

Got Calcium? Welcome to the Calcium-Alkali Syndrome

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ABSTRACT

We recommend changing the name of the milk-alkali syndrome to the calcium-alkali syndrome, because the new terminology better reflects the shifting epidemiology and understanding of this disorder. The calcium-alkali syndrome is now the third most common cause of hospital admission for hypercalcemia, and those at greatest risk are postmenopausal or pregnant women. The incidence of the calcium-alkali syndrome is growing in large part as a result of the widespread use of over-the-counter calcium and vitamin D supplements. Advertising for treatment or prevention of osteoporosis has long encouraged this use. Intricate mechanisms mediating the calcium-alkali syndrome depend on interplay among intestine, kidney, and bone. New insights regarding its pathogenesis focus on the key role of calcium-sensing receptors and TRPV5 channels in the modulation of renal calcium excretion. Restoring extracellular blood volume, increasing GFR and calcium excretion, and discontinuing calcium supplementation provide best treatment.

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In 1915, Bertram Welton Sippy introduced a Chicago cocktail to treat gastric and duodenal ulcers with hourly administration of milk, cream, eggs, and farina cereals, the Sippy diet, interrupted on the half-hour by a regimen of alkali comprising calcinated magnesia, sodium bicarbonate, and bismuth subcarbonate, which were known then as Sippy powders.¹ As the Sippy method gained popularity, some patients developed toxic manifestations including a strong distaste for milk, headache, nausea, vomiting, mental clouding, and renal failure that eventually came to be known as the milk-alkali syndrome from the work of Burnett.^{2–4} Approximately one third of cases resulted in permanent renal impairment.⁵

The incidence of milk-alkali syndrome declined with the arrival of histamine blockers and doxycycline for treatment of peptic ulcer disease; however,

the syndrome saw a resurgence beginning in the 1990s in large part as a result of postmenopausal women taking over-the-counter calcium and vitamin D supplements for treatment or prevention of osteoporosis, a chronic disorder affecting more than 10 million individuals in the United States.^{5,6} In the modern era, this syndrome is the third most common cause of hospital admission for hypercalcemia after hyperparathyroidism and hypercalcemia of malignancy, with reported incidence ranging from 8 to 38%.^{7,8}

The “milk” in milk-alkali syndrome no longer reflects the etiologic origin of the modern version of this disorder, and some suggest the condition be renamed the calcium-alkali or Rolaid-yogurt syndrome.^{9,10} We also recommend changing the name to the calcium-alkali syndrome in deference to a new epidemiology and emerging pathophysiology surrounding

renal calcium metabolism. The integral feature of the calcium-alkali syndrome is a history of excessive ingestion of calcium and often absorbable alkali, producing the classic triad of hypercalcemia, metabolic alkalosis, and varying degrees of renal insufficiency.^{5,11,12}

The earlier milk-alkali syndrome using the Sippy diet often presented with hyperphosphatemia after prolonged ingestion of phosphorus-containing milk with cream.¹³ In contrast, the modern version of calcium-alkali syndrome associates with hypophosphatemia or low-normal serum phosphorus levels as a result of the phosphorus-binding properties of calcium carbonate.^{5,11,14} This hypophosphatemia is more pronounced in elderly patients¹⁴ or those with eating disorders,¹⁵ who tend to have relatively low consumption of protein and therefore phosphorus; low phosphate levels stimulate the renal metabolism of calcitriol and, consequently, absorption of calcium by the gut.¹⁶ Levels of 1,25-hydroxyvitamin D in patients with the calcium-alkali syndrome, of course, are generally low in the setting of hypercalcemia, although some are in the low-normal range and perhaps inappropriate.

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ately high.^{11,14} These latter levels may depend on previous exposure to vitamin D supplementation, because vitamin D is often added to some over-the-counter calcium preparations, but more epidemiology is needed to clarify this exposure.

Whereas the milk-alkali syndrome from the Sippy diet tended to affect men with peptic ulcer disease, the demographic risk today for the calcium-alkali syndrome has changed in favor of postmenopausal women, pregnant women, transplant recipients, patients with bulimia, and those who are on dialysis.^{7,11,14,17} Older patients with aging bone metabolism are susceptible to targeted advertising for their health care advice regarding the use of calcium supplements for the treatment of osteoporosis.^{18,19} Pregnant women have an increased susceptibility to developing calcium-alkali syndrome as a result of hyperemesis, causing volume depletion and enhanced calcium absorption through the gut, possibly aggravated by prolactin or placental lactogen signaling.²⁰ Patients with anorexia nervosa occasionally have food fetishes rich in calcium,^{10,21} and cardiac transplant patients are sometimes given calcium carbonate.¹⁷ Dialysis patients who ingest large amounts of magnesium oxide and calcium carbonate also develop calcium-alkali syndrome,⁹ as can betel nut chewers in Asia because betel nuts are often blended with a lime paste made from ground oyster shells containing calcium oxide and calcium hydroxide.²² Several other medications, including aluminum hydroxide and magnesium hydroxide, provide a source of absorbable alkali in patients with calcium-alkali syndrome who also ingest large doses of calcium.²³ Thiazide use predisposes to calcium-alkali syndrome by enhancing renal calcium absorption by causing volume depletion and thereby promoting alkalosis. Furthermore, angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs associate with calcium-alkali syndrome by reducing GFR, which reduces calcium excretion.¹⁴

The pathogenesis of calcium-alkali syndrome is intricate and involves the interplay of multiple systems, including bone, intestine, and kidney.^{14,24} The av-

Table 1. Amount of elemental calcium in various supplements

Type	Trade Name	Elemental Calcium (mg)	Vitamin D (IU)
Calcium carbonate	Caltrate	600	400
	Centrum	200	400
	Centrum Ultra Women's	500	800
	Rolaids Extra Strength	471	
	Os-Cal	500	
	Tums	200	
	Tums Ultra	400	
	Viactiv	500	
Calcium citrate	Citracal Regular with Vitamin D	250	200
Calcium acetate	Phoslo	167	

erage healthy adult contains approximately 1 kg of calcium (or 25,000 mmol), with >99% found in bone and <1% (20 mmol) in the extracellular fluid.²⁴ Once calcium is absorbed through the gut and into the extracellular fluid space, the bone reservoir provides the principal site for buffering excess calcium. In elderly individuals, however, the net flux of calcium is out of bone, thereby making bone less functional as a reservoir; these patients are more susceptible to the syndrome when they begin taking supplemental calcium and alkali.¹⁴ Although the data are scant, levels of parathyroid hormone and 1,25-hydroxyvitamin D tend to be suppressed but not in all patients.^{11,14} Factors affecting the amount of calcium absorption include dietary intake, levels of 1,25-hydroxyvitamin D, and gastric acidity.²⁵ The amount of supplemental calcium generally considered to predispose to calcium-alkali syndrome is >4 g/d; however, there are reports that 1.0 to 1.5 g of calcium supplementation produce this syndrome.^{7,11} Nevertheless, when ingested levels of calcium are high, movement across the gut tends to be passive rather than regulated by 1,25-hydroxyvitamin D.^{26,27} Table 1 shows the amount of elemental calcium contained in various popular calcium supplements.

Multiple renal factors contribute to the development and maintenance of calcium-alkali syndrome. Hypercalcemia causes renal vasoconstriction, thereby decreasing GFR and reducing amounts of filtered calcium, self-propagating a vicious cycle.^{9,11} Whereas the overall characteristics of renal tubular

calcium handling are well described,^{11,14} recent studies on the role of the calcium-sensing receptors (CaSRs), which are located along the thick ascending loop of Henle and the distal nephron, provide new insights into the mechanism of calcium-alkali syndrome (Figure 1).

Hypercalcemia mimics the phenotype of Bartter syndrome by excess calcium occupying the CaSR on the basolateral side of the medullary thick ascending loop of Henle, which then impedes the luminal renal outer medullary potassium channel, thereby inhibiting sodium chloride transport through the sodium potassium-2-chloride co-transporter.^{14,25,28} In addition, this effect obliterates the voltage-driving force for calcium reabsorption and raises luminal calcium concentrations in the distal nephron.²⁵ Furthermore, metabolic alkalosis, initiated by alkali ingestion, increases the affinity of CaSR for calcium, thereby enhancing the inhibition of sodium and calcium reabsorption.¹⁴ The sodium loss contributes to volume depletion, which further stimulates increased absorption of bicarbonate along with calcium through the proximal tubule.

With increased calcium delivery to the distal nephron, the rate-limiting or fine-tuning site for calcium reabsorption is through a calcium channel called the transient receptor potential vanilloid member 5 (TRPV5), which is pH sensitive. Increased intracellular pH stimulates the activity of TRPV5, thereby enhancing calcium resorption and potentially worsening hypercalcemia.^{14,28} The activation of CaSR by the presence of increased luminal calcium also stimulates TRPV5-mediated

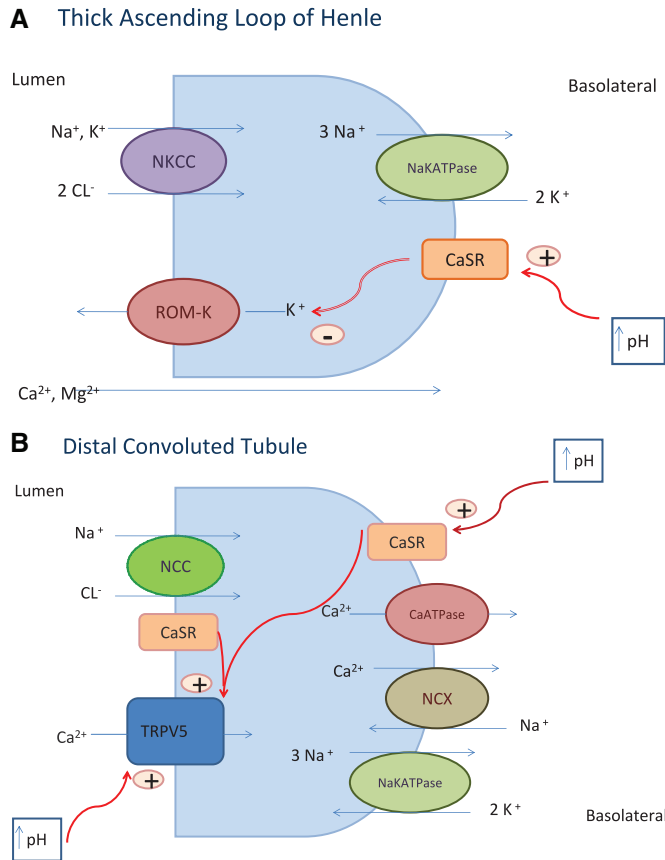


Figure 1. Mechanisms for renal calcium transport depend on the location of the CaSR and TRPV5 channel. (A) Thick ascending loop of Henle. (B) Distal convoluted tubule. NKCC, sodium potassium-2-chloride co-transporter; ROM-K, renal outer medullary potassium channel; NaKATPase, sodium-potassium ATPase; +, stimulates; -, inhibits; NCC, sodium chloride co-transporter; NCX, sodium-calcium exchanger.

calcium influx.²⁹ In the collecting duct system, luminal activation of CaSR as a result of excess luminal calcium concentration enhances both H⁺-ATPase pump activity and the downregulation of aquaporin 2 expression, leading to urinary acidification, systemic HCO₃⁻ generation, and polyuria. These latter effects have been proposed as a mechanism that normally protects the kidney from calcification induced by hypercalciuria but would tend to foster volume depletion and metabolic alkalosis.^{28,30} This latter hypothesis regarding hypercalciuria is controversial.³¹

The main therapy for the calcium-alkali syndrome is volume expansion with saline to break the self-propagating reclamation cycle induced by exposure to calcium alkali. Given that excess ingestion of calcium with or without vitamin

D is an integral feature of this syndrome, the obvious preventive strategy is to limit intake of elemental calcium to no more than 1.2 to 1.5 g/d and to avoid ingesting alkali to reduce the risk that alkalemia will further predispose to calcium-alkali syndrome.^{8,11,14}

DISCLOSURES

None.

REFERENCES

1. Sippy BW: Gastric and duodenal ulcer: Medical cure by efficient removal of gastric juice corrosion. *JAMA* 64: 1625–1630, 1915
2. Hardt LL, Rivers AB: Toxic manifestations following the alkaline treatment of peptic ulcer. *Arch Intern Med* 31: 171–180, 1923
3. Kirsner JB, Palmer WL: Alkalosis complicat-

- ing the Sippy treatment of peptic ulcer. *Arch Intern Med* 69: 789–807, 1942
4. Burnett CH, Commons RR, Albright F, Howard JE: Hypercalcemia without hypercalciuria or hypophosphatemia, mild alkalosis, calcinosis and renal insufficiency: A syndrome following the prolonged intake of milk and alkali. *N Engl J Med* 240: 787–794, 1949
5. Beall DP, Henslee HB, Webb HR, Scofield RH: Milk-alkali syndrome: A historical review and description of the modern version of the syndrome. *Am J Med Sci* 331: 233–242, 2006
6. Tang BMP, Eslick GD, Nowson C, Smith C, Bensoussan A: Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. *Lancet* 370: 657–666, 2007
7. Picolos MK, Lavis VR, Orlander PR: Milk-alkali syndrome is a major cause of hypercalcemia among non-endstage renal disease inpatients. *Clin Endocrinol* 63: 566–576, 2005
8. Beall DP, Scofield RH: Milk-alkali syndrome associated with calcium carbonate consumption: Report of seven patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. *Medicine* 74: 89–96, 1995
9. Hanada S, Iwamoto M, Kobayashi N, Ando R, Sasaki S: Calcium-alkali syndrome due to vitamin D administration and magnesium oxide administration. *Am J Kidney Dis* 53: 711–714, 2009
10. Muldowney WP, Mazbar SA: Rolaid's-yogurt syndrome: A 1990s version of milk-alkali syndrome. *Am J Kidney Dis* 27: 270–272, 1996
11. Medarov BI: Milk-alkali syndrome. *Mayo Clin Proc* 84: 261–267, 2009
12. Abreo K, Adlakha A, Kilpatrick S, Flanagan R, Webb R, Shakamuri S: The milk-alkali syndrome. *Arch Intern Med* 153: 1005–1010, 1993
13. Waked A, Geara A, El-Imad B: Hypercalcemia, metabolic alkalosis and renal failure secondary to calcium bicarbonate intake for osteoporosis prevention: “Modern” milk-alkali syndrome—A case report. *Cases J* 2: 61–88, 2009
14. Felsenfeld AJ, Levine BS: Milk alkali syndrome and the dynamics of calcium homeostasis. *Clin J Am Soc Nephrol* 1: 641–654, 2006
15. Munoz MT, Argente J: Anorexia nervosa in female adolescents: Endocrine and bone mineral density disturbances. *Eur J Endocrinol* 147: 275–286, 2002
16. Kumar R: Metabolism of 1,25-dihydroxyvitamin D3. *Physiol Rev* 64: 478–504, 1984
17. Kapsner P, Langsdorf L, Marcus R, Kraemer FB, Hoffman AR: Milk-alkali syndrome in patients treated with calcium carbonate after cardiac transplantation. *Arch Intern Med* 146: 1965–1968, 1986

18. Juby AG, Davis P: A prospective evaluation of the awareness, knowledge, risk factors and current treatment of osteoporosis in a cohort of elderly subjects. *Osteoporos Int* 12: 617–622, 2001
19. Kava R, Meister KA, Whelan EM, Lukachko AM, Mirabile C: Dietary supplement safety information in magazines popular among older readers. *J Health Commun* 7: 13–23, 2002
20. Pocolos MK, Sims CR, Mastrobattista JM, Carroll MA, Lavis VR: Milk-alkali syndrome in pregnancy. *Obstet Gynecol* 104: 1201–1204, 2004
21. Kallner G, Karlsson H: Recurrent factitious hypercalcemia. *Am J Med* 82: 536–538, 1987
22. Giou-Teng Yiang G-T, Hsu B-G, Harn H-J, Chang H, Wei C-H, Hu S-C: Betel nut induced milk-alkali syndrome. *Tzu Chi Med J* 17: 265–268, 2005
23. Ostermann ME, Girgis-Hanna Y, Nelson SR, Eastwood JB: Metabolic alkalosis in patients with renal failure. *Nephrol Dial Transplant* 18: 2442–2448, 2003
24. Houillier P, Froissart M, Maruani G, Blanchard A: What serum calcium can tell us and what it can't. *Nephrol Dial Transplant* 21: 29–32, 2006
25. Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML: Hypercalcaemia and metabolic alkalosis with betel nut chewing: emphasis on its integrative pathophysiology. *Nephrol Dial Transplant* 17: 708–714, 2002
26. Bronner F, Pansu D: Nutritional aspects of calcium absorption. *J Nutr* 129: 9–12, 1999
27. Bronner F: Mechanisms of intestinal calcium absorption. *J Cell Biochem* 88: 387–393, 2003
28. Riccardi D, Brown EM: Physiology and pathophysiology of the calcium-sensing receptor in the kidney. *Am J Physiol Renal Physiol* 298: F485–F499, 2010
29. Topala CN, Schoeber JP, Searchfield LE, Riccardi D, Hoenderop JG, Bindels RJ: Activation of the Ca²⁺-sensing receptor stimulates the activity of the epithelial Ca²⁺ channel TRPV5. *Cell Calcium* 45: 331–339, 2009
30. Renkema KY, Velic A, Dijkman HB, Verkaar S, Kemp AW, Nowik M, Timmermans K, Doucet A, Wagner CA, Bindels RJ, Hoenderop JG: The calcium-sensing receptor promotes urinary acidification to prevent nephrolithiasis. *J Am Soc Nephrol* 20: 1705–1713, 2009
31. Bergsland KJ, Coe FL, Gillen DL, Worcester EM: 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, 2009