Milk-Alkali Syndrome

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Milk-alkali syndrome (MAS) consists of hypercalcemia, various degrees of renal failure, and metabolic alkalosis as a result of ingestion of large amounts of calcium and absorbable alkali. This syndrome was discovered in the 1930s after treatment of peptic ulcer disease with milk and alkali was widely adopted at the beginning of the 20th century. With the introduction of histamine, blockers and proton pump inhibitors, the occurrence of MAS became rare; however, a resurgence of MAS has been witnessed because of the wide availability and increasing use of calcium carbonate, mostly for osteoporosis prevention. The aim of this review was to determine the incidence, pathogenesis, histologic findings, diagnosis, and clinical course of MAS. A MEDLINE search was performed with the keyword milk-alkali syndrome using the PubMed search engine. All relevant English language articles were reviewed.

REPORT OF A CASE

A 47-year-old woman was referred to the emergency department because of abnormal laboratory results. The patient had undergone routine laboratory work performed before elective neck surgery for cervical stenosis. The following abnormalities were found (reference ranges shown parenthetically): creatinine, 7.2 mg/dL (0.6-1.0 mg/dL); serum urea nitrogen, 50 mg/dL (7-18 mg/dL); total calcium, 21.1 mg/dL (7.7-10.3 mg/dL); bicarbonate, 43 mEq/L (21-32 mEq/L); phosphate, 2.6 mg/dL (2.5-4.9 mg/dL); ionized calcium, 10.04 mg/dL (4.80-5.60 mg/dL); sodium, 133 mEq/L (136-145 mEq/L); and venous serum pH, 7.52 (7.35-7.38). The patient reported recent memory impairment and profound fatigue. She was taking calcium carbonate (1000 mg) plus vitamin D (400 U) twice daily. The patient had no medical or family history of renal failure. She had a history of bulimia but claimed to be in remission. The patient was admitted to the intensive care unit, and aggressive hydration was initiated. On the basis of the laboratory findings and clinical picture, MAS was diagnosed.

On further questioning, the patient admitted to perhaps taking more calcium than she should have. The patient was self-medicating with additional antacids (calcium carbonate [Tums, GlaxoSmithKline, Research Triangle Park, NC]) besides her twice daily calcium supplements with vitamin D because of occasional heartburn and because she believed more calcium was good for her bones.

HISTORY

Milk-alkali treatment of peptic ulcer disease was developed in early 1910 by Sippy, who subsequently published his landmark article. Sippy proposed that gastric acidity was the fueling force behind chronic ulcer disease. His therapy was designed to protect the ulcer from gastric juice corrosion until the ulcer was healed. Bedrest was required for approximately 4 weeks. Every hour throughout the day, 90 mL of a mixture of milk and cream was administered orally. Halfway between feedings and every half hour after the last meal, substantial amounts of alkali (0.65-2.00 g of...
heavy calcined magnesia [magnesium oxide], sodium bicarbonate, and bismuth subcarbonate) were administered. Occasionally, doses of up to 6.5 g of sodium bicarbonate were given every hour. Sippy reported an excellent response to this regimen, even in cases of ulcer disease recurrent for years with resulting high-grade pyloric obstruction. Milk-alkali therapy shortly became the standard for ulcer treatment.

In 1923, Hardt and Rivers at Mayo Clinic described the toxic adverse effects of Sippy’s regimen, particularly in patients who required higher doses of alkali to control stomach acidity. Those patients would develop distaste for milk and experience headaches, irritability, dizziness, and occasionally nausea or vomiting. Three years earlier, MacCallum et al. induced severe alkalosis and “gastric tetany” in dogs, leading to convulsions and death by mechanical pyloric obstruction. Administering sodium chloride prolonged the animals’ lives. Hardt and Rivers found that patients who showed signs of toxemia were azotemic and had high serum bicarbonate levels. Although serum pH was not measured, the authors speculated that individuals had severe alkalemia, similar to that induced in animals by MacCallum et al. Preexistent renal failure and male sex seemed to be risk factors. The symptoms almost invariably disappeared within 24 to 48 hours after discontinuation of oral alkali. Serum calcium levels were not measured.

In 1936, Cope described several adverse effects of calcium carbonate–containing alkali therapy. He commonly found hypercalcemia, hyperphosphatemia, hypermagnesemia, azotemia, and increased bicarbonate levels in patients who had toxic symptoms. The symptoms and electrolyte abnormalities resolved with discontinuation of the antacid therapy. Renal function impairment persisted for weeks in some cases. The author expressed a strong belief that excessive calcium ingestion cannot be the sole cause of hypercalcemia: “It seems probable, therefore, that the renal impairment first occurs and that this renders the kidney unable to excrete sufficiently rapidly all the calcium, which continues to be absorbed from the gut.”

In 1949, Burnett et al. described a “milk and alkali syndrome” in a report of 6 male patients treated with milk and absorbable alkali (usually sodium bicarbonate) for peptic ulcer disease. The common findings were hypercalcemia without hypercalciiuria or hypophosphatemia, normal alkaline phosphatase level, alkalosis, renal insufficiency, corneal calcium deposits (band keratopathy), or other calcinosis (subcutaneous tissue, lung, falc cerebri, and lymph nodes). Except for renal failure, the majority of symptoms resolved shortly after discontinuation of the antacid therapy. Most of the patients developed chronic renal failure, and 4 died. The poor prognosis was strikingly different from the overall good outcome of the patients described by Cope. The authors concurred with Cope’s theory that kidney damage resulted from excessive intake of calcium and alkali, which subsequently led to inability to excrete calcium and hypercalcemia.

In 1957, Wenger et al. reviewed a series of 35 patients who had evidence of MAS among 3300 hospitalized patients with ulcers during a 10-year period. Similar to the Cope report, the patients had a good prognosis and fully recovered. No patient had persistent renal failure. The authors concluded that MAS is uncommon and generally reversible.

In 1963, Punsar and Somer reexamined all previously reported cases of MAS and, based on the chronicity of symptoms and prognosis, differentiated 2 forms: Burnett syndrome (chronic) and Cope syndrome (acute). Burnett syndrome is a chronic irreversible condition in which band keratopathy or other metastatic calcification was commonly seen. The most common symptoms in both forms were anorexia, dizziness, headache, confusion, psychosis, and dry mouth. Pruritus and pyuria were common in Burnett syndrome. Preexisting renal disease was observed in up to one-third of cases of Burnett syndrome. Hypercalcemia was present in all cases. Hyposthenuria was common. Urinary calcium excretion was generally normal. Among patients with Burnett syndrome, band keratopathy was seen in approximately 85% and nephrocalcinosis in more than 60%. The hallmark of Cope syndrome was an overall good prognosis, whereas mortality due to chronic renal failure was common in patients with Burnett syndrome. Before the widespread availability of parathyroid hormone (PTH) assays, differentiating between hyperparathyroidism and MAS was difficult and often was based on the clinical response to a diet low in calcium and absorbable alkali or on evidence of osteosclerosis.

**INCIDENCE**

In the first decades after the discovery of MAS, reports on the incidence in patients treated by the Sippy program varied widely, from 2% to 18%. Individual variations in the amount of ingested alkali may provide an explanation for this phenomenon. The mortality rate in the early days of MAS was reported to be 4.4%. In their original study, Wenger et al. found that the incidence of MAS among hospitalized patients with peptic ulcer disease was approximately 1%. After the clinical introduction of nonabsorbable alkali and histamine, blockers, the incidence of MAS decreased substantially. In the 1970s and 1980s, MAS was considered responsible for less than 1% to 2% of hypercalcemia.

In 2006, Beall et al described the “modern version” of MAS. During the past 20 years, a reemergence of MAS has
been noted with different demographics and clinical backgrounds. Calcium carbonate is the primary source of calcium and alkali. The increased use of calcium carbonate in postmenopausal women, patients receiving long-term corticosteroid therapy, and patients with renal failure, as well as the wide availability of nonabsorbable alkali, histamine, blockers, and proton pump inhibitors, has changed the profile of the typical patient with MAS. The male prevalence observed in the original MAS is no longer seen. Hyperphosphatemia is rare, reflecting the less prevalent consumption of large quantities of milk and dairy products and the phosphate-binding properties of calcium carbonate. Because of its resurgence, MAS is now considered the third most common cause of hypercalcemia, after hyperparathyroidism and malignant neoplasms, with a prevalence of 9% to 12% among hospitalized patients with hypercalcemia. Among the subset of patients with severe hypercalcemia (total calcium level >14 mg/dL), MAS is more prevalent than malignant neoplasms. Increased availability of over-the-counter calcium carbonate supplements and greater awareness of osteoporosis among medical professionals and consumers likely contribute to this trend. In a study by Kapsner et al, more than 20% of heart transplant recipients taking calcium carbonate (8-12 g) daily for corticosteroid-induced osteoporosis prevention established the diagnosis. What constitutes “excessive” is unclear but generally indicates at least 4 to 5 g of calcium carbonate daily. However, ingesting large amounts of calcium and absorbable alkali is a prerequisite for development of MAS. Among betel nut chewers, the lime paste (calcium oxide and calcium hydroxide) ingested during betel nut chewing serves as a source of calcium and alkali. The incidence of MAS among betel nut chewers is unknown. Several cases of MAS have also been described in pregnant women.

PATHOGENESIS

Despite extensive clinical experience, scant data are available on the pathogenesis of MAS. Throughout the years, several contributing factors have been proposed, including loss of gastric juice, preexisting renal disease, insufficient chloride intake, hemorrhage, anemia, impaired liver function, and warm weather. Ingestion of excessive quantities of calcium and absorbable alkali is a prerequisite for establishing the diagnosis. What constitutes “excessive” is unclear but generally indicates at least 4 to 5 g of calcium carbonate daily. However, ingesting large amounts of alkali and calcium alone does not result in alkalosis and hypercalcemia, respectively. McGee et al administered 1.3 to 2.0 g of a mixture of calcium carbonate and magnesium oxide hourly from 7 AM to 9 PM for 8 days to 17 individuals with healthy kidneys. No significant changes in serum bicarbonate levels were observed. The authors speculated that hypochloremia and dehydration were key factors in the development of alkalosis. In the first reports of toxicity due to the Sippy program, Hardt and Rivers noted a definite correlation between the incidence of alkalosis and the presence of kidney disease. Subsequent reports confirmed that preexisting renal disease seemed to be a predisposing factor. However, it is widely recognized that MAS can develop without renal impairment. Furthermore, even in patients with impaired renal function, large amounts of absorbable alkali do not lead to alkalosis in most individuals. Some authors found no preexisting kidney disease in most of their patients with MAS. Underlying renal disease does not seem to be a prerequisite but rather a contributing factor in the pathogenesis of MAS.

For hypercalcemia to develop, calcium intake must be excessive, but inability to excrete the excess calcium is also an essential part of the process. Because the skeletal system does not have unlimited calcium buffer capacity, tight regulation of calcium absorption from the small intestine and excretion by the kidneys are paramount to maintain serum calcium levels. Individual variations in the buffering capacity of bone may also have a role in the susceptibility to development of hypercalcemia.

The role of vitamin D and PTH in MAS is unclear. Limited data suggest that 1,25-dihydroxyvitamin D (1,25-OH vitamin D; also known as calcitriol) and PTH levels are suppressed in MAS. However, the extent of suppression varies, and calcitriol levels may remain well within the reference range. Increased intake of calcium results in decreased 25-hydroxylation of vitamin D by the kidneys, which leads to a marked decrease of fractional calcium absorption in the small intestine. Besides this active regulated mechanism, nonsaturable passive diffusion occurs. Individual variability of calcium absorption varies widely. In certain individuals, high urinary calcium excretion indicative of high intestinal absorption persists despite continuous calcium ingestion and suppressed 1,25-OH vitamin D levels. Under normal conditions, renal calcium excretion is a close reflection of calcium absorption. These “hyperabsorbers” readily excrete the excess calcium as long as their excretory capability is unaffected. However, if large quantities of calcium are continuously ingested and the renal excretory capacity is blocked, hypercalcemia may be a predictable result. Failure to fully suppress calcitriol levels may contribute to development of MAS in a subset of individuals with high oral calcium intake. The inability of some individuals to properly suppress 1,25-OH vitamin D levels, despite high calcium intake and absorption from the gut, has been well documented.
Although controversial (as previously discussed), preexistent renal insufficiency has been implicated in the pathogenesis of MAS. Medications that interfere with calcium excretion have also been considered risk factors. Thiazide decrease calcium excretion by inhibiting the thiazide-sensitive sodium chloride cotransporter and promote intravascular depletion and alkalora.48–50 It is well recognized that alkalosis decreases calcium excretion by increasing its tubular reabsorption.51,52 The mechanism seems to be PTH independent.53 However, hypercalcemia impairs the kidneys’ ability to excrete excess bicarbonate, possibly closing a vicious cycle that in susceptible individuals may lead to severe hypercalcemia and renal failure. The increased serum calcium level causes afferent arteriole constriction and reduction in the glomerular filtration rate (GFR).53,54 Also, hypercalcemia has a well-known natriuretic and diuretic effect, presumably by activating the calcium-sensing receptor, and leads to intravascular depletion.55,56 Aspiration of gastric content to control acidity in the original Sippy regimen can further exacerbate intravascular depletion, as does hypercalcemia-induced renal hypothenuria.56,57 The resulting GFR reduction further limits excretion of bicarbonate and calcium. The increasing serum calcium level propagates the toxic effects of calcium on the kidneys. Long-term exposure to high calcium levels can result in nephrocalcinosis, tubular necrosis, and other structural changes.58 An alkalotic environment is known to facilitate calcium precipitation.59,60 Aging results in a decreased capacity to handle excess calcium, probably because of decreased renal function and down-regulation of the calcium-sensing receptor in chronic renal disease, and may predispose patients to developing hypercalcemia.60,61 Hypokalemia due to gastric suctioning and vomiting may have an additional renal deleterious effect. The combination of calcium and absorbable alkali seems to be necessary for the development of MAS. Absorbable alkali alone does not produce alkalosis. Even large administered amounts of sodium bicarbonate are readily excreted by the kidneys without persistent alkalemia. This has been well documented in humans and animals.61–63

The PTH level should be depressed by the high serum calcium level in patients with MAS. However, data are limited. Occasional reports showed inappropriately elevated PTH levels.33,64 In at least some of those cases, use of C-terminal assays to measure PTH levels in the setting of renal failure could explain the high levels. Decreasing serum calcium levels have been contemplated as the cause of high PTH levels even if the patient is still hypercalcemic.64 Data to support this theory are lacking, but a similar phenomenon has been observed in hypercalcemia seen in the polyuric phase of rhabdomyolysis.65 Intact PTH measurements generally reveal appropriately suppressed hormone levels,2 but available data are scant. The low serum PTH level further contributes to alkalora by increasing urinary resorption of bicarbonate.66,67 Temporary hypocalemia is not unusual after treatment of MAS and likely reflects a suppressed PTH level.2

**HISTOLOGIC FINDINGS**

The available data on pathologic changes in the kidneys determined by biopsy and autopsy are limited. Burnett et al7 described nephrocalcinosis during the single autopsy performed in their series. Other autopsy reports described partial to complete glomerular hyalinization, thickening of the Bowman capsule, tubular atrophy, vascular changes, and diffuse lymphocytic infiltration.68–70 Extensive calcification of convoluted renal tubular cells and the tubular lamina was described as a striking feature.68 Scholz and Keating10 reported a case of focal calcification in the renal tubules that was apparent on a kidney biopsy specimen from a patient with MAS. Randall et al71 reported findings on kidney biopsy specimens from 2 patients. Tubular epithelium degeneration and granular (presumably calcium laden) material in and around the collecting tubules, as well as hyalinization of several glomeruli and thickening of the basement membrane, were described. In 1976, Junor and Catto72 reported a series of 3 cases in which kidney biopsy specimens showed focal calcium deposition within and adjacent to the renal tubules (Figure). Some correlation was found between the amount of calcium deposition and renal outcome. The 2 patients with persistent renal impairment had more prominent calcium deposition, as well as interstitial fibrosis, areas of inflammatory changes, and periglomerular fibrosis. The authors concluded that prognosis depends on the severity of the histologic changes apparent on the biopsy specimens and...
noted that calcium deposition in the kidneys is not usually seen radiographically.

**DIAGNOSIS AND CLINICAL COURSE**

The diagnosis of MAS requires a history of excessive calcium and absorbable alkali ingestion and findings of hypercalcemia, metabolic alkalosis, and variable degrees of renal impairment. The symptoms may develop within several days to several weeks and months after the start of therapy with absorbable alkali and calcium. Three forms of MAS have been described: acute, subacute (Cope syndrome), and chronic (Burnett syndrome). Because overlap among the 3 forms is substantial, they should be considered a continuum. The first symptoms may occur within a few days. Nausea, vomiting, anorexia, distaste for milk, headache, dizziness, vertigo, apathy, and confusion are early signs of toxemia. Muscle aches, psychosis, tremor, polyuria, polydipsia, pruritus, and abnormal calcifications are typical of the chronic phase. Ocular calcification is a classic physical sign that consists of keratopathy and calcium deposits in the conjunctiva. Keratopathy can be mistaken for arcus senilis. On closer inspection, individual minute corneal calcifications can generally be distinguished. The nasal and temporal areas of the circle contain the greatest concentration of calcium. Renal calcinosis is not uncommon (see "Histologic Findings" section). Other less common sites of metastatic calcification have been described, including periarticular tissue, subcutaneous tissue, central nervous system, liver, adrenal, bone, and lungs. A case was described in 1993 in which discovery of bilateral breast calcifications in a patient led to the diagnosis of MAS.

Withdrawal of the offending agents generally leads to quick resolution of the symptoms, except for renal failure, which invariably improves but does not always resolve completely. Keratopathy and conjunctival calcium deposits can be reversible. Hypercalcemia is always present and may be severe. The combination of an elevated serum bicarbonate level and alkalotic pH in the setting of renal failure always places MAS high on the differential diagnosis. A low to normal phosphate level is usually seen in the modern form of MAS as opposed to hyperphosphatemia, which was the norm in the classic syndrome. Levels of 1,25-OH vitamin D and intact PTH are generally suppressed. In less typical cases of MAS, the PTH level may need to be measured to exclude primary hyperparathyroidism. Conversely, misdiagnosing MAS as primary hyperparathyroidism was common in the past and likely still happens today. In a study by Beall and Scofield, approximately 10% of patients with MAS underwent unnecessary parathyroid exploration. Obtaining accurate medication and diet histories is paramount to establishing the correct diagnosis. Unusual sources of calcium, such as cheese, have been reported occasionally, especially in patients with pica or bulimia. Evidence of resorptive bone disease and renal stones, as well as failure to respond to withdrawal of calcium and alkali, strongly suggests hyperparathyroidism or some other etiology. However, hypercalcemia in advanced cases of MAS may be slow to resolve. As previously mentioned, PTH levels have been occasionally elevated in patients with MAS, and coexistence of hyperparathyroidism and MAS may need to be considered.

Supportive therapy and hydration after withdrawal of the offending agent are generally sufficient treatment in most cases. Recovery from the acute form usually occurs within 1 or 2 days. With the chronic form, symptomatic improvement is a slower process. In refractory cases, hemodialysis may occasionally be necessary. Furosemide may be used to enhance calciuresis. Administering bisphosphonates to patients with MAS has been reported, but no data are available to support the theory that bisphosphonates alter outcome. Hypercalcemia generally resolves within several days, although some evidence suggests that serum calcium levels can be elevated up to 6 months. Temporary hypocalcemia, which can be severe and symptomatic, is not unusual and may require replacement therapy. Slow recovery of the serum PTH level is likely responsible for this phenomenon. In some cases, the PTH level has been noted to increase by more than 1 order of magnitude as the serum calcium level decreases below physiologic levels.

**CONCLUSION**

The resurgence of MAS in the current era is a result of increased osteoporosis awareness and routine use of calcium supplements for prevention. The public needs to be educated about calcium supplementation and the potential adverse effects if the recommended dosage is exceeded. Daily elemental calcium intake of no more than 2 g is considered safe. However, even doses lower than 2 g daily may result in MAS if additional predisposing factors are present. Muldowney and Mazbar described a patient with bulimia who developed MAS by taking about 1.7 g of calcium daily. Reducing daily calcium intake or close monitoring may be prudent in patients taking thiazides, patients who have preexisting renal failure, or those who experience concurrent vomiting (bulimia or hyperemesis of pregnancy). Patients with bulimia seem to be particularly vulnerable because of the frequent combination of vomiting, diuretic use, and deviant eating habits. In these susceptible patient groups, supplementing calcium in a form that contains no absorbable alkali is probably a safer choice.
MILK-ALKALI SYNDROME

The exact pathomechanism of MAS remains uncertain, but a unique interplay between hypercalcemia and alkalois in the kidneys seems to lead to a self-reinforcing cycle, resulting in the clinical picture of MAS. Treatment is supportive and involves hydration and withdrawal of the offending agents. Physicians and the public need to be aware of the potential adverse effects of ingesting excessive amounts of calcium carbonate.

CASE OUTCOME

Our patient’s hypercalcemia resolved within 72 hours. Transiently, she had mild hypocalcemia, with a total calcium level of 6.9 mg/dL. As expected, her intact PTH level was suppressed at 10 pg/mL (reference range, 10-65 pg/mL). Her 25-OH cholecalciferol level was normal at 44 ng/mL (reference range, 20-100 ng/mL), and her 25-OH ergocalciferol level was undetectable, ruling out vitamin D toxic effects. After 1 week, the patient’s creatinine level stabilized at 1.4 mg/dL and remained in that range at follow-up for a few weeks later. The estimated GFR was 47 mL/min, consistent with persistent mild renal insufficiency. The patient was counseled on the nature of her condition, and she was advised to avoid taking excessive amounts of calcium. In the following months her serum creatinine normalized, and she remained asymptomatic.

REFERENCES

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