Clinical Investigation

Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients

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Hypomagnesemia can cause hypocalcemia. Because less than 1% of the total body magnesium (Mg) is in extracellular fluids, however, patients may be Mg-deficient despite normal serum Mg concentrations. To determine if hypocalcemia can be seen in patients who have normal serum Mg concentrations but low intracellular Mg, we studied the serum and mononuclear cell Mg contents in 82 alcoholic subjects, 30 of whom had hypocalcemia that could not be explained by other known causes of hypocalcemia. The mononuclear cell Mg content in both hypomagnesemic and normomagnesemic patients with and without hypocalcemia was significantly lower than in normal controls. The serum Mg level did not correlate with the mononuclear cell Mg or serum calcium level, but hypocalcemic patients had a significantly lower mononuclear cell content than normocalcemic patients. Six patients underwent parenteral Mg tolerance testing as an additional measure of Mg deficiency and had increased Mg retention. The serum calcium concentration returned to normal in hypocalcemic patients who were given magnesium intravenously.

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Hypomagnesemia is a common clinical finding.[1,2] Causes of magnesium (Mg) deficiency include the malabsorption syndromes, diarrhea, diabetes mellitus, alcohol abuse, hypophosphatemia and therapy with loop diuretics, aminoglycosides or a saline solution given intravenously. Many patients with hypokalemia, hypophosphatemia and hyponatremia also have hypomagnesemia.[3] Hypomagnesemia may result in hypocalcemia due to impaired parathyroid hormone release or skeletal and renal resistance to parathyroid hormone action.[4-8]

Low serum Mg concentrations usually reflect Mg depletion in tissues.[9,10] But tissue Mg deficiency can be seen even in the presence of normal serum Mg concentrations.[9,11-16] The clinical significance of normomagnesemic Mg deficiency is unclear, but some studies have described clinical complications known to be associated with Mg deficiency in patients with normal serum Mg concentrations. Mg supplementation in such cases resolved clinical problems such as hypocalcemia,[6,17] cardiac arrhythmias[14] and refractory hypokalemia.[16]

Although a single ideal test for assessing Mg deficiency has not yet been found,[18] one study suggested that bone Mg is the best measure of body Mg stores.[10] Measuring bone Mg is not practical clinically, however. Magnesium can also be measured in peripheral blood mononuclear cells, which are more readily accessible than bone. The mononuclear cell Mg content has been reported to be reduced in patients with reduced bone Mg content[19] and in normomagnesemic patients at risk for Mg deficiency.[13-15]

We have observed normomagnesemic patients at risk for Mg deficiency who manifest hypocalcemia that could not be explained by known causes of hypocalcemia such as hypoalbuminemia, renal failure and acute pancreatitis. To help assess if patients with "unexplained" hypocalcemia are Mg deficient despite normal serum Mg concentrations, we determined their mononuclear cell Mg content.

Study Design and Methods

Patients and Controls

Alcohol abuse is a known risk factor for Mg deficiency.[9,11,12,19,20] We therefore studied alcoholic patients admitted to the general internal medicine service of the Los Angeles County-University of Southern California Medical Center. Admitted patients' charts were screened for alcoholism an average of two mornings per week over an 18-month period. Patients with renal failure (serum creatinine > 1.5 mg per dl), acute pancreatitis, hypoparathyroidism and other known causes of hypocalcemia other than Mg deficiency were excluded (Table 1).[21] Patients who had already received Mg therapy were also excluded from study. A total of 82 patients were studied. Admission diagnoses included alcohol intoxication or withdrawal syndrome, pneumonia, cellulitis, gastritis, alcoholic liver disease, placement problems and combinations of the above. None of the patients had symptoms that could be attributed exclusively to Mg deficiency or to hypocalcemia. All but five of the patients, however, had nonspecific symptoms such as weakness, seizures and cardiac arrhythmias in which Mg deficiency or hypocalcemia could not be excluded as contributing factors.

Normal healthy volunteers (medical students and em-

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ABBREVIATIONS USED IN TEXT
Mg = magnesium
PBS = phosphate-buffered saline

ployees of the clinical research center) served as a control population. In our laboratory, we have previously not found any relation of mononuclear cell Mg content to age or sex in healthy subjects and therefore did not age- and sex-match our volunteer control subjects.

Protocol

Fasting morning blood specimens were drawn on all patients within 24 hours of admission to measure serum Mg, calcium, albumin and creatinine concentrations and the mononuclear cell Mg content. To further assess the presence of Mg deficiency, after informed consent was obtained, six patients also underwent low-dose parenteral Mg tolerance testing at the Clinical Research Center, as previously described.[22] A baseline spot urine test was done for Mg and creatinine. Then 0.2 mEq (2.4 mg) elemental Mg per kg lean body weight was infused as a 50% solution of magnesium sulfate in 50 ml dextrose and water over four hours. All urine was collected for 24 hours, starting with the infusion, to measure Mg and creatinine concentration. The percentage of Mg retained was calculated using the following formula:

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

with Cr meaning creatinine content.

A total of 21 hypocalcemic patients (10 with hypomagnesemia, 11 with normomagnesemia) received 32 to 64 mEq elemental Mg per day by constant intravenous infusion for three to five days. Mg tolerance testing was repeated on four of these patients three days after the Mg therapy was completed.

Methods

Serum and urine Mg levels were measured by atomic absorption spectrophotometry. Serum calcium, creatinine and albumin concentrations were measured by an AutoAnalyzer.

The mononuclear cell Mg content was measured using a modification of methods previously described.[13,23] Heparinized blood (10 to 15 ml) was mixed with an equal volume of phosphate-buffered saline (PBS) solution at pH 7.4, containing sodium chloride, 8.1 grams per liter (0.14 mol per liter); dibasic sodium phosphate, 1.22 grams per liter, and sodium biphosphate in water, 0.194 grams per liter. Twenty ml of Ficoll-Hypaque (Pharmacia Fine Chemicals) was then layered below the blood and PBS solution using a 20-gauge spinal needle and the preparation was centrifuged at 400 × g for 35 minutes. The mononuclear cell layer was collected from the Ficoll-Hypaque-plasma interface, washed with 10 ml PBS solution and centrifuged at 600 × g for ten minutes. The supernatant was then discarded and the pellet washed in another 10 ml PBS solution and centrifuged at 600 × g for ten minutes. The wash was repeated and the remaining pellet brought up in 1 ml distilled water and stored at −20°C until time of assay. Before the assay, the cells were thawed and lysed by sonication using a Heat Systems Ultrasonic Sonicator. The lysate was then centrifuged at 1,500 revolutions per minute for ten minutes to remove cellular debris. The Mg content of the lysate was measured by atomic absorption spectrophotometry. Lysate protein was measured by the method of Lowry.[24] In our laboratory, intraassay and interassay variability for lysate Mg content is 5% to 10%.

Statistics

The mean values of two groups were compared using the Wilcoxon non-paired ranked sum test, as the data were not normally distributed.

Results

In all, 36 of the 82 patients had hypomagnesemia (serum Mg < 1.7 mg per dl, mean 1.31 ± 0.04 [mean ± standard error of the mean]) and 46 had normomagnesemia (serum

TABLE 1.—*Causes of Hypocalcemia*

Hypoalbuminemia
Renal failure
Magnesium deficiency
Primary hypoparathyroidism
Pseudohypoparathyroidism
Acute pancreatitis
Massive transfusions with citrated blood
Hypermagnesemia (therapy for eclampsia)
Vitamin D deficiency
Osteoblastic tumor metastases
Hungry bone syndrome
Postthyroidectomy hypocalcemia
Rhabdomyolysis
Hyperphosphatemia

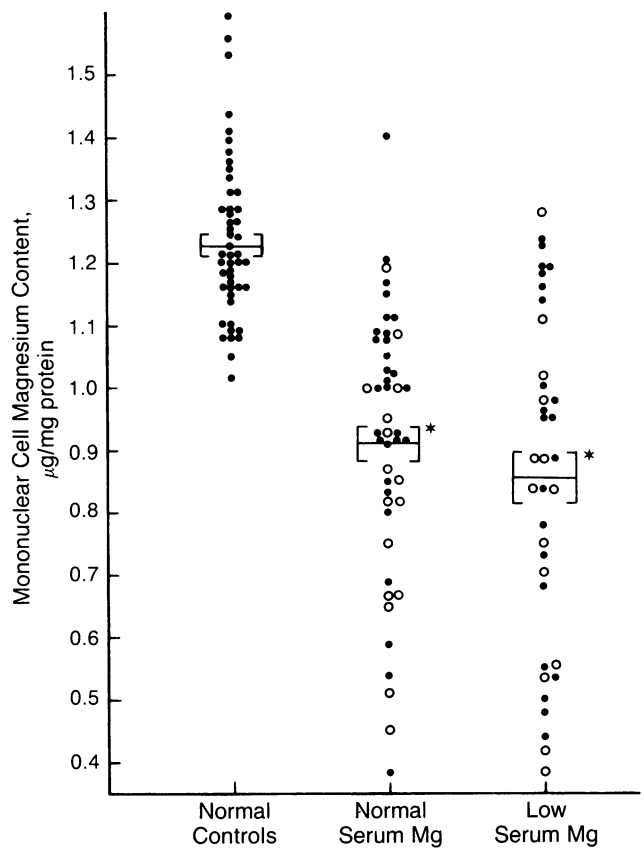

Figure 1.—Mean mononuclear cell magnesium (Mg) content in normal controls and in normomagnesemic and hypomagnesemic patients. ✶$P < .001$ compared with normal controls. Open circles indicate hypocalcemic patients.

TABLE 2.—*Serum Magnesium (Mg) and Calcium Concentrations and Mononuclear Cell Mg Content in Hypomagnesemic and Normomagnesemic Patients*

Patient Features	Serum Mg, mg/dl	Mononuclear Cell Mg, μg/mg	Calcium, mg/dl*
Low serum Mg, low serum calcium (N=14)	1.26±0.1	0.79±0.1†	8.0±0.1 (range 7.2-8.4)
Normal serum Mg, low serum calcium (N=16)	1.98±0.1	0.83±0.1†	8.0±0.1 (range 7.5-8.4)
Low serum Mg, normal serum calcium (N=22)	1.34±0.1	0.89±0.1†	8.8±0.1 (range 8.5-9.1)
Normal serum Mg and normal serum calcium (N=30)	1.94±0.1	0.96±0.1†	9.0±0.1 (range 8.5-10.3)

*Serum calcium has been corrected 0.8 mg per dl for every 1 gram per dl deviation from the mean normal serum albumin level of 4 grams per dl (from Broadus[25]).

†$P<.001$ compared with normal controls, 1.23±0.02 μg Mg per mg protein (mean±standard error of the mean).

Mg ≥ 1.7 mg per dl, mean 2.0±0.04). The mononuclear cell Mg levels in both groups of patients are shown in Figure 1 compared with normal controls. The mononuclear cell Mg content in the hypomagnesemic patients was 0.86±0.04 μg Mg per mg protein, significantly lower than in normal controls (1.23±0.02 μg Mg per mg protein, $P<.001$). Of even greater interest is the finding that the normomagnesemic patients also had a significantly reduced mononuclear cell Mg content compared with normal controls (mean = 0.91±0.03 μg per mg, $P<.001$). The mononuclear cell Mg content in hypomagnesemic patients was not significantly lower than in normomagnesemic patients. The serum Mg concentration did not correlate with the mononuclear cell Mg content.

The serum Mg level also did not correlate with the serum calcium concentration. A total of 14 of the 36 hypomagnesemic patients (39%) and 16 of the 46 normomagnesemic patients (35%) had hypocalcemia (corrected serum calcium <8.5 mg per dl) that could not be explained by hypoalbuminemia or clinical diagnoses known to cause hypocalcemia (Table 1).[21] The mean mononuclear cell Mg content of all hypocalcemic patients was significantly lower than the mononuclear cell Mg content of all normocalcemic patients (0.81 μg Mg per mg protein and 0.93 μg Mg per mg protein, respectively, $P = .018$; Wilcoxon non-paired ranked sum), but only a weak correlation was seen between the mononuclear cell Mg content and serum calcium level ($r = .26$, $P = .02$). Table 2 summarizes the serum Mg, serum calcium and mononuclear cell Mg contents in the different patient groups. Both hypomagnesemic and normomagnesemic hypocalcemic patients had mean mononuclear cell Mg content significantly lower than in normal controls. Of the 16 normomagnesemic, hypocalcemic patients, 14 (88%) had a mononuclear cell Mg content lower than that of the lowest normal control (Figure 1). The mononuclear cell Mg content in the hypomagnesemic, hypocalcemic patients was not significantly lower than in the normomagnesemic, hypocalcemic subjects.

Table 3 shows the mononuclear cell Mg content and retention of Mg in the patients who also underwent parenteral Mg tolerance testing. The serum creatinine concentrations in these patients were normal (0.95±0.04 mg per dl). All patients had significantly greater than normal Mg retention at 24 hours in addition to a low mononuclear cell content (normal Mg retention = 0% to 30%).

Magnesium retention normalized in the four patients who underwent repeat Mg tolerance testing after Mg supplementation. The mononuclear cell Mg content, however, increased in only three of six patients tested after five days of intravenous Mg therapy.

The serum calcium level returned to normal in the 10 hypomagnesemic and 11 normomagnesemic, hypocalcemic patients who received 32 to 64 mEq of elemental Mg per day by continuous intravenous infusion for three to five days after admission. Figure 2 shows the admission and post magnesium therapy corrected serum calcium values in the 11 normomagnesemic, hypocalcemic patients. The serum Mg level remained within the normal range during therapy.

Discussion

Hypomagnesemia is seen in about 10% of all patients admitted to public hospitals[2,26,27] and in as many as 65% of patients in medical intensive care units.[17] The clinical consequences of Mg deficiency other than hypocalcemia can include cardiac arrhythmias,[14,16,28,29] potassium wasting[16,29,30] and neuromuscular abnormalities.[31] These are reviewed elsewhere.[1,32,33]

Less than 1% of the total body Mg is in the extracellular space. Therefore, the serum Mg concentration may not be an accurate measure of intracellular Mg stores. Dehydration, hypoxia, acidosis and tissue breakdown may result in a rise of the serum Mg concentration into the normal or even elevated range despite depleted body stores.[9,34(p361)] Although low serum Mg levels usually indicate a depletion of Mg in tissues,[10] Mg deficiency can be present even with normal serum

TABLE 3.—*Data on Patients Who Underwent Parenteral Magnesium (Mg) Tolerance Testing**

Patient		Serum Mg, mg/dl	Mononuclear Cell Mg, μg/mg	Serum Calcium, mg/dl	Retention at 24 h, %
1	Before	1.9	0.93	8.0	64
	After	2.0	0.94	9.3	0
2	Before	1.8	0.90	8.3	82
	After	1.9	1.19	9.2	5
3	Before	1.9	0.75	8.0	72
	After	1.9	0.79	9.0	..
4	Before	1.9	0.87	8.0	65
	After	2.1	0.90	8.9	..
5	Before	1.1	0.68	9.3	95
	After	2.1	0.90	9.2	10
6	Before	0.9	0.96	9.1	80
	After	1.9	1.21	9.4	0
Normal		1.7-2.1	1.11-1.35 (mean±SD)	8.5-10.3	0-30 (mean±2SD)

SD=standard deviation

*On all patients, values shown are those obtained before and after 3 to 5 days of intravenous administration of magnesium sulfate, 32 to 64 mEq per day.

Mg values. This has been shown using measures of muscle Mg,[9,11,12] Mg balance studies,[9,11,20] parenteral Mg tolerance testing[9,11,20,22] and the mononuclear cell Mg content,[13-15] and is confirmed by our findings in this study.

The incidence and significance of normomagnesemic Mg deficiency have not been well studied because of the practical difficulty of assessing Mg depletion in normomagnesemic patients. Cardiac arrhythmias responsive to Mg therapy have been reported in normomagnesemic patients with low lymphocyte Mg contents.[14] Impaired parathyroid hormone release in a normomagnesemic, hypocalcemic patient has been reported in one patient whose calcium level returned to the normal range with Mg therapy.[6] We have also previously reported the cases of two normomagnesemic, hypocalcemic patients whose calcium levels returned to normal with Mg therapy,[17] but no measures of intracellular Mg were done to confirm the presence of Mg deficiency. About 22% of hypocalcemic patients have been reported to have overt hypomagnesemia.[3] In our study, 87% of the normomagnesemic patients with "unexplained" hypocalcemia had a low mononuclear cell Mg content, and their serum calcium concentrations returned to normal with Mg therapy. Therefore, our data show that patients with unexplained hypocalcemia who are at risk for Mg deficiency have a high probability of being Mg deficient even if the serum Mg concentrations are normal. Our findings also suggest that intracellular Mg deficiency may play a role in the pathogenesis of the hypocalcemia in these patients.

Other evidence for Mg deficiency in these normomagnesemic patients is provided by the data in the subgroup of patients who underwent parenteral Mg tolerance testing as an additional measure of Mg deficiency. In the presence of Mg deficiency, patients retain greater than normal amounts of parenterally administered Mg loads.[11,18,20] The patients in this study also showed increased Mg retention that resolved after Mg therapy, findings that are highly suggestive of Mg depletion.

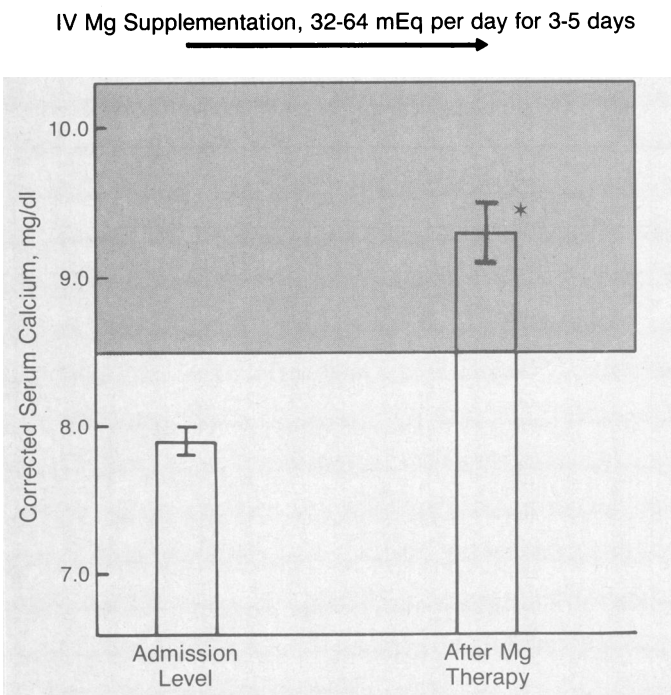

Figure 2.—Corrected serum calcium concentration in normomagnesemic patients with unexplained hypocalcemia before and after magnesium (Mg) supplementation therapy (N = 11). The shaded area indicates the normal range. $*P<.001$ compared with normal controls.

The mononuclear cell Mg content did not consistently increase with Mg therapy despite resolution of the hypocalcemia and normalization of Mg retention. This may reflect the long life span of mononuclear cells,[35(p247)] whose measured Mg content may lag behind acute clinical changes in Mg status and may not reflect rapid changes in the Mg content of the parathyroid glands, bone and kidney. This is further shown by the finding of a normal mononuclear cell Mg content in several hypomagnesemic patients. Thus, measures of the mononuclear cell Mg content alone may not be 100% sensitive or specific in the diagnosis of Mg deficiency in individual patients and may need to be interpreted with caution in patients experiencing rapid Mg losses or in those who have received Mg supplementation previously. The amount of time required to definitively alter the mononuclear cell Mg content after Mg repletion or depletion occurs is unclear.

In our patients, hypocalcemia in normomagnesemic patients was statistically as common as in hypomagnesemic patients (35% and 39%, respectively). Although the degree of hypocalcemia in most of these patients was mild, these findings indicate that in any given patient with Mg deficiency, some factor other than the degree of hypomagnesemia mediates the development of hypocalcemia. Our data show significantly lower mononuclear cell Mg contents in hypocalcemic patients than in normocalcemic patients and suggest that the intracellular Mg content may be more important than the serum Mg concentration in determining in which patients hypocalcemia will develop. Although we also saw a statistically significant correlation between the mononuclear cell Mg content and serum calcium levels, the correlation was weak. Therefore, other factors need to be considered. One study has shown that only a small portion (2%) of intracellular Mg is rapidly exchangeable, the rest being bound in intracellular organelles.[36] Thus, it is possible that free cytoplasmic Mg in the parathyroid glands or in the parathormone end-organ-responsive tissues, bone and kidney, is preferentially lowered in those patients in whom hypocalcemia develops. This may also explain why a rise in the total mononuclear cell Mg content is not seen in some patients after several days of Mg therapy despite resolution of the hypocalcemia and return of parenteral Mg tolerance to normal. Measuring the mononuclear cell Mg content using different techniques[37] might also help distinguish those patients in whom hypocalcemia develops from those in whom it does not.

Other possible causes of hypocalcemia other than Mg deficiency are summarized in Table 1 and discussed elsewhere.[21] Hypoalbuminemia is the most common cause of "false" hypocalcemia. For this reason, in this study we adjusted all measured total serum calcium concentrations for changes in the serum albumin concentration.[25(p1007)] The accuracy of formulas used to correct the serum calcium value for the albumin concentration is controversial,[38-40] and it is possible that measures of ionized calcium would yield different results. Renal failure, the most common cause of true hypocalcemia, was not present in our patients, and most of the other diagnoses listed in Table 1 other than Mg deficiency were also easily excluded clinically in our study population. Some of our patients may have had vitamin D deficiency, as alcoholism and liver disease have been associated with low total 25-hydroxycholecalciferol (vitamin D) concentrations.[41] Hypocalcemia due to vitamin D deficiency, however, would not have rapidly

corrected with Mg therapy and the small amounts of vitamin D that are present in patients' hospital diets. Although parathyroid hormone concentrations were not measured, primary hypoparathyroidism was excluded based on the absence of hyperphosphatemia and the normalization of serum calcium levels with Mg supplementation alone. Immunoreactive parathormone concentrations in Mg-deficient patients have been reported to be low, normal or high.[4-8]

Some authors have reported an association of hypocalcemia with sepsis, stress and critical illness.[42,43] The mechanism for hypocalcemia in such patients is unclear, however, and the status of body Mg stores was not assessed. Thus, although some of our patients suffered from infections and were under stress, we cannot explain their hypocalcemia on that basis alone and must consider what role their intracellular Mg deficiency may have played.

Finally, even though these patients had evidence of intracellular Mg depletion, it is possible that this was unrelated and incidental to their hypocalcemia and an as-yet-unidentified factor may have been responsible for the hypocalcemia. The resolution of the hypocalcemia may have occurred independent of Mg supplementation. Thus, further studies using varying degrees of Mg restriction and supplementation are needed before the resolution of the unexplained hypocalcemia in these patients could be attributed solely to Mg supplementation.

In summary, our data show that intracellular Mg depletion in the presence of normal serum Mg concentrations is a common finding in patients at high risk for Mg deficiency. Intracellular Mg deficiency may play a role in the pathogenesis of unexplained hypocalcemia in these patients, although one cannot yet definitely rule out other factors. Our findings suggest that in patients with normal serum creatinine concentrations who have persistent, unexplained hypocalcemia and who are at risk for Mg deficiency, a course of Mg therapy should be considered even if initial serum Mg concentrations are in the normal range. From 32 to 64 mEq of elemental Mg as a 50% solution of magnesium sulfate can be added to a patient's intravenous fluids each day as a continuous infusion for three to five days. Depending on the patient's oral Mg intake and ongoing medical problems and therapy, lower doses may be equally effective. Mg can also be administered by a controlled infusion pump in small amounts of dextrose and water in those patients who require fluid restriction, or it can be given intramuscularly in divided doses. In the presence of normal renal function, these doses of Mg rarely result in serum Mg concentrations of more than 2.5 mg per dl and are safe and inexpensive. Details of Mg treatment regimens are reviewed elsewhere.[1,32]

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