A clinical approach to common electrolyte problems:* 4. Hypomagnesemia

Charles Berkelhammer,† MD, FRCPC
Robert A. Bear,‡ MD, FRCPC, FACP

Magnesium plays a critical role in many cell functions. Hypomagnesemia may occur because of decreased intake or absorption, internal redistribution or increased loss of this element through either renal or nonrenal routes. Manifestations of magnesium deficiency include alterations in calcium, phosphate and potassium homeostasis along with cardiac disorders such as malignant ventricular arrhythmias refractory to conventional therapy, enhanced sensitivity to digoxin and, possibly, coronary artery vasospasm and sudden death. Other features of magnesium deficiency include a host of neuromuscular and neuropsychiatric disorders. In this review we detail mechanisms that may lead to magnesium deficiency, summarize the clinical features of the deficiency and provide a clinical approach to the diagnosis and treatment of this electrolyte disorder.

Le rôle du magnésium dans plusieurs fonctions cellulaires est fondamental. L'hypomagnésémie peut résulter d'une diminution de l'ingestion ou de l'absorption, d'une redistribution du magnésium corporel ou d'une perte excessive rénale ou extra-rénale. Elle se manifeste par des altérations de l'homéostase calcique, phosphatée et potassique, des troubles cardiaques tels des arythmies ventriculaires malignes résistant au traitement habituel, une augmentation de la sensibilité à la digoxine et peut-être un vasospasme des artères coronaires et la mort subite. Elle rend compte aussi d'un vaste éventail de troubles neuromusculaires et neuropsychiatriques. Les auteurs entrent dans le détail de la pathogénèse de la carence magnésienne, en résument les manifestations cliniques et proposent une conduite à tenir pour son diagnostic et son traitement.

Magnesium is one of the most abundant intracellular cations. Only 1% of the total body magnesium is present in the extracellular fluid, and 30% of this is protein-bound. Sixty percent of total body magnesium is found in bone, incorporated in the crystal mineral lattice or in the surface-limited exchangeable pool; 20% is located in skeletal muscle; the remainder exists in other body tissues, especially heart and liver. It is clear that, while determination of the serum magnesium concentration remains the best readily available test for magnesium deficiency, it provides only a rough index of total body magnesium stores.

Magnesium is required for the activation of numerous important enzyme systems, including those that involve adenosine triphosphate (ATP). This element also is essential for the transfer, storage and utilization of intracellular energy, for the metabolism of protein, carbohydrate, fat and nucleic acids, for maintenance of normal cell membrane function and for neuromuscular transmission.[1]

Magnesium balance is achieved through intestinal absorption and renal excretion. The mechanisms leading to hypomagnesemia (serum levels less than 0.7 mmol/L) involve any one or more of decreased intake or absorption, internal redistribution and increased renal or nonrenal loss (Table I).

Pathophysiologic aspects of magnesium deficiency

Decreased intake

Dietary deficiency: Decreased dietary intake of magnesium, if sustained for several weeks, can lead to significant magnesium depletion. Volunteers fed a magnesium-deficient diet (providing less than 0.4 mmol/d) had falling serum magnesium levels by 1 week; the levels at 30 to 80 days were 10% to 30% of the initial values.[2] Erythrocyte magnesium levels declined more slowly, to 60% to 80% of the initial values, over the same period. Although significant compensatory reductions in urinary and fecal magnesium excretion occurred after 1 week, small but measurable obligatory urinary and fecal losses persisted.

Magnesium deficiency occurs in children with protein–energy malnutrition.[3–7] The serum magnesium level is slightly lower than normal,[5,7] the urinary magnesium output is significantly reduced, the muscle magnesium level is reduced to almost half the normal value,[5,6] and there is excessive retention of magnesium during treatment.[5,7]

Loss of magnesium from skeletal muscle during protein–energy malnutrition exceeds the loss expected from a simple reduction in the cellular protein content; hence, the magnesium : nitrogen ratio in muscle biopsy specimens (a measure of the concentration of magnesium relative to that of protein) is reduced.[6] Conversely, during recovery whole-body retention of magnesium is relatively greater than that of nitrogen.[7,8]

Total starvation for 2 months in obese subjects led to a 20% reduction in the total body magnesium content.[8] Because of catabolic release of intracellular magnesium, normal serum magnesium levels may be maintained during total starvation despite evidence of magnesium deficiency as determined by negative magnesium balance and

*The first three parts of this series, on hyponatremia, potassium imbalances and hypophosphatemia respectively, were published in *CMAJ* in volume 128 (pages 1171 to 1174), volume 129 (pages 28 to 31) and volume 130 (pages 17 to 23).

†Resident in internal medicine, University of Toronto
‡Associate professor of medicine, Division of Nephrology, University of Toronto and St. Michael's Hospital, Toronto

Reprint requests to: Dr. Robert A. Bear, Division of Nephrology, St. Michael's Hospital, University of Toronto, 38 Shuter St. Annex, 5th floor, Toronto, Ont. M5B 1A6

marked reduction of skeletal muscle magnesium content.[8] In such patients, renal magnesium excretion is increased and is potentiated by the accompanying metabolic acidosis and ketoaciduria. Net negative balances of up to 5 mmol of magnesium per day have been recorded in fasting subjects.[8]

Reduced magnesium intake also occurs in areas that have drinking water with a reduced magnesium salt content ("soft water").[9,10]

Decreased intestinal absorption: Malabsorption is a major cause of magnesium deficiency. In one series 35% of patients with a variety of malabsorption syndromes were hypomagnesemic.[11] Hypomagnesemia can occur in various intestinal mucosal diseases, including celiac sprue, Whipple's disease, intestinal lymphangiectasia, radiation enteritis, systemic mastocytosis and terminal ileal diseases. Malabsorption secondary to massive intestinal resection, with resultant short bowel syndrome, is another frequent setting.[11-21] Thirty percent of patients with ileal bypass for treatment of obesity have acute symptomatic hypomagnesemia within the first few months after surgery,[19,20] and their mean serum magnesium levels may remain below normal.[21] Magnesium deficiency may also complicate severe cholestatic liver disease[22] or pancreatic insufficiency,[23] including that associated with cystic fibrosis.[24]

In these disorders the predominant mechanism leading to magnesium deficiency is one or more of reduced mucosal surface area, increased intestinal secretion of magnesium,[25] vitamin D deficiency[26] and, most often, the formation of insoluble magnesium soaps in the stool due to the complexing of magnesium with unabsorbed fat. The amount of fecal magnesium correlates with the degree of steatorrhea, and a positive magnesium balance can occur with the institution of a low-fat diet, pancreatic enzyme replacement therapy (in pancreatic insufficiency), treatment of vitamin D deficiency or treatment of the underlying disorder (such as with a gluten-free diet in celiac sprue).

In primary hypomagnesemia selective malabsorption of magnesium occurs as an isolated inherited abnormality. In early infancy tetany and convulsions occur as a result of severe hypomagnesemia and consequent hypocalcemia. The seizures and hypocalcemia respond poorly to calcium and vitamin D therapy but well to magnesium treatment.[27]

Table I—Mechanisms of magnesium deficiency

Decreased intake
Magnesium-deficient diet
Protein–energy malnutrition
Fasting
Liquid-protein, modified-fast diet
"Soft water"
Decreased intestinal absorption
Primary hypomagnesemia
Malabsorption syndromes (e.g., intestinal mucosal diseases, short bowel syndrome, ileal bypass or resection, severe cholestatic liver disease, pancreatic insufficiency)
Internal redistribution
Administration of glucose, amino acids and insulin
Acute pancreatitis
"Hungry bone syndrome"
Massive transfusion with citrated blood
Increased loss
Nonrenal
Prolonged large-volume diarrhea
Prolonged nasogastric suction or biliary fistula combined with parenteral administration of magnesium-free fluids
Renal
Intrinsic tubular disorders
Congenital renal magnesium wasting
Interstitial nephritis
Diuresis: during resolution of acute tubular necrosis, postobstructive, and following successful renal transplantation
Tubular injury induced by drugs (e.g., aminoglycosides, amphotericin B, cisplatin)
Extrarenal factors influencing renal magnesium handling
Hypercalciuria
Diuretic states induced by the administration of saline, furosemide or osmotic agents
Hyperaldosteronism
Short-term ethanol ingestion
Digoxin administration
Hypokalemia
Phosphate depletion
Organic aciduria

Internal redistribution

Acute hypomagnesemia can result from internal redistribution of magnesium through intracellular shifts, formation of magnesium complexes or deposition of magnesium in insoluble soaps. Increased shift of magnesium into cells occurs with increased cellular uptake of glucose and amino acids, as accompanies the administration of glucose, amino acids and insulin.[28] This mechanism is especially pronounced when an underlying intracellular magnesium deficit is coupled with a marked anabolic state, as may occur with refeeding after starvation or severe protein–energy malnutrition, with administration of hyperalimentation solutions to nutritionally depleted patients[29] and with insulin treatment of severe diabetic ketoacidosis.[30]

Increased catecholamine levels from any cause can increase magnesium uptake by adipocytes and can increase circulating levels of free fatty acids, which complex with free plasma magnesium. These mechanisms can contribute to the hypomagnesemia found in alcohol withdrawal syndrome.[31]

Shift of magnesium into cells also occurs with correction of acidosis in renal failure.[32]

Rarely, massive transfusion with citrated blood causes mild transient hypomagnesemia as a result of magnesium's complexing with citrate.[33]

In the "hungry bone syndrome" acute uptake of magnesium by bone

occurs in the healing phase that follows parathyroidectomy for severe hyperparathyroidism, and severe hypomagnesemia may develop.[29]

In acute pancreatitis, magnesium may form insoluble soaps in areas of fat necrosis.[22] Moderate hypomagnesemia develops in 30% of patients during the first week of their illness; occasionally more severe hypomagnesemia develops.

Increased loss

Nonrenal loss: Nonrenal magnesium losses occur through the gastrointestinal tract. Gastric, biliary and pancreatic fluids contain relatively little magnesium (0.5 to 1 mmol/L); however, loss of large volumes from prolonged nasogastric suction or a biliary fistula can result in severe magnesium depletion, particularly when combined with parenteral administration of magnesium-free fluids.[34–36]

Lower intestinal tract fluid has quite a high content of magnesium (5 to 7 mmol/L).[35] Hence, significant magnesium depletion can result from an intestinal fistula, a high ileostomy output and prolonged large-volume diarrhea, such as that complicating inflammatory bowel disease, laxative abuse, infectious gastroenteritis or villous adenoma, as well as secretory diarrhea.[16,36]

Rarely, nonrenal magnesium losses can occur with excessive lactation[37] or sweating[38] and with magnesium-free dialysis.[39]

Renal loss: Magnesium deficiency may develop secondary to renal magnesium wasting states; these can be subdivided into those caused by intrinsic tubular disorders and those produced by extrarenal factors that influence renal magnesium handling.

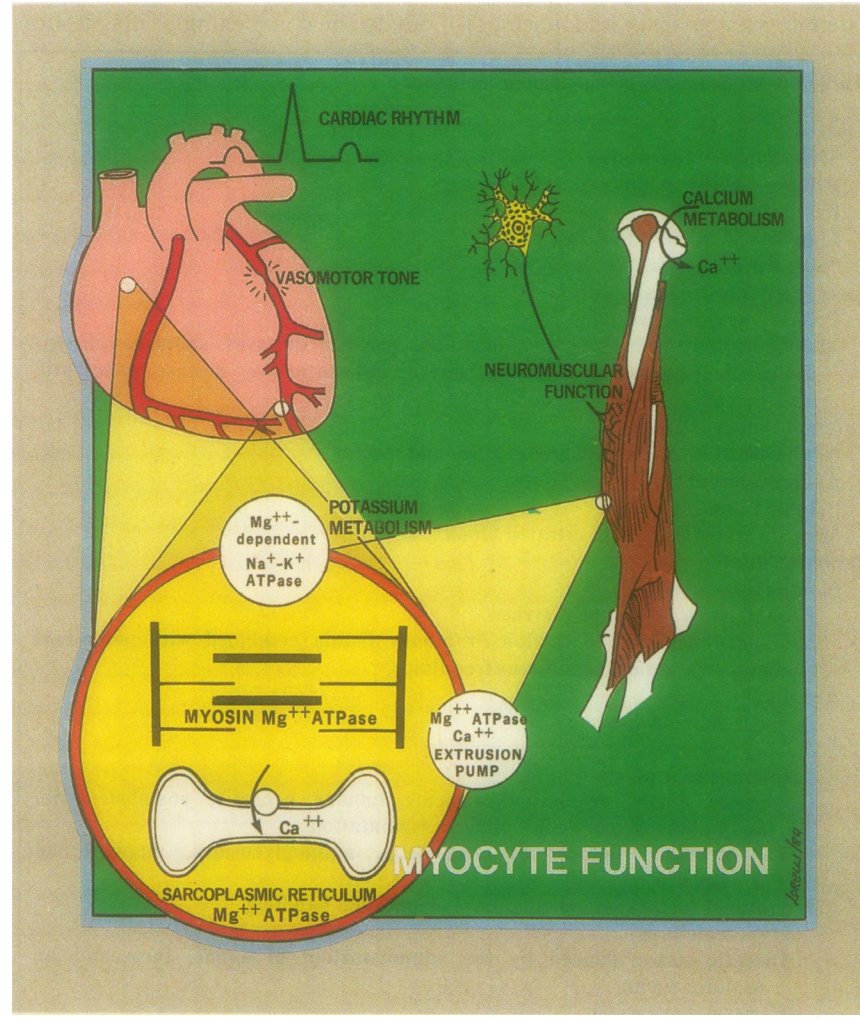
Intrinsic tubular disorders include the syndrome of congenital renal magnesium wasting[40] along with renal magnesium wasting caused by acute or chronic interstitial nephritis or by tubular damage associated with acute tubular necrosis, postobstructive states, renal transplantation and drugs.[32,41–47] Renal magnesium wasting also may be seen in renal tubular acidosis and Bartter's syndrome.[45,47]

In congenital renal magnesium wasting a selective defect in renal magnesium reabsorption leads to hypomagnesemia. Renal potassium wasting, hypokalemic metabolic alkalosis, hypercalciuria, hypocalcemia and nephrocalcinosis often occur in this disorder.[40] Aldosterone levels may be secondarily elevated; however, they return to normal with magnesium supplementation.[40] This syndrome may be confused with Bartter's syndrome.[47]

Impaired tubular function leading to renal magnesium wasting can occur in acute or chronic interstitial nephritis.[32,41] Diffuse tubular abnormalities associated with massive diuresis also can lead to transient severe hypomagnesemia. Clinically, this may be seen with the diuretic phase of acute tubular necrosis, with postobstructive diuresis and with the diuresis that sometimes follows successful renal transplantation.[46]

Drug-induced tubular injury can lead to renal magnesium wasting and hypomagnesemia. This is often accompanied by renal potassium wasting and hypokalemia, and occasionally by secondary hypocalcemia. Drugs producing inordinate renal magnesium losses include aminoglycosides,[44] amphotericin B,[45] carbenicillin[29] and cisplatin (cisplatinum).[42,43,48] Cisplatin has been reported to cause hypermagnesuria and hypocalcemic hypomagnesemia in approximately 50% of patients. The hypomagnesemia may persist for several weeks[42,43] or as long as 3 years after the last dose is administered.[48]

Extrarenal factors also influence renal magnesium handling and may



Magnesium plays a critical role in many cellular functions. For instance, it is required by adenosine triphosphatase (ATPase), which maintains the sodium–potassium gradient across all membranes and regulates intracellular calcium levels, myocyte function and calcium reuptake by the sarcoplasmic reticulum. Magnesium is also important for maintenance of cardiac rhythm, vasomotor tone, neuromuscular function and parathyroid hormone metabolism.

lead to renal loss of magnesium.

Magnesium reabsorption occurs predominantly in the ascending loop of Henle (65%), to a lesser extent in the proximal tubule (30%) and minimally in the distal segment (5%).[49,50] It is closely linked to sodium and calcium reabsorption in these segments. For example, an increased urinary calcium level competitively inhibits the renal tubular reabsorption of magnesium in the ascending loop of Henle.[49,50] Hypomagnesemia can occur, therefore, with hypercalciuria of any cause.

This effect is antagonized by the magnesium conserving action of parathyroid hormone in hypercalcemic hyperparathyroidism, which accounts for the variable serum magnesium level in this disorder.

Similarly, diuretic states induced by the administration of saline, diuretics or osmotic agents decrease renal sodium and renal magnesium absorption and lead to increased urinary magnesium loss.[49,50] Inhibition of reabsorption by furosemide is somewhat greater for magnesium than for sodium and calcium and can produce large increases in urinary magnesium excretion. Not surprisingly, the combined effect of hypercalciuria and forced diuresis with saline and furosemide, used in the treatment of various hypercalcemic states (such as malignant hypercalcemia) can cause significant hypomagnesemia; the serum magnesium concentration should be monitored in these situations.

Primary[51] or secondary[52] hyperaldosteronism induces sodium retention and a modest persistent expansion of the extracellular fluid volume, which can decrease the reabsorption of sodium and magnesium in the proximal tubule and the ascending loop of Henle. Although aldosterone enhances sodium reabsorption in the distal tubule, there is little effect on magnesium at this site, and magnesium wasting and hypomagnesemia occur. Similarly, hypomagnesemia can occur with the syndrome of inappropriate antidiuretic hormone secretion[53] and with Bartter's syndrome.[47]

Other extrarenal factors that can increase urinary magnesium excretion include short-term ethanol ingestion,[54,55,56] digoxin administration,[57] hypokalemia,[29] phosphate depletion[49] and organic aciduria,[29] as can occur with fasting, alcoholism or diabetic ketoacidosis.

Magnesium deficiency in specific clinical situations

Alcoholism

Chronic alcoholism is a common cause of magnesium deficiency, being associated with decreased magnesium intake, decreased intestinal absorption of magnesium because of liver disease or pancreatic insufficiency, increased gastrointestinal magnesium loss because of vomiting and diarrhea, and increased renal magnesium excretion because of ingestion of alcohol per se, ketoaciduria of starvation, hypophosphatemia, hyperaldosteronism or use of diuretics in the treatment of ascites. Increased intracellular uptake of magnesium occurs with intravenous administration of glucose when the patient is admitted to hospital. Additionally, hypomagnesemia may develop if acute pancreatitis causes precipitation of magnesium salts in areas of fat necrosis or if acute alcohol withdrawal leads to increased plasma free fatty acid levels and subsequent precipitation of complexes of magnesium and free fatty acids.[31,54–56]

Serum magnesium levels as low as 0.2 mmol/L have been reported in association with acute alcohol withdrawal.[58] However, in that study magnesium depletion in alcoholism was most consistently reflected in significantly reduced skeletal muscle magnesium content: the average content was 22.5 mmol/kg of fat-free dry solids in patients with symptoms of alcohol withdrawal but 35.5 mmol/kg in normal, healthy controls. The content returned to normal in the patients following intravenous magnesium replacement.

Diabetic ketoacidosis

About 7% of patients presenting with severe diabetic ketoacidosis have hypomagnesemia.[29] The catabolic effect of insulin deficiency leads to breakdown of intracellular organic compounds, release of magnesium from cells and excretion of magnesium in the urine. Magnesium excretion is enhanced by ketoaciduria and by the osmotic diuresis induced by glucosuria. The anabolic effects of insulin therapy drive magnesium back into cells, and 50% to 60% of patients become transiently hypomagnesemic after 12 hours of therapy.[30] Carpopedal spasms, hypocalcemia and hypomagnesemia developed during treatment of diabetic ketoacidosis in one child; these complications were refractory to calcium infusion but responsive to intramuscular administration of magnesium sulfate.[59] A fatal arrhythmia has been reported in a patient rendered hypomagnesemic during initial treatment of diabetic ketoacidosis.[60]

Total parenteral nutrition

Prolonged parenteral administration of fluids, including nutrient preparations without added magnesium, leads to hypomagnesemia or magnesium deficiency[9] on the basis of decreased intake and transcellular shift of magnesium induced by cellular uptake of glucose and amino acids.

Clinical manifestations of magnesium deficiency (Table II)

Manifestations of magnesium deficiency relate to its critical role in activating and generating ATP[1] and cyclic adenosine monophosphate (AMP)[61] and in regulating neuromuscular transmission.[1] Resultant alterations in intracellular potassium and calcium homeostasis also play a role in mediating the manifestations of magnesium deficiency.

Alterations in potassium, calcium and phosphate balance

Magnesium is important in regulating the intracellular potassium content. Intracellular magnesium activates membrane-bound magnesium-dependent sodium–potassium ATPase, which pumps sodium out of the cell in exchange for potassium. In addition, extracellular magnesium retards cell efflux of potassium on a biophysical basis. Thus, magnesium deficiency impairs the sodium–potassium pump and allows potassium to escape from the cell, to be lost in the urine. Hence, magnesium depletion can lead to potassium depletion.[2] In fact, hypokalemia occurs in

46% of hypomagnesemic patients;[62] total body potassium depletion may be profound, and massive supplementation of potassium may fail to correct it until the magnesium deficit is repaired.[63]

Hypocalcemia is a prominent manifestation of magnesium deficiency.[2] Several mechanisms together result in decreased mobilization of calcium from bone.[64] Hypomagnesemia shifts the normal heteroionic exchange of calcium and magnesium ions at the bone surface, which leads to an increased bone release of magnesium ions in exchange for increased bone uptake of calcium ions from the serum. Additionally, the release of parathyroid hormone and the target organ response to this hormone are altered in chronic severe hypomagnesemia. Although acute hypomagnesemia causes a rise in parathyroid hormone levels, chronic severe hypomagnesemia inhibits the release of parathyroid hormone, the result being decreased or inappropriately low parathyroid hormone levels for the degree of hypocalcemia. The response of bone to parathyroid hormone can also be diminished, and this results in "functional hypoparathyroidism". Impaired magnesium-dependent adenyl cyclase generation of cyclic AMP mediates the decreased release of parathyroid hormone and the skeletal resistance to this hormone in magnesium deficiency.[65]

Hypomagnesemic hypocalcemia is often refractory to calcium therapy alone but can respond to the administration of magnesium alone.

Magnesium depletion can also lead to phosphaturia and decreased intracellular phosphate content.[65]

Cardiac manifestations

Cardiac manifestations of magnesium deficiency are legion, including digoxin-mediated arrhythmias,[66] electrocardiographic changes,[67] and supraventricular and ventricular arrhythmias.[67–70] Evidence also suggests a role for magnesium deficiency in hypertension,[71–73] coronary artery vasospasm[74] and sudden death due to coronary artery disease.[10,75]

Patients receiving digoxin are predisposed to the development of magnesium deficiency and toxic effects of digoxin. Digoxin enhances urinary magnesium excretion,[57] as do diuretics given concomitantly for treatment of congestive heart failure. Magnesium deficiency enhances digoxin uptake by the myocardial cell,[76] and both inhibit the myocardial cell sodium–potassium pump. This results in a decrease in intracellular potassium content, changes in resting membrane potential and disturbances in the repolarization phase. The calcium channel blocking effect of magnesium decreases in magnesium deficiency, and the intracellular calcium content rises. The result is an enhanced sensitivity to the toxic effects of digoxin and the development of digoxin-mediated arrhythmias. These arrhythmias may be refractory to conventional antiarrhythmic agents but may respond well to intravenous magnesium sulfate therapy.[66–69]

Cardiac arrhythmias independent of digoxin may be associated with magnesium depletion. These include ventricular premature beats, ventricular tachycardia (often multifocal), torsades de pointes and ventricular fibrillation.[67–70] Supraventricular arrhythmias (atrial fibrillation and paroxysmal supraventricular tachycardias) are less common. These arrhythmias also may be refractory to conventional antiarrhythmic agents but responsive to magnesium sulfate.

Electrocardiographic changes occurring in magnesium deficiency are nonspecific and include wide QRS complexes and tall, peaked T waves in moderate magnesium deficiency, and prolonged PR, QRS and QT intervals, ST-segment depression and flat, broad T waves with prominent U waves in severe magnesium deficiency.[67,68] These changes probably reflect alterations in the relative concentrations of intracellular and extracellular potassium and calcium in the myocardial tissue.

The results of several studies have suggested an association between dietary magnesium deficiency and the risk of sudden death from coronary artery disease.[10,74,75] Cities in Ontario that had drinking water with a decreased magnesium content ("soft water") demonstrated a 20% to 30% higher rate of sudden death from coronary artery disease than areas that had drinking water with a high magnesium content ("hard water").[10] Myocardial magnesium content in persons with an accident-related death was reduced by 7% in the cities having "soft water" compared with those having "hard water".[10] It is conceivable that the magnesium content of "hard water" exerts a protective effect on the myocardium of individuals with otherwise marginal dietary magnesium intake.

Table II—Manifestations of magnesium deficiency

Alterations in potassium, calcium and phosphate balance
Hypokalemia
Hypocalcemia
Hypophosphatemia
Cardiac manifestations
Predisposition to digoxin-mediated arrhythmias
Electrocardiographic changes (including prolonged QT interval)
Cardiac arrhythmias (including ventricular premature beats, ventricular tachycardia, torsades de pointes, ventricular fibrillation)
Alterations in vascular tone and blood pressure
Increased vascular smooth muscle tone and reactivity, leading to spasm
Increased blood pressure
Neuromuscular manifestations
Chvostek's and Trousseau's signs
Muscle twitching and tremor
Spontaneous carpopedal spasms
Muscle cramps
Muscle (including respiratory) weakness
Paresthesia
Neuropsychiatric manifestations
Personality changes (including apathy, depression, agitation, confusion, delirium)
Seizures
Vertigo, nystagmus, ataxia, coma, movement disorders (rarely)

Sudden death associated with prolonged QT intervals and ventricular tachycardia has been reported in avid dieters using a liquid-protein, modified-fast diet.[77,78] Negative magnesium balance (due to renal losses) occurs in these patients.[79] Although not necessarily reflected in the serum magnesium level, an intracellular or skeletal magnesium deficit (or both types), which may contribute to the cardiac manifestations, is suggested.

Effects on vascular tone and blood pressure

Evidence exists for a role for magnesium in regulating vascular tone and contractility, as well as vascular reactivity to a variety of neurohumoral vasoactive substances.[71-74,80-83]

Increased dietary intake of magnesium has been correlated with a decreased incidence of hypertension in a recent survey performed by the National Center for Health Statistics in the United States.[71] High-renin essential hypertension has been associated with lower mean serum levels of magnesium than normotension or other subgroups of essential hypertension, although the precise mechanism of the association is not clear.[72] In rats fed a magnesium-deficient diet the microvascular lumen sizes decreased and the arterial blood pressure rose.[73] In-vitro studies have demonstrated increased vascular tone (spasm), as well as potentiated contractile responses to catecholamines, in coronary arteries bathed in magnesium-deficient media.[74] In-vivo studies have produced vasodilatation and vasoconstriction of cerebral arterioles through increases and decreases respectively in the magnesium concentration of the cerebrospinal fluid.[80] Similarly, magnesium deficiency induces spasm and potentiates the contractile response to prostaglandin $F_{2\alpha}$ of umbilical vessels, which suggests a mechanism for the effectiveness of magnesium sulfate in the treatment of pre-eclampsia.[81] Finally, the addition of magnesium supplements to the diuretic treatment of hypertension has led to a significant reduction in both systolic and diastolic blood pressures after 6 months when compared with the pressures of controls not receiving the supplements.[82]

Magnesium deficiency is thought to lead to an increase in vascular smooth muscle tone and reactivity by modulating uptake, content and distribution of calcium in the smooth muscle cell.[83] Ultimately, the intracellular calcium content rises and its intracellular distribution is altered. The mechanisms whereby magnesium deficiency results in this effect include the following: decreased biophysical regulation of calcium channels, leading to increased cellular influx of calcium; decreased cellular efflux of calcium or increased permeability of the cell to calcium (from decreased activity of various membrane-bound magnesium-dependent calcium exchange and extrusion pumps); and decreased sarcoplasmic reticulum reuptake of calcium (from decreased activity of magnesium-requiring ATPases and decreased magnesium-requiring formation of cyclic AMP). Increased intracellular cytoplasmic calcium can then activate the actin–myosin contractile proteins.

Neuromuscular manifestations

Magnesium deficiency can result in various nonspecific neuromuscular signs and symptoms. Concomitant hypocalcemia and hypokalemia may contribute as well.

Magnesium is known to decrease acetylcholine release from nerve terminals and to depress the excitability of nerve and muscle membranes.[1] Magnesium plays an important role in muscle contraction and relaxation by regulating calcium channels, facilitating sarcoplasmic reticulum reuptake of calcium via magnesium-dependent ATPase and cyclic AMP, and facilitating actin–myosin interaction via magnesium-dependent ATPase.[1] Dogs rendered magnesium deficient exhibit muscle composition changes (specifically, gains in sodium, chloride and calcium), as well as altered resting transmembrane electrical potential.[65]

Clinical manifestations of magnesium deficiency include Chvostek's and Trousseau's signs, spontaneous carpopedal spasms, muscle weakness, muscle fasciculation, muscle cramps, fine and coarse tremors, and paresthesia.[1,2,9,29,84] Electromyograms may reveal rapidly firing, high-pitched potentials.[8]

Neuropsychiatric manifestations

Magnesium deficiency may be associated with personality changes including apathy, depression, agitation, confusion, anxiety and delirium. Severe magnesium deficiency may contribute to the apathy of apathetic hyperthyroidism.[85] Magnesium deficiency interferes with thiamine utilization and may aggravate Wernicke–Korsakoff's syndrome.[9]

Rarely, magnesium deficiency leads to seizures and, hence, may be a contributing factor in alcohol withdrawal seizures. Vertigo, nystagmus, ataxia, coma and movement disorders such as asterixis, athetoid and choreiform movements, and myoclonic jerks have been described.[27]

Other manifestations

Magnesium deficiency can, rarely, lead to decreased red blood cell survival and subsequent anemia,[86] dysphagia due to esophageal spasm,[87] and anorexia, nausea and decreased gut motility.[2]

Since urinary magnesium acts as an inhibitor of crystal nucleation, hypomagnesuria associated with magnesium deficiency may play a role in predisposition to urinary calculus formation.[88]

Clinical approach to the diagnosis of magnesium deficiency

Magnesium deficiency should be suspected in individuals predisposed to its development who exhibit the symptoms, signs and laboratory features of magnesium depletion. Unfortunately, the precise clinical diagnosis of magnesium depletion is difficult. Since 99% of total body magnesium is located in the intracellular stores or in bone, serum magnesium levels do not always reflect intracellular or total body magnesium stores. Hence, a normal serum magnesium level can occur in the presence of a total body magnesium deficiency.[8,58] Other measures of magnesium balance that have been described include the erythrocyte magnesium level, which reflects the serum magnesium concentration at the time of red cell formation and may be normal in acute hypomagnesemia, the

muscle magnesium content, which largely reflects the size of the bound intracellular magnesium stores and may be a useful index of chronic magnesium depletion,[36,58] and the magnesium content of the surface-limited pool of bone, which is readily exchangeable with serum magnesium and provides a good estimate of total body magnesium. However, these measures and other techniques to determine an individual's magnesium status generally are not available.

A practical clinical approach to establishing the diagnosis and the cause of magnesium deficiency involves determining the serum magnesium level and the urinary magnesium excretion, then administering a magnesium load (Fig. 1). Since 30% of serum magnesium is protein-bound, severe hypoalbuminemia should be ruled out, as it could cause spurious hypomagnesemia with a normal serum content of ionized magnesium. High urinary magnesium excretion (more than 1.5 to 2.5 mmol/d) in the presence of a low serum magnesium level (less than 0.7 mmol/L) suggests increased renal loss of magnesium as the mechanism of magnesium deficiency. Decreased urinary magnesium excretion (less than 0.5 to 1 mmol/d) in the presence of hypomagnesemia suggests renal conservation of magnesium and a magnesium-deficient state due to decreased intake or absorption, redistribution or nonrenal magnesium loss.[89]

In the absence of renal magnesium wasting syndromes, a magnesium load test can be performed.[89-91] After a baseline 24-hour urine collection, 30 mmol of magnesium sulfate is administered in 500 mL of 5% dextrose in water over 8 to 12 hours; urine is collected for 24 hours from the beginning of the infusion. Individuals with normal magnesium stores will excrete more than 60% of the administered load within 24 hours, whereas magnesium-deficient patients will excrete less than 50%.[90] With the dose of magnesium sulfate reduced to 33 mEq (16.5 mmol) over 6 hours, Thoren[91] considered a retention of greater than 20% to 25% to be evidence of magnesium deficiency. This test should be performed with caution in patients with renal insufficiency, disturbances in cardiac conduction or advanced respiratory insufficiency.

Treatment

Clinicians should recognize the conditions that predispose to the development of magnesium deficiency, so that prophylactic measures may be taken. For example, 2.5 mmol of magnesium sulfate may be added prophylactically to each litre of intravenous fluid in the treatment of diabetic ketoacidosis. Magnesium requirements during total parenteral nutrition are approximately 6 to 15 mmol/d; magnesium administration optimizes nitrogen retention.[92] Potassium-sparing diuretics such as amiloride, triamterene and, to a lesser extent, spironolactone have magnesium-sparing properties and may be useful in the prevention of magnesium deficiency secondary to long-term diuretic therapy. Prophylactic addition of 3 g of magnesium sulfate, given intravenously, to high-dose cisplatin chemotherapy regimens may be effective in preventing hypomagnesemia.[93]

Patients with mild, asymptomatic magnesium deficiency are best treated by the institution of a diet high in magnesium-containing food (meat, seafood, green vegetables, dairy products, nuts and cereals). In more severe deficiency states and in patients with ongoing renal or gastrointestinal losses, magnesium salt supplementation is necessary.

When magnesium losses are continuous, oral therapy may be undertaken with magnesium glucoheptonate, magnesium oxide or magnesium citrate. Approximately 20 to 50 mmol of magnesium per day, given in divided doses, may be required, depending on the extent and route of the loss.

Magnesium sulfate is commonly used for intravenous or intramuscular therapy and is available in ampoules of a 50% solution, 2 mL (1 g) of which equals 4 mmol of elemental magnesium. Since magnesium sul-

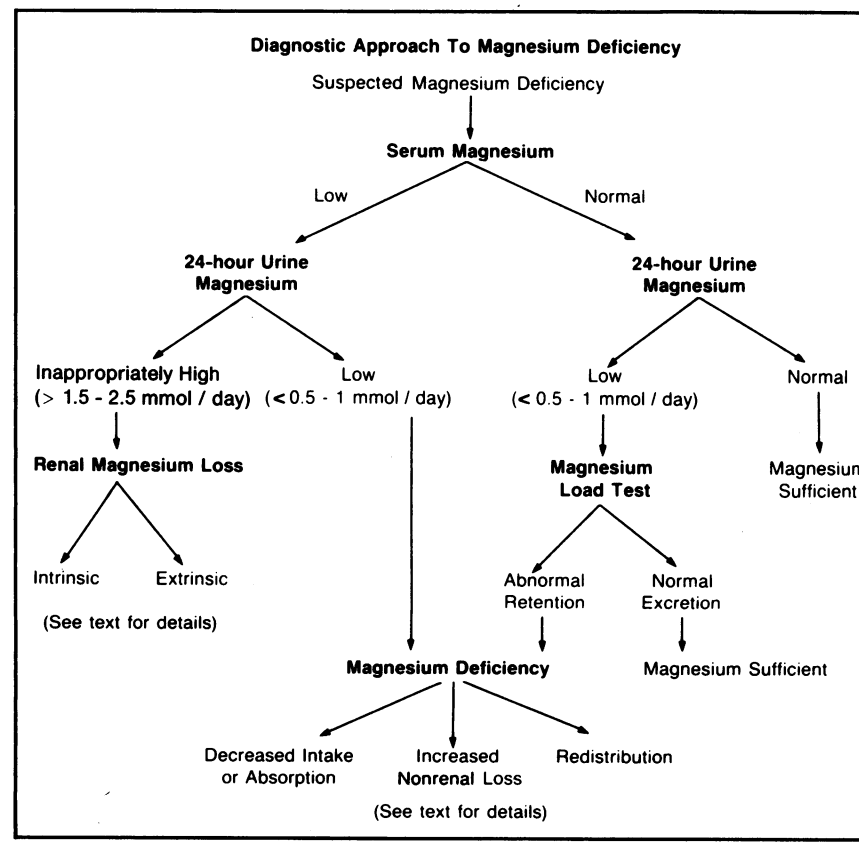


Fig. 1—Measurement of the serum magnesium concentration and the 24-hour urinary magnesium excretion is required for the diagnosis of magnesium deficiency. An inappropriately high urinary magnesium excretion in the presence of a low serum magnesium level suggests renal magnesium loss. A low serum level with low urinary excretion suggests magnesium deficiency with renal conservation. A normal serum level with low urinary excretion requires a magnesium load test for confirmation of magnesium deficiency.

fate is painful and sclerosing it should be diluted before administration.

Since the actual magnitude of the magnesium deficit is difficult to determine, replacement therapy will be empiric. The typical deficit required to produce symptomatic hypomagnesemia is 0.5 to 1 mmol/kg of body weight; hence, the minimal deficit in a patient may be estimated from the patient's weight. Twice the estimated deficit is required for parenteral replacement therapy since up to 50% of the administered magnesium will be excreted in the urine despite the presence of substantial total body magnesium depletion. Half the estimated deficit can be given in the first 24 hours of therapy and the remainder over the next 2 to 5 days.[9] One author recommends instead continuous intravenous administration of 40 mmol (10 g) of magnesium sulfate in the first 24 hours, followed by 24 mmol (6 g) per day over the next 2 to 5 days.[9] In addition, an initial loading dose of 24 mmol can be given over 3 hours.

In emergencies due to hypomagnesemia, such as the occurrence of convulsions or malignant ventricular tachyarrhythmias, one can give 8 mmol (2 g) of magnesium sulfate in 10 mL of 5% dextrose and water intravenously over 10 minutes, followed by 40 mmol (10 g) in 500 mL over 5 hours.[68,70] Magnesium sulfate can be administered intramuscularly in a dosage of 2 g every 4 hours for 24 hours, followed by 1 g every 6 hours; however, this route of administration can be painful.[9]

In patients with hypokalemia and hypomagnesemia, both potassium and magnesium should be replaced. Patients with symptomatic hypocalcemic hypomagnesemia may require calcium replacement in addition to magnesium since the calcium level may not rise for 4 to 5 days; calcium treatment alone is ineffective.

Complications of parenteral magnesium therapy include neuromuscular and respiratory depression, flushing and hypotension. Calcium gluconate should therefore be readily available as an antidote. The dosage should be substantially reduced in the presence of renal insufficiency, and monitoring of muscle stretch reflexes and the serum magnesium level is mandatory.

References

1. Anast CS, Gardner DW: Magnesium metabolism. In Bronner F, Coburn JW (eds): *Disorders of Mineral Metabolism*, vol 3, Acad Pr, New York, 1981: 423–506
2. Shils ME: Experimental human magnesium depletion. *Medicine (Baltimore)* 1969; 48: 61–85
3. Cadell JL, Goddard GR: Studies in protein–calorie malnutrition. I. Chemical evidence for magnesium deficiency. *N Engl J Med* 1967; 276: 533–535
4. Cadell JL: Studies in protein–calorie malnutrition. II. A double blind clinical trial to assess magnesium therapy. Ibid: 535–540
5. Nichols BL, Alvarado J, Hazlewood CF et al: Magnesium supplementation in protein–calorie malnutrition. *Am J Clin Nutr* 1978; 31: 176–188
6. Metcoff J, Frenk S, Antonowicz I et al: Relations of intracellular ions to metabolite sequences in muscle in kwashiorkor. A new reference for assessing the significance of intracellular concentrations of ions. *Pediatrics* 1960; 26: 960–972
7. Linder GC, Handsen JDL, Karabus CD: The metabolism of magnesium and other inorganic cations and of nitrogen in acute kwashiorkor. *Pediatrics* 1963; 31: 552–568
8. Drenick EJ, Hunt IF, Swendseid ME: Magnesium depletion during prolonged fasting of obese males. *J Clin Endocrinol Metab* 1969; 29: 1341–1348
9. Flink EB: Nutritional aspects of magnesium metabolism. *West J Med* 1980; 133: 304–312
10. Anderson TW, Neri LC, Schreiber GB et al: Ischemic heart disease, water hardness and myocardial magnesium. *Can Med Assoc J* 1975; 113: 199–203
11. Booth CC, Barbouris N, Hanna S et al: Incidence of hypomagnesaemia in intestinal malabsorption. *Br Med J* 1963; 2: 141–144
12. Goldman AS, Van Fossan DD, Baird EE: Magnesium deficiency in celiac disease. *Pediatrics* 1962; 29: 948–952
13. Arnaud SB, Newcomer AD, Go VLW: Hypomagnesemia and vitamin D deficiency in patients with non-tropical sprue (abstr). *Clin Res* 1976; 24: 564
14. Broitman SA, McCray RS, May JC et al: Mastocytosis and intestinal malabsorption. *Am J Med* 1970; 48: 382–389
15. MacIntyre I, Hanna S, Booth CC et al: Intracellular magnesium deficiency in man. *Clin Sci* 1961; 20: 297–305
16. Martin HE: Clinical magnesium deficiency. *Ann NY Acad Sci* 1969; 162: 891–900
17. Opie LH, Hunt BG, Finley JM et al: Massive small bowel resection with malabsorption and negative magnesium balance. *Gastroenterology* 1964; 47: 415–420
18. Fletcher RD, Henley AA, Sammons HG et al: A case of magnesium deficiency following massive intestinal resection. *Lancet* 1960; 1: 522–525
19. Lipner A: Symptomatic magnesium deficiency after small-intestinal bypass for obesity. *Br Med J* 1977; 1: 148
20. Hocking MP, Duerson MC, O'Leary JP et al: Jejunoileal bypass for morbid obesity: late follow-up in 100 cases. *N Engl J Med* 1983; 308: 995–999
21. Parfitt AM, Miller MJ, Thomson DL et al: Metabolic bone disease after intestinal bypass for treatment of obesity. *Ann Intern Med* 1978; 89: 193–199
22. Kobayashi A, Utsunomiya T, Ohbe YO et al: Intestinal absorption of calcium and magnesium in hepatobiliary disease in infancy. *Arch Dis Child* 1974; 49: 90–96
23. Hersch T, Siddiqui DA: Magnesium and the pancreas. *Am J Clin Nutr* 1973; 23: 362–379
24. Orenstein SR, Orenstein DM: Magnesium deficiency in cystic fibrosis. *South Med J* 1983; 76: 1586
25. Avioli LV, Berman M: Magnesium 28 kinetics in man. *J Appl Physiol* 1966; 21: 1688–1694
26. Levine BS, Brautbar N, Walling MW et al: Effects of vitamin D and diet on magnesium metabolism. *Am J Physiol* 1980; 239: 515–523
27. Paunier L, Radde IC, Kooh SW et al: Primary hypomagnesemia with secondary hypocalcemia in an infant. *Pediatrics* 1968; 41: 385–402
28. Aikawa JR: Effect of glucose and insulin on magnesium metabolism in rabbits. *Proc Soc Exp Biol Med* 1980; 103: 363–366
29. Parfitt AM, Kleerekoper M: Clinical disorders of calcium, phosphorus, and magnesium metabolism. In Maxwell MH, Kleeman CR (eds): *Clinical Disorders of Fluids and Electrolyte Metabolism*, 3rd ed, McGraw, New York, 1980: 947–1152
30. Martin HE, Smith K, Wilson ML: The fluid and electrolyte therapy of severe diabetic acidosis and ketosis. *Am J Med* 1958; 24: 376–389
31. Flink EB, Shane SR, Scobbo RR et al: Relationship of fatty-free acids and magnesium in ethanol withdrawal in dogs. *Metabolism* 1979; 28: 858–865
32. Randall RE: Magnesium metabolism in chronic renal disease. *Ann NY Acad Sci* 1969; 162: 831–846
33. McLellan BA, Reid SR, Lane PL: Massive blood transfusion causing hypomagnesemia. *Crit Care Med* 1984; 12: 146–147
34. Kellaway GN, Ewen K: Magnesium deficiency complicating gastric suction. *NZ Med J* 1962; 6: 137–142
35. Gerst PH, Porter MR, Fishman RA: Symptomatic magnesium deficiency in surgical patients. *Ann Surg* 1964; 159: 402–406
36. Lim P, Jacob E: Tissue magnesium level in chronic diarrhea. *J Lab Clin Med* 1972; 80: 313–321
37. Greenwald JH, Dubin A, Cardon L: Hypomagnesemic tetany due to excessive lactation. *Am J Med* 1963; 35: 845–860
38. Consolazio CF, Matoush LO, Nelson RA et al: Excretion of sodium, potassium, magnesium, and iron in human sweat and the relation of each to balance and

requirements. *J Nutr* 1963; 79: 407–415
39. Parsons FM, Edwards GF, Anderson CK et al: Regression of malignant tumours in magnesium and potassium depletion induced by diet and haemodialysis. *Lancet* 1974; 1: 243–244
40. Evans RA, Carter JN, George CRP et al: The congenital 'magnesium-losing kidney'. Report of two patients. *Q J Med* 1981; 197: 39–52
41. Mennes P, Rosenbaum R, Martin K et al: Hypomagnesemia and impaired parathyroid hormone secretion in chronic renal disease. *Ann Intern Med* 1978; 88: 206–209
42. Schilsky RL, Anderson T: Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. *Ann Intern Med* 1979; 90: 929–931
43. Lyman NW, Hemalatha C, Viscuso RL et al: Cisplatin-induced hypocalcemia and hypomagnesemia. *Arch Intern Med* 1980; 140: 1513–1514
44. Bar RS, Wilson HE, Massaferri EL: Hypomagnesemic hypocalcemia secondary to renal magnesium wasting: a possible consequence of high-dose gentamicin therapy. *Ann Intern Med* 1975; 82: 646–649
45. Burgess JL, Birchall R: Nephrotoxicity of amphotericin B with emphasis on changes in tubular function. *Am J Med* 1972; 53: 77–84
46. Davis BB, Preuss HG, Murdaugh HV Jr: Hypomagnesemia following the diuresis of post-renal obstruction and renal transplant. *Nephron* 1975; 14: 275–280
47. Mace JW, Hambridge KM, Gotlin RW et al: Magnesium supplementation in Bartter's syndrome. *Arch Dis Child* 1973; 78: 485–487
48. Schilsky RL, Barlock A, Ozols RF: Persistent hypomagnesemia following cisplatin chemotherapy for testicular carcinoma. *Cancer Treat Rep* 1982; 66: 1767–1769
49. Dirks JH: The kidney and magnesium metabolism. *Kidney Int* 1983; 23: 771–777
50. Quamme GA, Dirks JH: Renal magnesium transport. *Rev Physiol Biochem Pharmacol* 1983; 97: 69–110
51. Horton R, Biglieri EG: Effect of aldosterone on the metabolism of magnesium. *J Clin Endocrinol Metab* 1962; 22: 1187–1192
52. Cohen MI, McNamara H, Finberg L: Serum magnesium in children with cirrhosis. *J Pediatr* 1970; 76: 453–455
53. Neilsen B, Thorn NA: Transient excess urinary excretion of antidiuretic material in acute intermittent porphyria with hyponatremia and hypomagnesemia. *Am J Med* 1965; 38: 345–350
54. Mendelson JH, Ogata M, Mello NK: Effects of alcohol ingestion and withdrawal on magnesium states of alcoholics: clinical and experimental findings. *Ann NY Acad Sci* 1969; 22: 918–933
55. Kalbfleisch JM, Lindeman RD, Ginn HE et al: Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. *J Clin Invest* 1963; 42: 1471–1475
56. Heaton FW, Pyrah LN, Beresford CC et al: Hypomagnesaemia in chronic alcoholism. *Lancet* 1962; 2: 802–805
57. Massry SB: Pharmacology of magnesium. *Annu Rev Pharmacol Toxicol* 1977; 17: 67–82
58. Lim P, Jacob E: Magnesium status of alcoholic patients. *Metabolism* 1972; 21: 1045–1051
59. Zipf WB, Bacon B, Spencer ML et al: Hypocalcemia, hypomagnesemia and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. *Diabetes Care* 1979; 2: 265–268
60. McMullen JK: Asystole and hypomagnesaemia during recovery from diabetic ketoacidosis. *Br Med J* 1977; 1: 690
61. Rude RK, Baker AJ, Watts RS: Renal cortical adenylate cyclase: characterization of magnesium activation. *Endocrinology* 1983; 113: 1348–1355
62. Andre PG, Andre C: Is there a role for routine estimations of plasma magnesium? *Clin Biochem* 1983; 16: 191–194
63. Webb S, Scade DS: Hypomagnesemia as a cause of persistent hypokalemia. *JAMA* 1975; 233: 23–24
64. Shils ME: Magnesium, calcium and parathyroid hormone interactions. *Ann NY Acad Sci* 1980; 355: 165–178
65. Cronin RE, Knochel JP: Magnesium deficiency. *Adv Intern Med* 1983; 28: 509–532
66. Seller RH, Cangiano J, Kim KE et al: Digitalis toxicity and hypomagnesemia. *Am Heart J* 1970; 79: 57–68
67. Burch GE, Giles TD: The importance of magnesium deficiency in cardiovascular disease. *Am Heart J* 1977; 94: 649–657
68. Iseri LT, Freed J, Bures AR: Magnesium deficiency and cardiac disorders. *Am J Med* 1975; 58: 837–846
69. Topac EJ, Lerman BB: Hypomagnesemic torsades de pointes. *Am J Cardiol* 1983; 52: 1367–1368
70. Isen LT, Chung P, Tobis J: Magnesium therapy for intractable ventricular tachyarrhythmias in normomagnesemic patients. *West J Med* 1983; 138: 823–828
71. McCarron DA: Calcium and magnesium nutrition in human hypertension. *Ann Intern Med* 1983; 98: 800–805
72. Resnick LM, Laragh JH, Sealey JE et al: Divalent cations in essential hypertension: relations between serum ionized calcium, magnesium and plasma renin activity. *N Engl J Med* 1983; 309: 868–891
73. Attura BM, Attura BJ, Begrewold A et al: Magnesium deficiency and hypertension: correlation between magnesium deficiency diets and micro-circulatory changes in situ. *Science* 1984; 223: 1315–1317
74. Turlapaty PDMV, Altura BM: Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science* 1980; 208: 198–200
75. Johnson CJ, Peterson DR, Smith EK: Myocardial tissue concentrations of magnesium and potassium in men dying suddenly from ischemic heart disease. *Am J Clin Nutr* 1979; 32: 967–970
76. Goldman RH, Klelger RE, Schweizer E et al: The effect on myocardial ^{3}H-digoxin in magnesium deficiency. *Proc Soc Exp Biol Med* 1971; 136: 747–749
77. Isner JM, Sours HE, Paris AL et al: Sudden, unexpected death in avid dieters using the liquid-protein–modified-fast diet. *Circulation* 1979; 60: 1401–1412
78. Sours HE, Frattali VP, Brand CD et al: Sudden death associated with very low calorie weight reduction regimens. *Am J Clin Nutr* 1981; 34: 453–461
79. Licata AA, Lantigua R, Amatruda J et al: Adverse effects of liquid protein fast on the handling of magnesium, calcium and phosphorus. *Am J Med* 1981; 71: 767–772
80. Seelig JM, Wei EP, Kontos HA et al: Effect of changes in magnesium ion concentration on cat cerebral arterioles. *Am J Physiol* 1983; 245: H22–H26
81. Altura BM, Altura BT, Carella A: Magnesium deficiency-induced spasms of umbilical vessels: relation to pre-eclampsia, hypertension, growth retardation. *Science* 1983; 221: 376–378
82. Dyckner T, Wester PO: Effect of magnesium on blood pressure. *Br Med J* 1983; 286: 1847–1849
83. Altura BM, Altura BT: Magnesium ions and contraction of vascular smooth muscles: relationship to some vascular diseases. *Fed Proc* 1981; 40: 2672–2679
84. Dhingra S, Solven F, Wilson A et al: Hypomagnesemia and respiratory muscle power. *Am Rev Respir Dis* 1984; 129: 497–498
85. Marks P, Ashraf H: Apathetic hyperthyroidism with hypomagnesaemia and raised alkaline phosphatase concentration. *Br Med J* 1978; 2: 821–822
86. Elin RJ, Alling DW: Survival of normal and magnesium-deficient erythrocytes in rats: effect of magnesium-deficient diet vs splenectomy. *J Lab Clin Med* 1978; 91: 666–672
87. Hamed IA, Lindeman RD: Dysphagia and vertical nystagmus in magnesium deficiency. *Ann Intern Med* 1978; 89: 222–223
88. Johansson G: Magnesium and renal stone disease. *Acta Med Scand [Suppl]* 1982; 661: 13–18
89. Narins RG, Jones ER, Stom MC et al: Diagnostic strategies in disorders of fluid, electrolytes and acid–base homeostasis. *Am J Med* 1982; 72: 496–520
90. Bohmer T, Mathiesen B: Magnesium deficiency in chronic alcoholic patients uncovered by an intravenous loading test. *Scand J Clin Lab Invest* 1982; 42: 633–636
91. Thoren L: Magnesium metabolism. A review of the problems related to surgical practice. *Prog Surg* 1971; 9: 131–156
92. Freeman JB, Whittine MF, Stegink LD et al: Effects of magnesium infusions on magnesium and nitrogen balance during parenteral nutrition. *Can J Surg* 1982; 25: 570–574
93. Macauley VM, Begent RHJ, Newlands ES: Prophylaxis against hypomagnesemia induced by cis-platinum combination chemotherapy. *Cancer Chemother Pharmacol* 1982; 9: 179–181