Clinical Investigation

Low Intracellular Magnesium in Patients With Acute Pancreatitis and Hypocalcemia

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To determine the role of magnesium deficiency in the pathogenesis of hypocalcemia in acute pancreatitis, we measured magnesium levels in serum and in peripheral blood mononuclear cells in 29 patients with acute pancreatitis, 14 of whom had hypocalcemia and 15 of whom had normal calcium levels. Only six patients had overt hypomagnesemia (serum magnesium < 0.70 mmol per liter [1.7 mg per dl]). The mean serum magnesium concentration in hypocalcemic patients was not significantly lower than in normocalcemic patients, but the mononuclear cell magnesium content in hypocalcemic patients with pancreatitis was significantly lower than in normocalcemic patients with pancreatitis (P < .01). The serum magnesium level did not correlate with that of serum calcium or the mononuclear cell magnesium content, but the latter did significantly correlate with the serum calcium concentration (r = .81, P < .001). Most patients with hypocalcemia had a low intracellular magnesium content. Three normomagnesemic, hypocalcemic patients with alcoholic pancreatitis also underwent low-dose parenteral magnesium tolerance testing and showed increased retention of the magnesium load. We conclude that patients with acute pancreatitis and hypocalcemia commonly have magnesium deficiency despite normal serum magnesium concentrations. Magnesium deficiency may play a significant role in the pathogenesis of hypocalcemia in patients with acute pancreatitis.

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Hypocalcemia has been reported to occur in 10% to 80% of patients with acute pancreatitis and is considered a poor prognostic sign.[1-9] The origin of hypocalcemia in acute pancreatitis remains unclear. Magnesium (Mg) deficiency is a known cause of hypocalcemia,[10-15] and patients with acute pancreatitis often have risk factors for magnesium deficiency such as alcohol abuse or diabetes mellitus.[16-18] The role of Mg deficiency in the pathogenesis of hypocalcemia in patients with pancreatitis has been largely unexplored, however. Although a few studies have reported hypomagnesemia in some patients with acute pancreatitis,[2,3,7,8] serum Mg concentrations are usually normal. Magnesium is primarily an intracellular cation, however, and thus serum Mg concentrations may not adequately reflect tissue Mg stores.[16] Low intracellular Mg content is not an uncommon finding in patients with normal serum Mg concentrations.[15-20] We have reported hypocalcemia in normomagnesemic patients with low mononuclear cell Mg, where the hypocalcemia resolved with magnesium therapy.[15] Magnesium deficiency in normomagnesemic patients can also be shown indirectly by a finding of increased retention of a parenterally administered magnesium load.[17-21] In this study, we sought to determine if patients with acute pancreatitis and hypocalcemia have depleted tissue Mg stores that may play a role in the pathogenesis of the hypocalcemia.

Study Design

Patients

We studied 29 patients admitted to the general internal medicine service of the Los Angeles County-University of Southern California Medical Center with the diagnosis of acute pancreatitis. Informed consent was obtained. Patients with an admission clinical diagnosis of acute pancreatitis were selected within 4 to 24 hours of admission based on their availability to have blood drawn on the days that were chosen for study by the investigators. Patients with serum creatinine concentrations of greater than 132.6 μmol per liter (1.5 mg per dl), intensive care unit patients, hemodynamically unstable patients, and patients who had already received magnesium therapy were excluded. In 19 patients pancreatitis had developed as a result of alcohol abuse, and 10 had pancreatitis due to biliary tract disease. Two of the patients with biliary tract disease also had diabetes mellitus. No patient had pancreatic ascites. Of the 29 patients, 14 had hypocalcemia and 15 had normocalcemia (hypocalcemia was defined as a corrected serum calcium concentration of less than 2.12 mmol per liter [8.5 mg per dl]; serum calcium was corrected 0.2 mmol per liter (0.8 mg per dl) for every 1 gram per dl deviation of serum albumin from the mean normal serum albumin level of 40 grams per liter [4 grams per dl]).

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ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
Mg = magnesium
PTH = parathyroid hormone

Protocol

Fasting morning blood specimens were drawn on all patients to measure serum Mg, calcium, albumin, creatinine, and mononuclear cell Mg content. To further assess for the presence of magnesium deficiency, three normomagnesemic, hypocalcemic patients who agreed to further study after informed consent was obtained underwent low-dose parenteral Mg tolerance testing at the Clinical Research Center, as previously described.[15,21] The percentage of Mg retained was calculated using the following formula:

$$\% \text{ Mg retained} = \left[1 - \frac{\text{Postinfusion urine Mg} - (\text{preinfusion urine Mg/Cr} \times \text{postinfusion urine Cr})}{\text{total elemental Mg infused}}\right] \times 100,$$

in which Cr is the creatinine concentration.

After our initial assessment of the patients on admission, no further interventions were made in their care, and the patients were managed by their primary physicians as they judged to be appropriate.

Methods

Serum and urine magnesium levels were measured by atomic absorption spectrophotometry. Serum calcium, creatinine, and albumin concentrations were measured by an AutoAnalyzer. Mononuclear cell Mg content was measured using methods previously described.[15,22]

Statistics

Biostatistical analysis was provided by the University of Southern California Clinfo Vax computer. The Wilcoxon nonpaired ranked sum test was used to compare the differences between groups, as the data were not normally distributed.

Results

Table 1 shows the serum magnesium, serum calcium, and mononuclear cell Mg content in the hypocalcemic patients and the normocalcemic patients on admission evaluation.

The mean serum Mg concentration in hypocalcemic patients was not significantly lower than in normocalcemic patients. Only 6 of the 29 patients studied (2 hypocalcemic and 4 normocalcemic) had low (<0.70 mmol per liter [1.7 mg per dl]) serum Mg concentrations. Serum Mg levels did not significantly correlate with serum calcium concentration.

The intracellular Mg content was lower than in normal laboratory controls in most patients in both the hypocalcemic and normocalcemic groups (Figure 1). In addition, the mononuclear cell Mg content was significantly lower in hypocalcemic patients than in normocalcemic patients (0.89 ± 0.05 and 1.08 ± 0.03 μg magnesium per mg protein, respectively, $P < .01$), and the mononuclear cell Mg content correlated with the serum calcium concentration ($r = .81$, $P < .001$). Of note is that 14 of the 15 hypocalcemic patients (93%) had a low intracellular magnesium content (Figure 1). The one who did not had pancreatitis due to biliary tract disease and no known risk factors for magnesium deficiency. Patients with alcoholic pancreatitis had a significantly lower mononuclear cell Mg content than patients with biliary pancreatitis (0.94 ± 0.03 and 1.07 ± 0.07 μg magnesium per mg protein, respectively [$P < .05$]).

TABLE 1.—*Serum Magnesium (Mg), Serum Calcium, and Mononuclear Cell Mg Content in Hypocalcemic and Normocalcemic Patients With Acute Pancreatitis*

Patient Characteristic	Serum Mg, mmol/liter (mg/dl)	Mononuclear Cell Mg, μg/mg protein	Serum Calcium, mmol/liter (mg/dl)
Hypocalcemic, n=14 . .	0.74±0.02 (1.81±0.06)*	0.89±0.05†	1.94±0.03 (7.76±0.12)†
Normocalcemic, n=15 .	0.76±0.04 (1.85±0.09)	1.08±0.03	2.23±0.01 (8.92±0.06)
Normal range	0.70–0.86 (1.7-2.1)	1.11-1.35‡	2.12-2.57 (8.5-10.3)

*Mean ± standard error of the mean.
†$P < .01$ compared with normocalcemic patients.
‡Normal laboratory controls (Ryzen et al[15] and Ryzen et al[20]).

Table 2 shows the data on the three hypocalcemic, normomagnesemic patients who underwent parenteral magnesium tolerance testing. Retention of the magnesium load given was elevated in all three patients.

We attempted to evaluate the hospital course of the hypocalcemic patients we studied on admission. Unfortunately, more than half were lost to follow-up before their hypocalcemia resolved—two signed out of the hospital against medical advice, two were transferred to another facility, and four were discharged before the hypocalcemia resolved. Of the remaining six hypocalcemic patients, some received magnesium supplements from their primary physicians and some did not; some began eating early in the course of their hos-

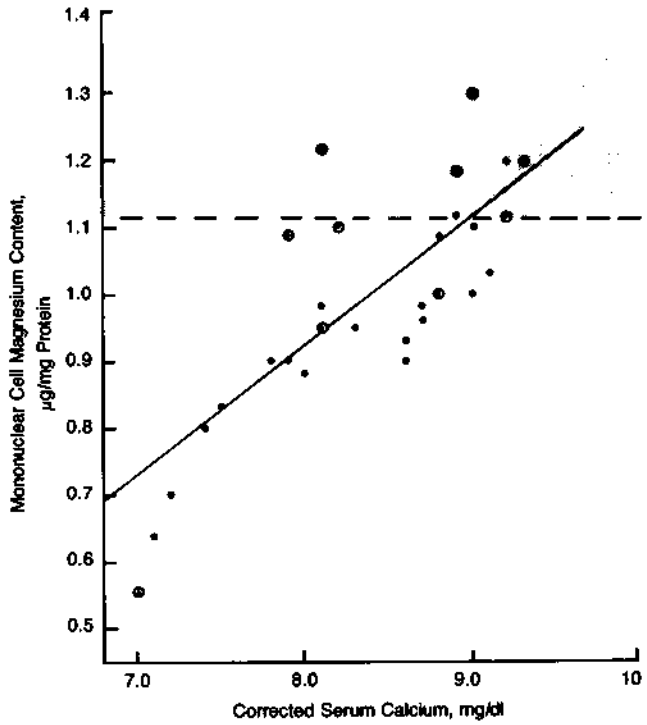

Figure 1.—The graph shows a correlation of serum calcium concentration (in milligrams per deciliter) with mononuclear cell magnesium content (micrograms per milligram of protein; $r = .81$, $P < .001$). The filled circles indicate patients with alcoholic pancreatitis, and the open circles with dots are patients with biliary pancreatitis. The shaded area represents the normal range for mononuclear cell magnesium content (mean ± standard deviation).

TABLE 2.—*Patients Who Underwent Parenteral Magnesium (Mg) Tolerance Testing*

Patient	Serum Mg, mmol/liter (mg/dl)	Serum Calcium, mmol/liter (mg/dl)	Mononuclear Cell Mg, μg/mg protein	Retention at 24 h, %
1	0.74 (1.8)	1.77 (7.1)	0.64	66
2	0.78 (1.9)	1.85 (7.4)	0.80	55
3	0.78 (1.9)	2.02 (8.1)	0.98	45
Normal range	0.70-0.86 (1.7-2.1)	2.12-2.57 (8.5-10.3)	1.11-1.35*	<25†

*Normal laboratory controls (Ryzen et al[15] and Ryzen et al[20]).
†Normal subjects (Ryzen et al[21]).

pital stay, and others remained fasting for prolonged periods of time; some received vigorous intravenous hydration and some did not. No patient died. Although hypocalcemia eventually resolved in all six patients, the number of patients in each subgroup was too small for meaningful statistical analyses.

Discussion

In a number of studies an attempt has been made to elucidate the cause of the hypocalcemia that is seen in patients with acute pancreatitis.[1-8,23-26] Hypoalbuminemia accounts for the presence of hypocalcemia in some but not all patients.[4] Renal failure may be responsible for hypocalcemia in a minority of patients with acute pancreatitis.[8] Edmondson and co-workers originally proposed that hypocalcemia in pancreatitis occurs as a result of saponification of calcium in and around the necrotic pancreas.[3] Although this explanation may apply to a few patients such as those with massive pancreatic ascites,[26] the prolonged duration and intensity of hypocalcemia in patients without ascites suggest a primary disturbance in calcium metabolism. Glucagon release from the inflamed pancreas with the subsequent stimulation of calcitonin secretion has been proposed as a mechanism to explain the hypocalcemia, but glucagon and calcitonin concentrations have not been consistently elevated in such patients.[24,25] Shifts of calcium from extracellular to intracellular spaces have also been reported in experimental pancreatitis in animals.[27]

Impaired parathyroid hormone (PTH) function or PTH end-organ resistance, or both, may contribute to hypocalcemia in acute pancreatitis. Immunoreactive PTH concentrations in acute pancreatitis are variable; some patients have low PTH concentrations or concentrations of PTH that are inappropriately low for the degree of hypocalcemia, and others show elevated PTH concentrations with impaired generation of adenosine 3′:5′-cyclic phosphate (cyclic AMP).[1,2,5-7] End-organ resistance to PTH action has been hypothesized to be due to the hypovolemia that patients with pancreatitis usually manifest, whereby impaired perfusion of bone may result in bony infarcts and impaired mobilization of calcium from bone. Indeed, hypocalcemia is less likely to occur when hypovolemia is absent.[1,23]

Alternatively, magnesium deficiency is a known cause of both impaired PTH release and end-organ resistance to PTH,[10-14] but the role of magnesium deficiency in the pathogenesis of the hypocalcemia of pancreatitis is unclear. Overt hypomagnesemia has been reported in about 25% of patients with pancreatitis,[8] similar to what we found in this study, where 21% of patients had hypomagnesemia. In one study, hypocalcemia was found to be more common and more profound in patients with pancreatitis who had hypomagnesemia; a significant correlation between serum calcium and serum magnesium levels was also noted.[8] We did not find a correlation between serum calcium and serum magnesium levels in this study, but we did find a significant correlation between serum calcium levels and intracellular Mg content (Figure 1). Our study is the first report of depleted intracellular Mg content in hypocalcemic patients with acute pancreatitis. All but one of our hypocalcemic patients with pancreatitis had a low intracellular Mg content. The finding of increased retention of a parenterally administered magnesium load in the three hypocalcemic, normomagnesemic patients with low mononuclear cell Mg content who were studied provides additional evidence for Mg deficiency. Subjects who are not Mg deficient would be expected to retain less than 25% of the magnesium load given.[21]

Further evidence suggesting a possible role of magnesium deficiency in the pathogenesis of the hypocalcemia of pancreatitis is the finding that hypocalcemia is more common and persists longer in patients with alcoholic pancreatitis than in those with pancreatitis of other causes.[28] Our finding that serum calcium was lower in patients with alcoholic pancreatitis than in those with biliary pancreatitis thus supports the hypothesis that magnesium deficiency predisposes patients with acute pancreatitis to the development of hypocalcemia. It is well known that persons with alcoholism are commonly Mg deficient even if serum Mg concentrations are normal.[15-21] Patients with acute pancreatitis are usually dehydrated, and dehydration can result in falsely normal or even increased serum Mg concentrations despite depleted intracellular Mg stores.[19] It is thus not surprising that only a few patients with pancreatitis were hypomagnesemic, but most had depleted intracellular Mg. These cellular Mg deficits may have predisposed some patients to the development of hypocalcemia. Of interest was the finding that the only patient with hypocalcemia who did not have depressed intracellular Mg content was a patient with pancreatitis of a biliary cause (Figure 1). This patient also had no other risk factors for magnesium deficiency. In this patient, factors other than a low tissue Mg content were probably responsible for the hypocalcemia. The two other patients with biliary pancreatitis who did have low mononuclear cell Mg content were diabetic, and diabetes mellitus is another known risk factor for magnesium deficiency.[16]

Not all patients with low intracellular Mg were hypocalcemic. Malregulation of the adenylate cyclase-cyclic AMP system in the parathyroid glands and PTH end organs is thought to be the cause of the hypocalcemia of magnesium deficiency.[29] Concentrations of PTH in Mg-deficient patients can be low, normal, or high.[10-14] We did not measure PTH levels or end-organ responsiveness to PTH in our subjects. Previous reports of PTH concentrations in patients with pancreatitis and hypocalcemia have also shown PTH concentrations to be low, normal, or high,[1,7] but the intracellular Mg content was not measured in those patients. In this study we also did not measure ionized calcium concentrations, choosing instead to adjust the total measured serum calcium concentrations for the serum albumin. We deliberately excluded intensive care unit patients, as in such patients the correlation of corrected serum calcium concentrations with ionized serum calcium concentrations is not good.[30] It is still possible, however, that our classification of particular pa-

tients into hypocalcemic and normocalcemic groups might have been different had we measured ionized calcium levels. Thus, perhaps some of the patients with low intracellular Mg content and normal "corrected" serum calcium concentrations might really have low ionized calcium concentrations, and vice versa.

Finally, even though our patients had evidence of intracellular magnesium depletion, it is possible that this was unrelated to their hypocalcemia and that an as-yet-unidentified factor is primarily responsible for the hypocalcemia of acute pancreatitis. Although our data clearly do not prove definitively that the depleted tissue magnesium content was responsible for or even contributed to the hypocalcemia in these patients, our finding that almost all patients with acute pancreatitis and hypocalcemia have depleted intracellular Mg content should be borne in mind when deciding on the proper management of patients with acute pancreatitis and hypocalcemia. Specifically, our data suggest that Mg repletion therapy should be considered even in a normomagnesemic patient with pancreatitis who has hypocalcemia, especially if that person has risk factors for magnesium deficiency such as alcoholism or diabetes mellitus and renal function is normal. Hypocalcemia is considered a poor prognostic sign in patients with acute pancreatitis[9] and is thought to reflect the severity of the disease. What is not clear is if the hypocalcemia itself contributes to the morbidity. Hypocalcemia can contribute to hypotension in critically ill patients[31] and is a poor prognostic sign in critically ill patients in general.[32] Moreover, if hypocalcemia is a reflection of magnesium deficiency, it is thus possible that other clinical manifestations of magnesium deficiency such as cardiac arrhythmias,[33] respiratory muscle weakness,[34] and refractory hypokalemia[35] may contribute to patients' morbidity. Indeed, clinical complications known to be associated with magnesium deficiency such as cardiac arrhythmias[36] and refractory hypokalemia[37] have been seen in patients with normal serum Mg levels but depleted tissue Mg content, with clinical improvement with magnesium therapy. In this study, we unfortunately could not assess adequately the role of Mg deficiency in determining the prognosis, as only patients without severe disease were selected for study, and they received variable therapy by their primary physicians after our initial evaluation of them on admission.

In Mg-deficient hypocalcemia, resistance to calcium and vitamin D supplementation is seen, and Mg supplementation is recommended for optimal management.[16] We have previously reported treatment of normomagnesemic patients with depleted intracellular Mg stores and unexplained hypocalcemia with Mg supplementation, with resolution of the hypocalcemia.[15] We have found that 32 to 64 mEq of elemental Mg as magnesium sulfate can be added to a patient's intravenous fluids each day as a continuous infusion without producing hypermagnesemia, provided renal function is adequate. This can be administered for three to five days to help replete tissue Mg stores and correct hypocalcemia, or at least until the patient is eating normally and not receiving medications such as intravenous saline or aminoglycosides that can result in urinary Mg losses.[16] Magnesium homeostasis and clinical disorders of Mg deficiency are reviewed in detail elsewhere.[16,38]

In summary, we have found depletion of intracellular Mg in most patients with hypocalcemia and pancreatitis. Further studies are needed to determine the clinical significance of this finding and the potential benefits of Mg supplementation in such patients.

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