

Functional Hypoparathyroidism in Hepatic Cirrhosis

L. Cohen, R. Kitzes and A. Laor

Zusammenfassung

Vier unbehandelte Patienten mit durch Biopsie gesicherter, nichtalkoholischer Leberzirrhose wiesen erniedrigte Konzentrationen an Magnesium und ionisiertem Kalzium im Serum auf; andererseits lagen die Gesamtkalzium-, Bikarbonat- und Parathormonspiegel im Normbereich. Magnesiumzufuhr führte zur Normalisierung des Serum-Magnesiums und zu einem 2- bis 5-fachen Anstieg der Parathormonspiegel, die allmählich wieder zur Norm abfielen. Das ionisierte Kalzium stieg in den ersten 48 Stunden nach Magnesiumzufuhr trotz hoher Serum-Parathormon-Spiegel nicht signifikant an und normalisierte sich erst, nachdem die Zufuhr beendet war.

Die beste Erklärung für diese Befunde ist das Vorliegen eines funktionellen Hypoparathyroidismus aufgrund eines Magnesiummangels.

Summary

Four untreated patients with biopsy proven non-alcoholic hepatic cirrhosis presented with low serum magnesium and ionized calcium concentrations but normal serum total calcium, bicarbonate and parathormone levels. Magnesium replacement led to normalization of the serum magnesium and to a 2–5 fold rise in parathormone levels which gradually fell back to normal. Serum ionized calcium failed to rise significantly in the first 48h of magnesium repletion despite high serum parathormone levels and normalized only with its termination.

Functional hypoparathyroidism secondary to magnesium deficiency seems to be the best explanation for these findings.

Department of Medicine B and the Clinical Pharmacology Unit, Lady Davis Carmel Hospital, Haifa, Israel

Résumé

Chez quatre patients non traités, atteints d'une cirrhose du foie que la biopsie avait révélé ne pas être d'origine éthylique, les concentrations sériques de magnésium et de calcium ionisé étaient basses, mais celles de calcium total, de bicarbonates et de parathormone étaient normales. L'administration de magnésium a normalisé la magnésémie et a multiplié par 2 à 5 les taux de parathormone, qui sont ensuite revenus à la normale. Malgré les taux élevés d'hormone parathyroïdienne, les concentrations sériques de calcium ionisé n'ont pas augmenté de façon significative au cours de 48 premières heures de la réplétion magnésienne et ne se sont normalisées qu'à la fin de celle-ci. Une hypoparathyroïdie secondaire à la carence en magnésium semble être la meilleure explication possible de ce phénomène.

Introduction

Hypomagnesemia, magnesium < 1.2 mEq/L, is present in 23 % of patients with hypocalcemia, calcium corrected for hypoalbuminemia < 8.6 mg/dl. [22, 23]. Evidence has been presented that a magnesium deficiency state exists in hepatic cirrhosis [6]. The following are four cases with non-alcoholic hepatic cirrhosis with decreased serum magnesium and ionized calcium concentrations but normal serum total calcium and parathormone levels. Magnesium repletion normalized both serum magnesium and ionized calcium concentrations.

Patients and Methods

Eighteen patients with biopsy proven non-alcoholic hepatic cirrhosis were screened for serum total calcium, ionized calcium and magnesium concentrations. In four untreated patients, decreased serum magnesium and ionized calcium but normal serum total calcium concentrations were found. Parathormone was assayed and found to be within the normal range. Magnesium replenishment by administering 1mEq Mg/kg body weight in the first day and 0.5 mEq Mg/Kg body weight for the next four days, was done [11]. Daily serum total calcium, ionized calcium, magnesium, albumin and parathormone determinations were done.

Serum total calcium and magnesium were measured by atomic absorption spectrophotometry. Ionized calcium was measured with an ionized calcium analyzer (Radiometer). Immunoassay of C-terminal parathormone was done with an appropriate kit. Serum total calcium and magnesium were corrected for hypoalbuminemia by the following formula: Adjusted calcium = measured calcium + $0.025(40 - \text{albumin})$ [15] Adjusted magnesium = measured magnesium + $0.005(40 - \text{albumin})$ [12]. The Student paired t test and 95 % confidence intervals for the mean computed by using the Student t distribution were used for statistical analysis. All patients

participating in the study granted informed consent.

Results

The corrected serum magnesium, calcium and ionized calcium concentrations before and after magnesium repletion are brought in table 1. Serum magnesium ($P < 0.01$) and ionized calcium ($P < 0.005$) concentrations increased significantly after magnesium repletion. No significant change in serum total calcium concentration was found.

Serum parathormone levels before and after magnesium repletion are brought in table 2. Serum parathormone increased in each case after magnesium repletion (2–5 fold). In each patient as magnesium rose with replacement therapy, parathormone rose simultaneously. A rise in ionized calcium also occurred in each case but this was delayed for 48h. Parathormone subsequently fell into the normal range as ionized calcium became normal. Serum bicarbonate and endogenous creatinine clearances were normal.

Discussion

Adamski et al. [1] found normal serum total calcium but decreased ionized calcium in compensated hepatic cirrhosis. In hepatic cirrhosis with portal hypertension both serum total calcium

and ionized calcium were decreased. The decrease in ionized calcium was the earliest disturbance detectable. It preceded the drop in serum total calcium and soon attained a critical minimum. Further changes in advanced cirrhosis were negligible.

The serum ionized calcium is the physiologically active fraction of serum total calcium that is critically regulated by the parathyroid glands.

Decreased serum total and ionized magnesium were found in hepatic cirrhosis. Erythrocyte, lymphocyte, skeletal muscle, bone and cerebrospinal fluid magnesium were also found to be decreased. So were the exchangeable magnesium and the urinary excretion of magnesium. A magnesium deficiency state exists therefore in hepatic cirrhosis [6].

Darnis found low serum and erythrocyte magnesium in 17 out of 27 patients with hepatic cirrhosis, 15 out of the 27 patients were frankly hypocalcemic [8, 9].

In experimental magnesium deficiency in man urinary calcium excretion falls rapidly despite a constant calcium intake. Magnesium — deficient patients have a reduced urinary calcium excretion, normal bone calcium concentration and a positive calcium balance. During magnesium depletion calcium absorption is either not impaired or increased [7]. Bone biopsies have been reported from two magnesium —

deficient patients but no abnormalities were found [14]. Most patients have either low or “inappropriately normal” serum parathormone levels in the face of hypocalcemia [7]. The hypocalcemia is refractory to treatment with calcium and vitamin D but is correctable by replenishment of magnesium alone. The neuromuscular symptoms seen in magnesium deficiency respond poorly, if at all, to calcium replacement alone. A sustained response is only observed after magnesium replacement. In magnesium deficiency states the regulatory mechanisms that maintain serum calcium in the normal range are impaired.

A curvilinear (second degree quadratic curve) relationship between serum magnesium and calcium in patients with hypomagnesemia was reported by Allgrove et al. [3] suggesting that, whilst the effects of mild hypomagnesemia may be relatively slight, more severe degrees of hypomagnesemia may result in profound hypocalcemia. When the serum magnesium concentration was above 1 mEq/L the mean serum total calcium concentration was within the normal range. This may explain some of the reports of normocalcemic hypomagnesemia [20, 21]. Our patients

Tab. 1: Serum Mg_c, Ca_c and ionized Ca before and after Mg-repletion

	Mg _c		Ca _c		ICa	
	B	A	B	A	B	A
M ± SD	1.16 ± 0.02	1.72 ± 0.17	4.80 ± 0.38	4.81 ± 0.33	1.70 ± 0.03	2.42 ± 0.09
95 % CI	1.12 – 1.20	1.44 – 2.00	4.20 – 5.40	4.27 – 5.34	1.64 – 1.76	2.27 – 2.57
NR	1.4 – 2.0		4.25 – 5.49		2.28 – 2.58	

Mg_c = corrected magnesium (mEq/L)
 ICa = ionized calcium (mEq/L)
 A = after magnesium repletion
 NR = normal range (mEq/L).

Ca_c = corrected calcium (mEq/L)
 B = before magnesium repletion
 CI = confidence intervals

Tab. 2: Serum PTH before and after Mg-repletion

B	A _{max}
4.40	8.8
3.80	15.2
2.85	14.2
4.10	16.4

PTH = Parathormone (I.U.), normal range up to 4.5 I.U.

Mg = magnesium; B = before magnesium repletion,

A_{max} = maximal value after magnesium repletion.

belong to this group with the possible exception that in spite of having a serum total calcium within the normal range their ionized calcium was below normal. In the face of decreased ionized calcium their normal serum parathormone can be looked upon as "inappropriately normal" or "inappropriately low".

Hypomagnesemic patients with normal serum parathormone levels show a marked increase in parathormone level in response to normalization of their serum magnesium. This suggests that all patients with hypocalcemia due to acquired magnesium deficiency have at least relative hypoparathyroidism. The relatively reduced parathormone levels during hypocalcemia might play some role in its maintenance [16, 17].

The presence of normal parathormone levels in hypocalcemic magnesium deficient patients indicate that a state of end-organ resistance to parathormone exists [14, 16, 17, 10, 19]. In our patients during the course of magnesium repletion, serum ionized calcium concentrations failed to rise significantly in the first 48h despite normal to high serum parathormone levels. When hypoparathyroid patients are treated with parathormone extract the rise in serum calcium is generally maximal in the first 24h [5]. The delayed calcemic response to endogenous parathormone in our patients suggests the presence of skeletal end-organ resistance to parathormone which is not rapidly reversible by normalization of serum magnesium. The end-organ resistance may be primarily responsible for the hypocalcemia observed in those patients in whom serum parathormone levels have been found to be normal. In addition a defect in the renal reabsorption of calcium may also contribute to the delayed rise in the serum calcium.

Allgrove et al [3] found a significant positive correlation between serum magnesium and parathormone at the time of presentation. Moderate hypomagnesemia was associated with raised parathormone values, as magnesium depletion became more profound parathormone was lower and it was undetectable when serum magnesium was as low as 0.4 mEq/L. No such relationship existed between parathormone and serum calcium. They also found, that end-organ resistance was associated with mild degrees of magnesium deficiency and no end-organ resistance when parathormone was low or undetectable as a result of severe magnesium deficiency. They suggested therefore, that resistance to parathormone in magnesium depletion is likely to be due to high concentrations of circulating parathormone.

In magnesium-deficiency states there is a failure at two levels in the parathormone mechanism designed to maintain calcium homeostasis. These two stages are related to the degree of magnesium deficiency, with bone resistance occurring first followed by failure of parathormone secretion as the deficiency becomes more severe [18, 13, 4, 2].

Hepatic cirrhosis, being a magnesium-deficient state, can be associated therefore with functional hypoparathyroidism.

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For the authors: *Leon Cohen* M.D., M.Sc., Head Dept. of Medicine B and the Metabolic Unit, Lady Davis Carmel Hospital, Haifa 34362, Israel.