Modern Nutrition in Health and Disease

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B. Magnesium

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Human magnesium deficiency was first described in a small number of patients in 1934.[1] Understanding of the prevalence of this deficiency, its symptomatology, relationships to other electrolytes and association with various disease states has come slowly. The observations of Flink and coworkers indicating depletion of this ion in alcoholics[2] were an important step forward. Beginning 5 years later, a series of clinical case reports began to focus attention on hypomagnesemia in malabsorptive states. Endocrine disorders, abnormalities in the newborn, renal tubular defects and iatrogenic influences have been added to the list. With increasing ease and frequency of measurement of magnesium in body fluids[3] it has become obvious that human depletion occurs much more commonly than had been assumed previously.

BODY PARTITION

Magnesium shares some of the attributes of calcium in its characteristics of absorption and storage in bone, a similarity to potassium in being an important intracellular constituent and a resemblance to sodium in the efficiency with which the normal kidney retains the ion when serum levels fall. This eclectic state is of additional interest, since it is now apparent that a deficiency of magnesium affects the metabolism of each of the other three ions in some manner.

The adult human weighing 70 kg contains approximately 20 to 28 gm of magnesium,[4-6] equaling 1,667 to 2,400 mEq of this ion (1 mEq = 0.5 mM = 12 mg). About 55 per cent is present in bone and about 27 per cent in muscle. Muscle, liver, heart and pancreas contain about the same amount (approximately 16 mEq per kg wet weight).[6,7] Erythrocyte content varies from 4.3 to 6.2 mEq/L depending on method.[7] Normal serum levels also vary depending on method but, with atomic absorption methods, the range is usually 1.5 to 2.1 mEq/L.[8] Magnesium ion in erythrocytes and plasma exists in free, complexed and protein-bound forms; in plasma the approximate percentages are 55, 13 and 32, respectively.[7] Cerebrospinal fluid magnesium is greater than that of plasma (approximately 2.5 mEq/L) despite the absence of protein; about 55 per cent is free and the remainder is complexed.[7] Magnesium in sweat averages 0.6 mEq/L in man in a hot environment.[9]

Thirty per cent of bone magnesium is in a surface-limited pool present either within the hydration shell or on the crystal surface. In adult man, the larger fraction of bone magnesium does not appear to be associated with bone matrix but is an integral part of the bone crystal. Both magnesium pools are increased in patients with chronic renal failure.[9a] In vitro studies suggest that surface magnesium rapidly reflects changes in serum magnesium levels, whereas the deeper pool is probably deposited at the time of bone formation with mobilization being dependent upon the resorptive processes.[9a]

INTAKE, EXCRETION AND HOMEOSTASIS

Magnesium intake varies greatly because of the widely variable content of different foods.[6] Fifteen to 40 mEq per day is probably an average range for healthy individuals in the United States and western Europe.[10] Of this intake approximately 60 to 70 per cent is excreted in the stools by most individuals.[7,10] The remainder (other

infection occurring in close proximity to the magnesium therapy—often make it difficult and potentially misleading to ascribe certain clinical manifestations specifically to magnesium deficiency.

There are four recorded efforts to induce magnesium deficiency experimentally in human volunteers.[13,76–78] In the study in which symptomatic depletion occurred,[13,46,47] plasma magnesium fell progressively on the magnesium-deficient diet (< 0.8 mEq per day) to levels which were 10 to 30 per cent those of control periods (Fig. 7B–1). Erythrocyte magnesium declined more slowly and to a lesser degree. Urine and fecal magnesium decreased to extremely low levels within 7 days. Hypocalcemia occurred in 6 of the 7 subjects, despite adequate calcium intake and absorption and no prior evidence of gastrointestinal or parathyroid abnormalities. Hypocalciuria was noted early in the depletion in all cases. Serum phosphate was normal or slightly low in all but one subject and urinary excretion was usually unaffected. Most deficient subjects developed hypokalemia and negative potassium balance; serum sodium remained normal and the subjects were in positive sodium balance.

Neurologic signs occurred in 5 of the 7 after deficiency periods ranging from 25 to 110 days. Hypomagnesemia, hypocalcemia and hypokalemia were present in all consistently symptomatic patients (Figs. 7B–1 and 7B–2). Despite the hypocalcemia,

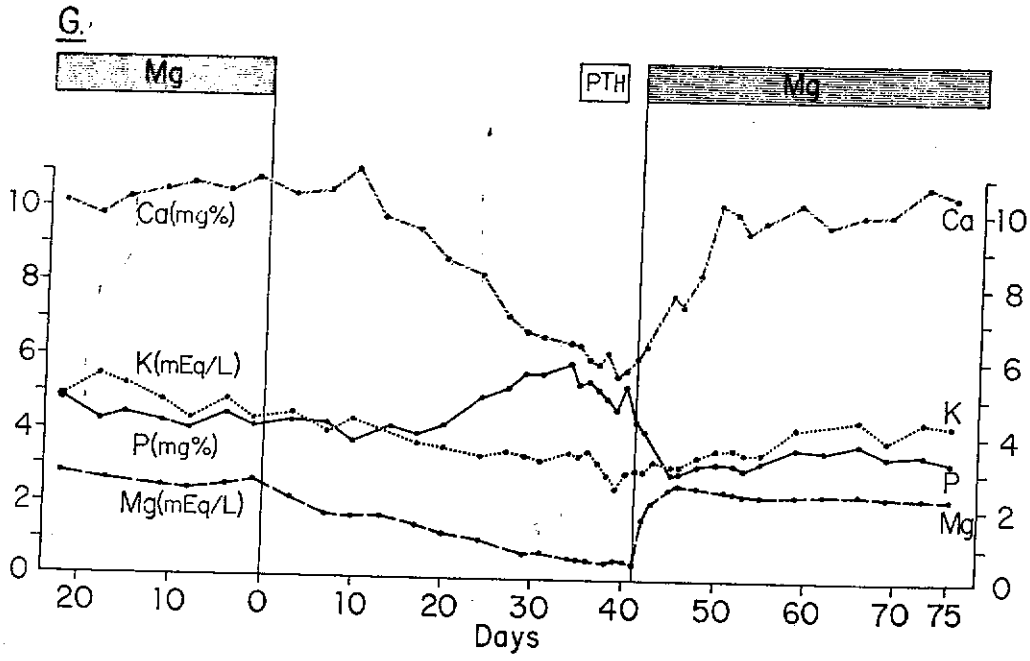

Fig. 7B–2. Blood chemistries in subject on experimental magnesium (Mg) depletion. Mg was omitted after a month on the control diet. The rise in serum inorganic phosphate (P) with Mg depletion in this patient was unique among the depleted subjects. On depletion day 25 Trousseau and Chvostek signs first occurred and the former became progressively stronger as plasma calcium (Ca), Mg and potassium (K) continued to decline. On depletion day 35, parathyroid hormone (PTH) was given i.m. at 50 units t.i.d. for 5 days; this had no effect on plasma Ca but appeared to decrease P. On day 41, anorexia, nausea, paresthesias and generalized muscle spasticity developed; 17 mEq of Mg IV was then given with rapid improvement. This was followed by similar amounts of Mg IM 12 and 15 hours later. Dietary Mg (40 mEq daily) was resumed on the third repletion day. (From Shils.[13] Used by permission of Williams and Wilkins.)

deep tendon reflexes were either normal or decreased. The electromyogram revealed rapid-firing high-pitched potentials during the deficiency period in the 5 patients tested. The electroencephalogram showed no changes related to the deficiency. Anorexia, nausea and apathy occurred frequently and heralded exacerbation of the neurologic changes. When electrocardiographic changes occurred, they were compatible with coexisting hypocalcemia or hypokalemia. All abnormalities reverted to normal with reinstitution of magnesium. Strongly positive potassium balances associated with negative sodium balances occurred as magnesium was retained, electrolytes returned to normal and urine magnesium and calcium rose.

It is concluded from this study that magnesium is essential for the normal metabolism of potassium and calcium in adult man, that magnesium is essential for the mobilization of calcium from bone, that the signs and symptoms are associated with complex electrolyte changes occurring secondarily to magnesium deficiency, that the alterations in various electrolytes in blood and tissues and their relative intakes influence the development and manifestation of clinical and biochemical changes and that the occurrence in clinical situations of otherwise unexplained hypokalemia and hypocalcemia should suggest the possibility of significant magnesium depletion.

In another study, hypomagnesemia occurred with hypocalciuria, but without hypocalcemia or symptoms of deficiency, in 2 subjects ingesting 2 to 5 mEq of magnesium per day.[78] The 4 subjects in the remaining two experimental studies did not become hypomagnesemic within the 20 to 38 days of deficiency.[76,77] The numerous differences in types of subjects and diet composition in these experimental studies have been discussed.[13]

The signs and symptoms noted in the experimental depletion[13,46,47] covered a wide spectrum, including personality change, spontaneous generalized muscle spasm, tremor, fasciculations and Trousseau and Chvostek signs. These have been described separately or in various combinations in clinical cases of hypomagnesemia.[2,49,51,55,57,58,65,66,70] The subjects in the experimental study[13] had no coma, convulsions, significant myoclonic jerks or athetoid movements, which have been reported to occur in certain cases.[2,49,55,58,67,69–71,79,80] Convulsions with or without coma seem to occur much more frequently in acutely deficient infants than in adults. Normoreflexia or hyporeflexia was noted in association with hypocalcemia and positive Trousseau signs in the experimental depletion; hyperreflexia was never seen.[13] The clinical literature on this point is contradictory: hyperreflexia has been reported frequently in symptomatic cases with hypomagnesemia, while others have noted normal or depressed reflexes.[2,50,51,54] Our experience and that of others are not in accord with statements that the Chvostek sign, but not the Trousseau sign, is elicited in magnesium deficiency.[55,81] The development of anorexia, nausea and vomiting, heralding exacerbation of neurologic symptoms, has been one of the more striking observations in experimental depletion.[13,46]

A striking change in the hypomagnesemic subjects becoming symptomatic in the experimental study was the development of hypocalcemia and hypokalemia.[13,46] The clinical literature is also in disagreement about the relationship of magnesium deficiency to hypocalcemia and to latent or overt tetany (defined here as a positive Trousseau sign or spontaneous carpopedal spasm). Some investigators have expressed the opinion that tetany is not a manifestation of magnesium deficiency per se.[2,50,55,82–84] However, there is increasing evidence that the hypocalcemia developing with marked magnesium deficiency cannot be effectively treated with calcium administration alone; it does improve with magnesium administration.[48,

[51,52,54,56–58,70,80,85–87] It is worth emphasizing that continued parenteral administration of large amounts of calcium is potentially dangerous in the magnesium-depleted individual because of the predisposition toward soft tissue calcification in this deficiency.

Another type of clinical picture has been noted in which hyperirritability, tetany and other neuromuscular abnormalities occurred in a setting of hypomagnesemia and *normocalcemia*; these responded to magnesium but not to calcium salts.[49,67,68,71,88] This author has not observed this syndrome in any one of numerous cases of clinical magnesium depletion or in his experimental studies in man.

There is increasing support for the view that hypokalemia and total-body depletion of this ion occur in serious magnesium depletion in adults.[13,45,58,78] However, the majority of cases of neonatal tetany associated with hypomagnesemia and hypocalcemia showed normal serum potassium; no data are given on potassium balance or body stores. In malnourished children with magnesium depletion hypokalemia is often present.[67,68]

In experimental human magnesium depletion serum magnesium began to decline early and before changes occurred in red cell concentration;[13] normal muscle magnesium content was found in the presence of reduced serum levels.[78] Reports of the relation among serum, muscle and bone levels of this ion in the clinical literature on magnesium deficiency are conflicting. They include findings of decreased serum and muscle magnesium with normal bone level,[83] normal serum and erythrocyte levels with decreased muscle magnesium and potassium,[89] reduced serum level with normal muscle content,[57] reduced muscle levels in association with normal serum, erythrocyte and bone magnesium levels[90] and consistently reduced serum concentrations with variable muscle levels.[91] Alfrey et al.[92] measured muscle, erythrocyte and bone magnesium in patients with reduced, normal and increased serum magnesium levels. Muscle magnesium content was shown to vary directly with muscle potassium levels and independently of other body magnesium stores. While serum magnesium did not consistently reflect muscle magnesium concentration, there was a highly significant correlation between serum and bone magnesium levels. Bone and extracellular fluid magnesium are the major magnesium pools in man which are decreased during magnesium depletion and increased during magnesium excess.

Hypomagnesemia has been described in chronic heart failure.[25k] Decreased food intake and/or impaired absorption, use of certain diuretics and digitalis toxicity may be contributing factors. The deficiency may predispose to the occurrence of cardiac arrhythmias and may aggravate digitalis toxicity. Administration of magnesium may be useful in hypomagnesemic or digitalis-toxic tachyarrhythmias.[25k]

Associations have been made between hardness of drinking water and mortality from cardiovascular disease in areas of England, Wales, Scotland, the United States and Sweden, with softer water being associated with a higher mortality rate.[93] Preliminary data indicating lower magnesium levels in the coronary arteries in men in soft water areas are insufficient at present to allow more than speculation; even if corroborated, the lower magnesium levels may be related to pathologic changes unrelated to magnesium intake or metabolism.

Thirty-seven per cent of infants born to diabetic mothers have been found to be hypomagnesemic during the first 3 days of life, and this was related to the severity of maternal diabetes and prematurity.[94]

TREATMENT OF MAGNESIUM DEPLETION

The amount and route of magnesium administration will depend upon the severity of depletion and its etiology. Sympto-