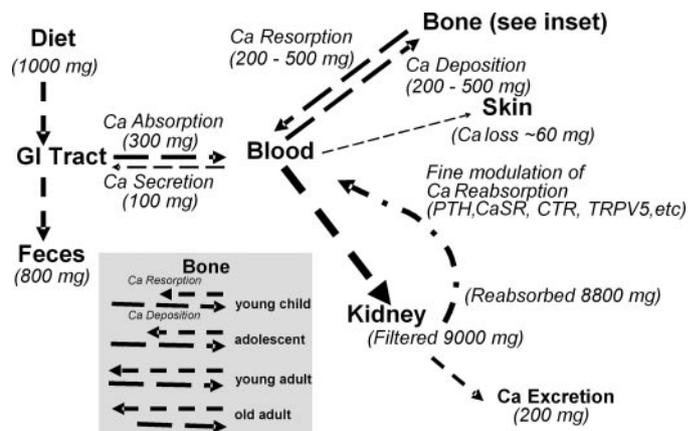


Figure 1. Schematic of calcium balance in a young adult who ingested 1000 mg/d dietary calcium. In the schematic, the calcium balance is neutral (zero). The dermal (skin) calcium loss, which rarely is measured, is not included in the numbers. The amount of calcium involved in bone formation and resorption rate is shown to be 200 to 500 mg/d (42,132,133), but it also has been shown that the amount of calcium that is involved in bone formation and resorption is much smaller than the total exchangeable calcium bone pool, which has been shown by radioisotope studies to be 3 to 6 g/d (42,132–134). Also shown in the inset is that whereas the bone balance of calcium (influx versus efflux) is neutral in a young adult, the influx of calcium is greater than the efflux of calcium in the young child and adolescent. Conversely, in the old adult, the influx of calcium to bone is less than the efflux of calcium from bone. Calcium balance also is affected by calcium intake. Greater calcium intake will improve calcium balance in all four groups, but the difference between young and old still is maintained. The mg values in the figure represents per day; Ca, calcium.

Hypercalcemia develops in the milk alkali syndrome because the input of calcium (dietary intake and intestinal absorption) exceeds the output (primarily renal excretion). The amount of calcium carbonate that has been reported to induce the milk alkali syndrome has varied from 4 to 60 g/d (4). This wide range of ingested calcium indicates that factors besides calcium intake contribute to the development of the milk alkali syndrome. Factors that can increase calcium input include increased dietary calcium intake, ingestion of supplemental calcium, enhanced intestinal absorption of calcium usually from stimulation by vitamin D that is present in some calcium supplements, and other dietary factors. Also, the oral ingestion of calcium-containing compounds has been shown to increase directly gastric acid secretion (25,26) by stimulating the CaSR (27), which in turn increases the availability of free calcium for absorption. Also, acid digestion of protein releases L-amino acids, which, in turn, may promote calcium absorption in the small and large intestines (27). Conceptually, calcium absorption might be expected to be better if there are no available phosphorus-containing foodstuffs or other potential chelators of calcium in the intestinal lumen. However, calcium absorption may be as good or even better with meals (28,29). Such a result may have to do with the acidity of the meal and its carbohydrate content, protein breakdown, and the presence of bile salts (30,31).

It is likely that bone, the primary repository for calcium, increases calcium uptake but becomes saturated during high calcium exposure. The capacity of bone to increase calcium uptake per unit of bone changes with age as does the extent of bone remodeling (Figure 1) (32–35). The potential role of variations in the capacity for buffering by bone is probably important for the development of hypercalcemia and the milk alkali syndrome because a decrease in calcium bone-buffering capacity can increase the susceptibility to the development of hypercalcemia. Besides age, several factors presumably can alter bone-buffering capacity: Calcium intake, hypo- and hypercalcemia, and high and low PTH values. For example, in children and adolescents in whom skeletal growth is a continual process, the net movement of calcium is to bone. Therefore, in childhood and adolescence, calcium is preferentially deposited in bone, and despite high calcium intake and efficient intestinal absorption of calcium, renal calcium excretion is low (32–34). In a study in prepubertal identical twins, it was shown that increasing the daily calcium intake from 908 to 1612 mg increased bone mineral density (36). In the young adult, in whom longitudinal growth has ceased, the net movement of calcium to and out of bone approaches zero (32–34). With aging, the net movement of calcium is out of bone. Therefore, it seems that the lower the bone turnover, the less capacity bone has for buffering calcium, a phenomenon that has been shown in renal osteodystrophy (Figure 1) (37).

Because of its direct effect on PTH secretion, the serum calcium concentration is a major factor that contributes to the movement of calcium to and out of bone. In disorders of hypocalcemia, characterized by high PTH levels that drive bone remodeling, such as the secondary hyperparathyroidism of renal failure, vitamin D deficiency, and the rare disorder of

calcitriol resistance (38), the low serum calcium concentration probably contributes to the development of rickets or osteomalacia (38–41). At least in the disorder of calcitriol resistance from 1- α hydroxylase deficiency, large amounts of intravenously administered calcium or high calcium intake in animal diets that contain lactose has resulted in healing of rickets and osteomalacia in humans and the knockout mouse (38,40,41). In disorders of non-PTH-induced hypercalcemia, such as the milk alkali syndrome, suppression of PTH probably contributes to low bone turnover, which in turn would reduce the calcium-buffering capacity of bone.

The main route of calcium elimination is renal excretion. A reduction in calcium excretion results from a decrease in GFR and/or an increase in tubular calcium reabsorption. Other sites of calcium loss from the body include intestinal secretion and skin losses (42,43), but their effect is relatively small. As shown in Figure 2, when hypercalcemia develops, the normal response is rapid suppression of PTH values, which results in less calcium efflux from bone, and a greater capacity to excrete calcium as the trophic effect of PTH on renal calcium reabsorption is removed. The magnitude of this trophic effect of PTH was shown many years ago by Nordin and Peacock (44,45). When calcium was infused to normalize serum calcium values in

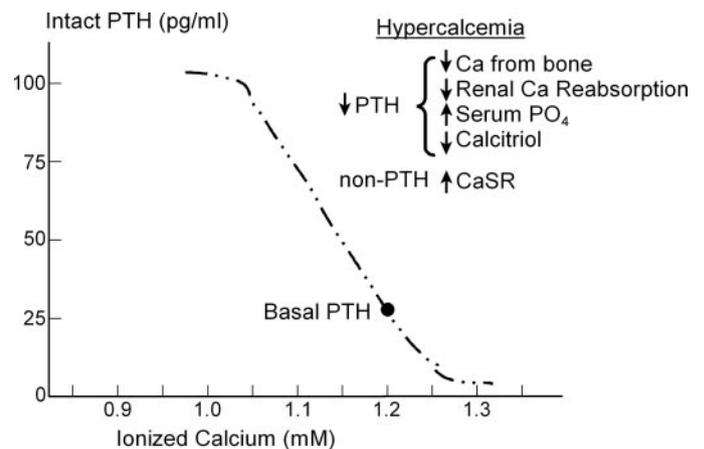


Figure 2. Effect of hypercalcemia and parathyroid hormone (PTH) suppression on factors that affect bone calcium efflux and calcium excretion. The sigmoidal relationship between the ionized calcium concentration and PTH is shown for normal humans. In the basal state, the baseline PTH value in the young adult is approximately 25 pg/ml as measured with an intact PTH assay. When hypercalcemia is induced, the resulting decrease in the PTH acts to reduce calcium efflux directly from bone and indirectly *via* an increase in the serum phosphorus and a decrease in the serum calcitriol concentration. The reduction in PTH also acts to enhance renal calcium excretion. A reduction in serum calcitriol values reduces intestinal calcium absorption and may enhance renal calcium excretion *via* its action on the calcitriol-sensitive calcium channel in the distal tubule (transient receptor potential vanilloid receptor 5/6 [TRPV5/6]). Finally, independent of PTH, hypercalcemia activates the calcium-sensing receptor (CaSR), which enhances calcium excretion by its action in the thick ascending limb of the loop of Henle (TALH).

hypoparathyroid patients, renal calcium excretion was approximately three-fold greater than that in normal humans with intact parathyroid glands (44,45). In the normal human, hypercalcemia-induced PTH suppression also acts (1) to decrease renal phosphorus excretion, and the resulting increase in serum phosphorus reduces bone efflux of calcium (46); and (2) to suppress calcitriol production, which reduces both intestinal calcium absorption (47) and renal reabsorption of calcium (48). Another important mechanism for enhanced renal calcium excretion during hypercalcemia is the activation of the CaSR in the thick ascending limb of Henle (TALH) (49).

Whereas raising serum calcium facilitates renal calcium excretion, several consequences of hypercalcemia limit calcium excretion and contribute to the maintenance of hypercalcemia (Figure 3). First, the development of hypercalcemia directly decreases the GFR, reducing the amount of calcium filtered (50). Second, hypercalcemia activates the CaSR in the TALH and medullary collecting duct. The ensuing natriuresis and diuresis result in volume depletion, which, in turn, decreases the GFR and the filtration of calcium (49). Third, the presence of metabolic alkalosis acts to increase tubular reabsorption of calcium (51,52). Fourth, in the presence of chronic kidney disease, downregulation of the CaSR may reduce calcium excretion further (53). To provide a better understanding of potential variations in the development of the milk alkali syndrome, we focus on several factors—age, serum phosphorus, metabolic alkalosis and vitamin D—all of which can affect the generation and maintenance of hypercalcemia in the milk alkali syndrome.

Age

The milk alkali syndrome first was described in middle-aged men with peptic ulcer disease. More recently, the milk alkali syndrome has been reported in older women who receive calcium supplements for osteoporosis. Aging has several effects that affect calcium homeostasis. These include a decrease in the efficiency of intestinal calcium absorption (54–56), a reduced

capacity to deposit calcium in bone (57), and a decrease in renal function (58). In general, the overall effect of aging is a reduced capacity to handle a calcium load that sensitizes the elderly to the development of hypercalcemia. Several factors can decrease intestinal calcium absorption in the elderly, including a relative insensitivity to vitamin D. Furthermore, a reduction in gastric acidity or the use of a proton pump inhibitor may limit gastric liberation of free calcium and thereby reduce intestinal calcium absorption (59,60). The reduction in intestinal absorption of calcium that is associated with aging functions to counteract the decrease in bone-buffering capacity and the reduced capacity to excrete calcium that is seen with decreased renal function. However, under certain circumstances, such as a marked increase in calcium intake and/or supplemental vitamin D, both used for treatment of osteoporosis, the “protective” effect of reduced intestinal calcium absorption may be lost.

In humans, the kidney plays a critical role in preventing hypercalcemia. However, with aging, the decline in GFR and other factors may limit the renal excretion of calcium. Increased PTH values in the elderly population (58) may reduce the capacity to suppress completely PTH secretion during initial increases in the serum calcium concentration. Renal function is decreased in the elderly, and downregulation of the CaSR has been reported in chronic kidney disease (53), which, in turn, could limit the capacity to excrete calcium during the development of hypercalcemia. Many elderly patients are on thiazides for control of BP. In addition to decreasing calcium excretion by inducing a mild volume depletion with a reduction in GFR (61), thiazides directly enhance calcium reabsorption in the distal tubule by inhibiting the thiazide-sensitive Na-Cl co-transporter and also promote alkalosis (62,63). Moreover, many older individuals are on angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory agents, loop diuretics, and low-sodium diets, all of which can reduce the GFR, which in turn would reduce the capacity to excrete a calcium load.

Once hypercalcemia develops, it contributes to its own maintenance because of volume depletion from increased sodium and water excretion. The resulting decrease in the GFR further reduces the capacity to excrete a calcium load. The role of a reduced GFR in the maintenance of hypercalcemia is best demonstrated by the use of intravenous saline to treat hypercalcemia and the attendant volume depletion. Restoration to a normal volume status increases the GFR and the renal capacity to excrete calcium.

In summary, various factors combine to regulate renal excretion of calcium, including GFR, PTH, vitamin D, and the CaSR. Abnormalities in any of these may heighten the risk for development of hypercalcemia (Figure 3). In the elderly, a lower GFR, a higher PTH, vitamin D supplementation, and downregulation of the CaSR are not uncommon and may combine to decrease the excretion of a calcium load.

Phosphorus

The phosphorus load is another variable that can affect the development of the milk alkali syndrome. Besides the characteristic findings of hypercalcemia, alkalosis, and renal failure in the milk alkali syndrome that are seen with the treatment of

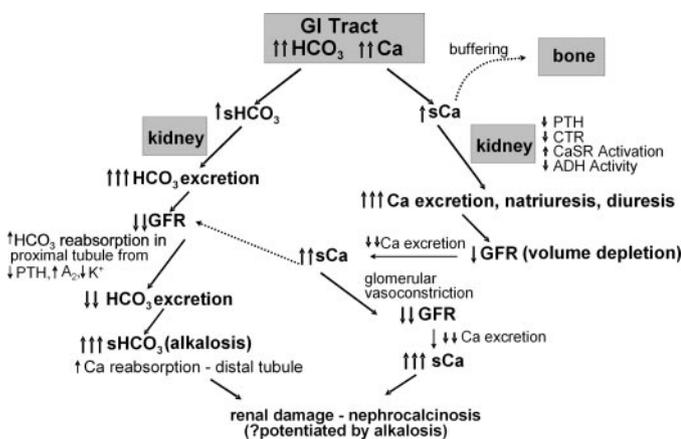


Figure 3. Schematic of how hypercalcemia and metabolic alkalosis are generated and maintained in the milk alkali syndrome. GI, gastrointestinal; HCO₃, bicarbonate; CTR, calcitriol; ADH, antidiuretic hormone; A₂, angiotensin 2; K⁺, potassium. An “s” preceding the name indicates serum.

peptic ulcer disease, increases in serum phosphorus values were reported. The increases in serum phosphorus values resulted from the ingestion of phosphorus-rich milk together with the development of hypercalcemia, which suppressed PTH values and reduced phosphorus excretion. However, patients in whom the milk alkali syndrome develops as a result of calcium carbonate supplementation for osteoporosis or from self-treatment of dyspepsia often present with hypophosphatemia or low normal serum phosphorus values (12,13). In these patients, there is no phosphorus supplementation because milk is not given and the calcium-containing antacids act as phosphate binders (64,65). Moreover, the effect of a phosphate binder could be more pronounced in the elderly patient, in whom dietary phosphorus and protein ingestion often is reduced (66).

Hypophosphatemia that is induced by oral administration of calcium carbonate potentially could operate at several levels to promote the development of the milk alkali syndrome. Hypophosphatemia stimulates calcitriol production, which can augment intestinal calcium absorption. Most patients who present with the milk alkali syndrome have renal insufficiency, which in turn impairs the capacity to produce calcitriol. However, it is possible that before the onset of renal insufficiency, stimulation of calcitriol by hypophosphatemia may contribute to the development of the milk alkali syndrome. Hypophosphatemia also can contribute to the generation and maintenance of the milk alkali syndrome by increasing the release of calcium and alkali from bone (46,67–69).

Metabolic Alkalosis

Metabolic alkalosis has the capacity to affect calcium homeostasis at several critical sites. These include the parathyroid gland, intestine, kidney, and bone.

Parathyroid Gland. Acute metabolic alkalosis has been shown to suppress PTH secretion in animal studies (70). *In vitro* studies have shown that metabolic alkalosis increases the sensitivity of the CaSR to extracellular calcium (71,72), which in turn would inhibit PTH secretion. If chronic metabolic alkalosis also suppresses PTH secretion, then it could decrease bone turnover and thereby decrease the capacity for bone buffering of calcium.

Intestine. Recent studies have shown that pH regulates the activity of the transient receptor potential vanilloid receptor 6 (TRPV6) epithelial calcium channel (73,74). This channel, present on the brush border membrane (BBM) of the duodenum, is involved in calcium absorption (73). However, because the channel is present on the BBM, it is unclear whether systemic and/or luminal pH regulates TRPV6 activity at this site. The CaSR is widely expressed throughout the small and large intestines (75,76). Although the predominant location of the CaSR in the small intestine is along the basal surface of the intestinal epithelial cells, there also is some apical staining. In the duodenum, the extracellular calcium concentration has been shown to stimulate the expression of calbindin, a protein that is important for duodenal absorption of calcium (49). Although the mechanism of calcium stimulation of calbindin is not known, one possibility is *via* the CaSR. In the remainder of

the small and large intestines, the role of the CaSR on intestinal calcium absorption is not known, but it may regulate fluid secretion at these sites (76). Whether systemic metabolic alkalosis, which has been shown to enhance directly the activity of the CaSR in the kidney (71,72), has a similar effect on the CaSR in the intestinal epithelial cell is not known. If it does, then it could have important effects on intestinal calcium absorption.

Kidney.

Clinical and Animal Studies. Metabolic alkalosis enhances calcium reabsorption. Even when a bicarbonate infusion produces metabolic alkalosis and concomitant volume expansion, a setting in which increased distal sodium delivery would be expected to enhance calcium excretion, increased delivery of bicarbonate to the distal nephron has been shown to increase calcium reabsorption (51). However, metabolic alkalosis is seen much more often in association with volume depletion and chloride losses such as with vomiting. In metabolic alkalosis that is seen with volume depletion, there is enhanced bicarbonate reabsorption in the proximal tubule (PT) and also increased delivery of bicarbonate to the distal tubule, both of which would act to increase calcium reabsorption (Figure 3).

The acid load that is produced by a high-protein diet or ingestion of ammonium chloride has been shown to increase urine calcium excretion (77–83). Alkali treatment alone or given together with a high-protein diet or ammonium chloride reduces urine calcium excretion and improves calcium balance (77,78,80–84). Some studies of alkali treatment also have shown that the decrease in urine calcium excretion occurs independent of calcium regulatory hormones such as PTH and calcitriol. Whereas supplemental alkali treatment did not change plasma pH or bicarbonate levels, urine pH did increase from the 5.5 to 6 range to the 6.5 to 7.0 range (80,81,83,85). Therefore, the enhanced calcium reabsorption could be, at least in part, from an increase in luminal pH in the distal tubule.

In the studies in which the calciuric effects of metabolic acidosis were reduced with alkali treatment, urine pH increased to the 6.5 to 7 range, but plasma pH and bicarbonate values did not change (80,81,83,85). However, as shown in the two patients with the milk alkali syndrome presented in this review, urine pH values were higher than in the aforementioned studies, as were serum bicarbonate and arterial pH values. As is discussed in the next section, each of the components of metabolic alkalosis—the alkalemia, bicarbonate in the urine, and high urine pH—has the capacity to reduce calcium excretion at different nephron sites.

Studies of Individual Nephron Segments. Most filtered calcium is reabsorbed in the PT primarily by paracellular movement. In the TALH, calcium reabsorption also occurs primarily *via* the paracellular route, but under certain circumstances, transcellular reabsorption may occur (86). Fine tuning of calcium reabsorption occurs in the distal convoluted tubule (DCT) by active transcellular processes. The overall effect of metabolic alkalosis on the renal handling of calcium is to enhance calcium reabsorption. However, as shown in Figure 4, the effect of alkalosis on calcium handling in the various nephron sites that

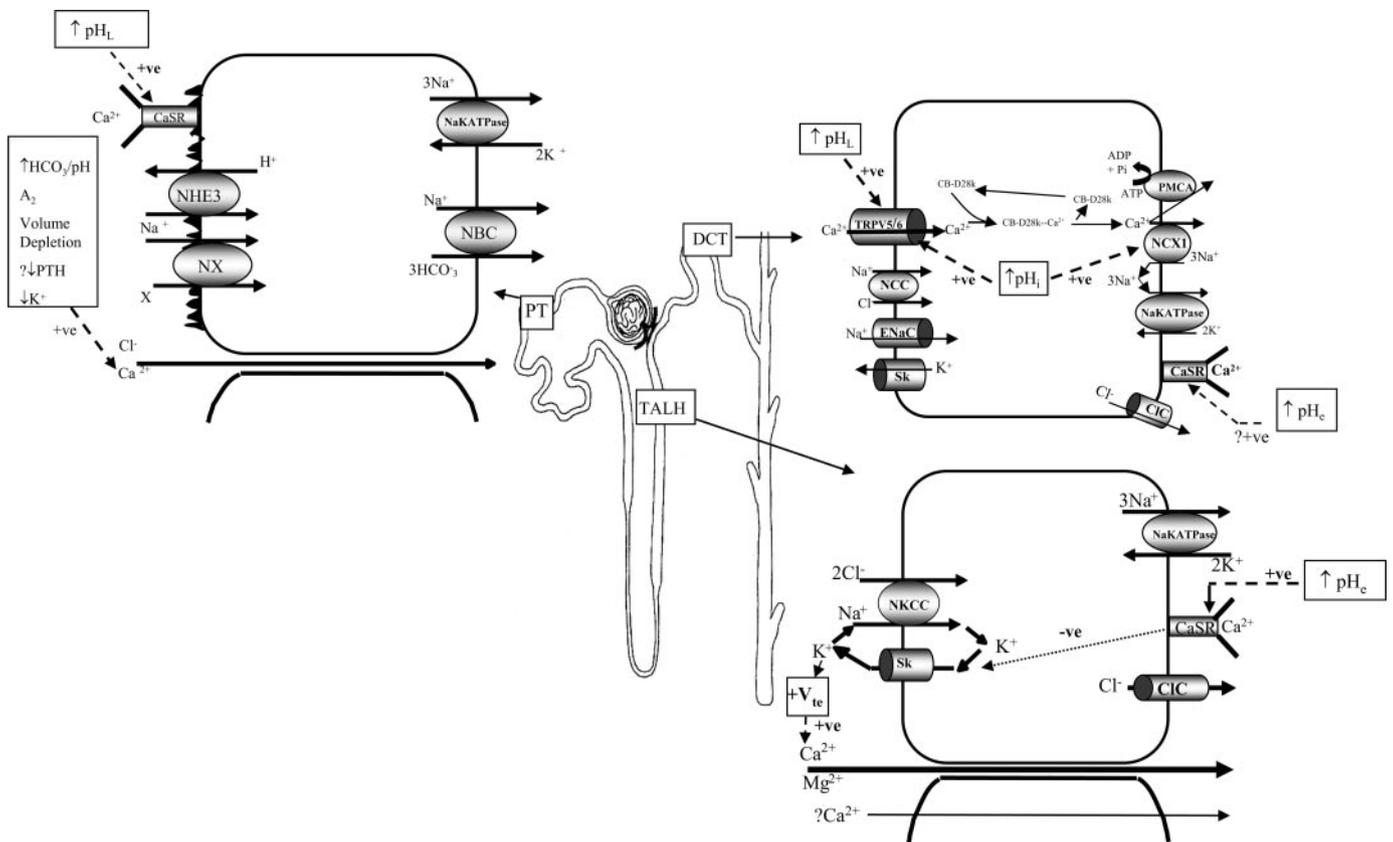


Figure 4. Schematic diagram of how metabolic alkalosis increases calcium reabsorption in the proximal tubule (PT), TALH, and distal convoluted tubule (DCT). The schematic diagram provides information on the enhancing effects of metabolic alkalosis on calcium reabsorption in the PT, TALH, and DCT. For details of known and potential interactions in each segment, see the text. +ve, positive effect (broken line); -ve, negative effect (dotted line); pH_L , pH lumen; pH_i , pH intracellular; pH_e , pH extracellular; NHE3, sodium hydrogen exchanger 3; NX, sodium X co-transporter with X = glucose, amino acids, organic acids, phosphate, and sulfate; NaKATPase, sodium potassium ATPase; NBC, sodium bicarbonate co-transporter; NKCC, sodium potassium 2-chloride co-transporter; Sk, secretory potassium channel; CIC, chloride channel; $+V_{te}$, positive transepithelial voltage; NCC, sodium chloride co-transporter; ENaC, epithelial sodium channel; PMCA, plasma membrane calcium ATPase pump; NCX1, sodium calcium co-transporter 1; CB-D28k, calbindin 28k.

are involved in renal calcium handling is complex and operates *via* different processes.

In the PT, factors that generate and maintain the metabolic alkalosis (Figure 3) also enhance calcium reabsorption. As shown in Figure 4, part of the interaction involves direct effects of bicarbonate, *per se*, on the stimulation of calcium transport. The importance of bicarbonate in the renal handling of calcium in the PT, independent of systemic pH, initially was suggested by clearance studies in dogs (51,52). Subsequent micropuncture studies in the rat showed that bicarbonate reabsorption in the PT also stimulated calcium reabsorption (87). Also, factors that are associated with hypercalcemia increase bicarbonate reabsorption in the PT. As a result of PTH suppression, bicarbonate reabsorption in the PT is enhanced by stimulation of the Na^+/H^+ exchanger (88,89). Volume depletion that is induced by hypercalcemia stimulates angiotensin 2 production and hypokalemia, both of which stimulate bicarbonate reabsorption in the PT (90,91).

The driving force for increased calcium reabsorption in the PT is stimulation of sodium reabsorption together with the

enhanced bicarbonate reabsorption. This occurs *via* enhanced activity of the sodium-hydrogen exchanger (Figure 4). The increased sodium reabsorption stimulates paracellular reabsorption of filtrate, which in turn increases paracellular calcium reabsorption *via* solvent drag. Furthermore, the increase in sodium reabsorption in the earlier segments of the PT further enhances the chloride gradient across the tubular epithelium, resulting in increased paracellular chloride reabsorption in more distal portions of the PT. This further enhances fluid and calcium reabsorption *via* the paracellular route.

As shown in Figure 4, the CaSR is located on the BBM of the PT. The function of the CaSR in the PT is not completely understood but may affect the regulation of phosphorus rather than of calcium (92,93). It also has been suggested that the CaSR may affect regulation of 1α -hydroxylase activity (94).

Metabolic alkalosis also may affect renal calcium handling at more distal sites by stimulating the CaSR and the epithelial calcium channels TRPV5/6 through changes in extracellular, intracellular, and luminal pH (Figure 4). As in the PT, calcium reabsorption in the TALH under basal conditions occurs pri-

marily *via* the paracellular route, but transcellular calcium transport may occur after stimulation by PTH (86). In the TALH, sodium, chloride, and potassium reabsorption occurs primarily *via* the sodium-potassium-2 chloride co-transporter (NKCC), which is located on the luminal surface of the cell. The concentration of potassium in the lumen of the TALH is an order of magnitude lower than that of sodium and chloride and therefore may limit activity of the NKCC. However, a secretory potassium (K) channel that is located on the luminal membrane allows some of the reabsorbed potassium to leak back into the lumen, providing adequate potassium for the proper functioning of the NKCC (95). In addition, the potassium movement increases the positive charge in the lumen, which provides a driving force for paracellular reabsorption of calcium and magnesium.

As shown in Figure 4, stimulation of the CaSR located on the basolateral surface of the TALH inhibits the secretory K channel and also may inhibit the NKCC, both of which are present on the luminal surface of TALH cells (96). The resultant decrease in luminal-positive charge decreases the electrical gradient needed for the transepithelial paracellular movement of luminal Ca and Mg, thereby reducing reabsorption of these cations. Furthermore, PTH-dependent transcellular transport of calcium also is inhibited by stimulation of the CaSR (86). The precise role, if any, for modulation of the CaSR by pH in the TALH is unclear. It has been postulated that the CaSR may serve as an extracellular pH sensor in some tissues (71). Because the NKCC also transports NH_4^+ , pH regulation of the CaSR theoretically could serve to regulate an important step in the excretion of acid and regeneration of bicarbonate. Besides a direct inhibitory effect of a higher pH on the NKCC (97,98), ammonium reabsorption could be inhibited further by alkalosis-induced activation of the CaSR, resulting in inhibition of the secretory K channel and the NKCC (Figure 4). Such a result would tend to minimize the degree of alkalemia. However, the inhibitory effect of an increasing pH on the NKCC also would decrease calcium reabsorption in the TALH and result in excessive calcium losses, but stimulation of calcium reabsorption by metabolic alkalosis in the DCT could offset any increase in calcium delivery from the TALH.

In the DCT (Figure 4), calcium reabsorption occurs transcellularly and is regulated by several factors, including extracellular calcium, PTH, calcitriol, and calcitonin. The rate-limiting step for calcium reabsorption is the entry of luminal calcium into the cell *via* the TRPV5 calcium channel (73). The TRPV6 calcium channel also may play a role, although it is far less abundant than TRPV5 in the DCT. Calcium that enters the cell is buffered and shuttled across the cell by calbindin D28k and extruded *via* either a sodium calcium exchanger or a plasma membrane calcium ATPase pump, both of which are present in the basolateral membrane (48,99,100). The relative importance of these two transporters in transcellular calcium flux is unclear, but the activity of each is regulated by PTH (101–103) either directly or indirectly through changes in membrane polarity (104). A CaSR is located on the basolateral membrane of the DCT and may be a mechanism by which extracellular calcium regulates transcellular calcium transport at this

nephron site. Whether the CaSR in the DCT regulates calcium transport in an analogous manner to the CaSR in the cortical TALH is unknown, but results from cell culture studies of mixed cortical TALH and DCT cells suggest that activation of the CaSR could block PTH-mediated calcium reabsorption in the DCT (105). The potential effect of metabolic alkalosis on the CaSR in the DCT has yet to be defined.

Huang and associates (106,107) showed that increasing both luminal pH and intracellular pH enhances the activity of TRPV5/6, promoting calcium reabsorption in the DCT (Figure 4). Because TRPV5/6 is located only on the luminal surface, it is likely that the stimulatory effect of an increased extracellular pH (73) is mediated *via* changes in the intracellular pH.

In summary, the overall effect of metabolic alkalosis on renal calcium handling depends on a variety of factors, most but not all of which act to increase calcium reabsorption. These factors include (1) a decreased volume status, such as might be seen during hypercalcemia in the milk alkali syndrome; (2) increased reabsorption of sodium and bicarbonate in the PT; (3) a possible direct effect of metabolic alkalosis on the CaSR in the TALH; and (4) the effect of luminal and systemic alkalosis on TRPV5/6 transporters in the DCT.

Bone

It is important to recognize that two vital functions of bone are (1) calcium regulation and (2) structural support with its necessity for bone remodeling (108). However, these two critical functions of bone do not necessarily act in concert. Moreover, it should be recognized that plasma calcium regulation is not dependent on the rate of bone resorption (108). Metabolic alkalosis may affect directly both calcium regulation and structural support. *In vitro* studies have shown that metabolic alkalosis favors the influx of calcium to bone (109,110). Even though Burnett *et al.* (7) and Rifkind *et al.* (111) reported patients who had milk alkali syndrome and had osteosclerosis by x-ray, the capacity to increase bone mass with calcium supplementation may be age dependent and applicable primarily to children and adolescents (33–36). Several observations suggest that alkali therapy can prevent bone loss in the elderly. The possible role of incipient or “eubicarbonatemic” metabolic acidosis on increasing bone loss has become a major focus of interest (112). Studies have shown that supplementation with potassium bicarbonate reduces net acid and calcium excretion and presumably bone loss (82,85,113). In studies in children with renal tubular acidosis, correction of acidosis with alkali treatment was shown to improve skeletal growth (114). Thiazide diuretics have been reported to be bone sparing (63,115,116) and may reduce the rate of hip fractures and bone loss in postmenopausal osteoporosis (117–119). This result has been attributed to their widely known effect as an enhancer of renal tubular reabsorption of calcium, but thiazide diuretics also induce metabolic alkalosis, which independently enhances the reabsorption of calcium and also may prevent bone loss (51,52).

The decreased efflux of calcium from bone that is seen with metabolic alkalosis is associated with a suppression of osteoclasts and stimulation of osteoblast activity (109,110). Whether pH directly regulates osteoblast/osteoclast activity is unclear.

At least suggesting the possibility for pH sensitivity is the possible presence of more than one CaSR in bone, the functions of which are unclear (120–123). It is interesting that in a CaSR deletion model in mice, hyperparathyroidism, hypercalcemia, and hypophosphatemia developed, but the expected bone changes of hyperparathyroidism were absent. Rather, bone changes that are consistent with osteomalacia were seen, suggesting that the CaSR may function to maintain bone mineralization (124). It is tempting to speculate that stimulation of the bone CaSR *via* increased pH might account for bone calcium accumulation with metabolic alkalosis, but even though metabolic alkalosis may promote calcium deposition in bone, saturation of bone-buffering capacity eventually occurs in the milk alkali syndrome.

Vitamin D

Calcitriol, the active form of vitamin D, promotes intestinal absorption of calcium. Besides having a reduced efficiency for intestinal calcium absorption (54–56), the elderly also have an increased incidence of vitamin D insufficiency (125,126). While vitamin D insufficiency may adversely affect intestinal calcium absorption, it could further increase PTH values (127), which are already increased in the elderly (128,129). Such increases in PTH values could decrease serum phosphorus values (58,127) and also act to increase calcium reabsorption in the distal tubule.

A recent review suggested that a subset of patients may develop the milk alkali syndrome because serum calcitriol values are not suppressed appropriately despite hypercalcemia, PTH suppression, and renal failure (130). Another consideration is that many patients with osteoporosis also may receive treatment with vitamin D. Therefore, there is a possibility that high 25-hydroxyvitamin D levels could contribute to a failure to suppress calcitriol values appropriately. At present, there is limited information in the milk alkali syndrome that originated from two small series (13,18) and several case reports (15,17,24) regarding 25-hydroxyvitamin D levels and the suppression of calcitriol. Even with vitamin D supplementation as high as 800 IU/d, 25-hydroxyvitamin D levels have been reported to be normal or even low (13,15) (as reported in patient 1). In the small number of serum calcitriol values reported, 11 were low and four were low normal (13,15,17,18,131) (as reported in patient 2). Therefore, it could be argued that in a minority of patients, the failure to suppress calcitriol levels fully could contribute to the development of the milk alkali syndrome in a setting in which the ingestion of calcium is high. It also seems that in most patients who present with the milk alkali syndrome, calcitriol is appropriately suppressed. However, whether in early stages before the development of renal failure and hypercalcemia calcitriol is suppressed appropriately during high calcium ingestion, when there is a potential for hypophosphatemia from calcium-containing phosphate binders, remains to be determined.

Conclusion

A detailed review of the milk alkali syndrome was performed because this syndrome still has clinical relevance today

with a recent study showing it to be the third most common cause of admissions for hypercalcemia (13). Therefore, its recognition remains important for patient care. Even though the demographics of the patients who develop the milk alkali syndrome may have shifted to the elderly patient who is being treated for osteoporosis, the two cases presented illustrate that the milk alkali syndrome sometimes is seen in patients who self-treat for dyspepsia. Finally, a review of the pathophysiology of the milk alkali syndrome is particularly intriguing because the generation and the maintenance of hypercalcemia are not dependent on hormonal factors such as high PTH or vitamin D levels; rather, it is an example of excessive ingestion of calcium and alkali overwhelming the homeostatic system for calcium regulation.

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