

Disorders of Magnesium Metabolism

ABSTRACT

Magnesium plays an important role in many physiologic functions and disorders of magnesium homeostasis are common in hospital populations. As magnesium is mainly an intracellular ion, assessment of magnesium status is difficult. Of all the methods used for assessing magnesium status, the magnesium tolerance test is currently the best one. Hypomagnesemia, which is much more

frequent than hypermagnesemia, is commonly caused by an increased gastrointestinal or renal loss of magnesium. Hypomagnesemia will lead to hypocalcemia and neuromuscular manifestations such as tetany, muscle weakness and cardiovascular effects such as arrhythmias. If hypomagnesemia is detected, it should be treated to prevent development of complications.

KEY WORDS: Hypomagnesemia, hypermagnesemia, hypocalcemia, hypokalemia.

Magnesium is the fourth most abundant cation in the body and within the cell it is the second most abundant cation after potassium. Magnesium plays an essential physiologic role (see Table 1), and this role is achieved through its ability to form chelates with important intracellular-anionic ligands, especially ATP and its ability to compete with calcium for binding sites, proteins and membranes.¹ Over 300 enzyme reactions are dependent on magnesium and the Km for magnesium of these enzymes is near the intracellular free magnesium concentration. Magnesium affects myocardial contractility and electrical activity of the myocardial cells, and the specialized conducting system of the heart by its ability to influence movement of ions such as sodium, potassium, and calcium across the sarcolemmal membrane. There is also evidence to suggest that magnesium may affect the vascular smooth muscle tone. Changes in intracellular magnesium concentration can induce changes in cell proliferation or maturation. Magnesium is therefore essential for the synthesis of nucleic acids and proteins, for intermediary metabolism, and energy producing/energy consuming reactions, and for specific actions in different organs such as the neuromuscular and cardiovascular systems.

Magnesium metabolism

The normal human adult contains approximately 1,000 mmols of magnesium (22-26 g) and the distribution within the body is given in Table 2. Only about 30% of magnesium in bone and 20-30% of magnesium in muscle are readily exchangeable. In the soft tissues, magnesium is present mainly bound to ligands such as ATP and RNA, nucleoproteins and lipoproteins.

In normal adults, serum magnesium concentrations range between 0.70-1.10 mmol/l. At physiologic pH and body temperature, approximately 20% of total serum magnesium is protein-bound and 80% is ultrafiltrable. Of the ultrafiltrable fraction most is in ionized form (65% of the total), the remainder is complexed with various anions such as phosphate and citrate. Of the protein bound fraction 60-70% is associated with albumin and the rest is bound to globulins.² Acid-base disturbances have little or no effect on the distribution of serum magnesium between the different fractions.

Intracellular free ionized magnesium constitutes only 0.5-5% of the total cellular magnesium, the remaining fraction is found as ATP-bound magnesium, which accounts for nearly 80% of the intracellular magnesium or sequestered within

mitochondria and endoplasmic reticulum. Intracellular free magnesium measured using fluorescent dye is about 0.5 mmol/l.³ However, this varies between different cells and within cells. The concentration of intracellular magnesium is maintained within narrow limits even when the extracellular fluid (ECF) magnesium concentration varies. However, very little is known about the mechanisms involved in the regulation of intracellular magnesium.

Magnesium balance

The recommended daily allowance (RDA) for magnesium is 4.5 mg/kg/day for adults. The daily requirement is higher during pregnancy, lactation, following debilitating illness, those on high intakes of calcium, phosphate, and high fat diet, and those under environmental stresses.

Foods rich in magnesium are cereal grain, nuts, legume, chocolates, and green vegetables that are rich in magnesium-containing chlorophyll. Dairy products and beverages are poor in magnesium.⁴ Drinking water, especially 'hard water,' which contains up to 30 mg/l of magnesium, is an important source. Refining or processing of food and cooking, especially boiling, will result in loss of magnesium.

Although plasma magnesium concentration is kept within narrow limits, the exact physiologic mechanisms that regulate

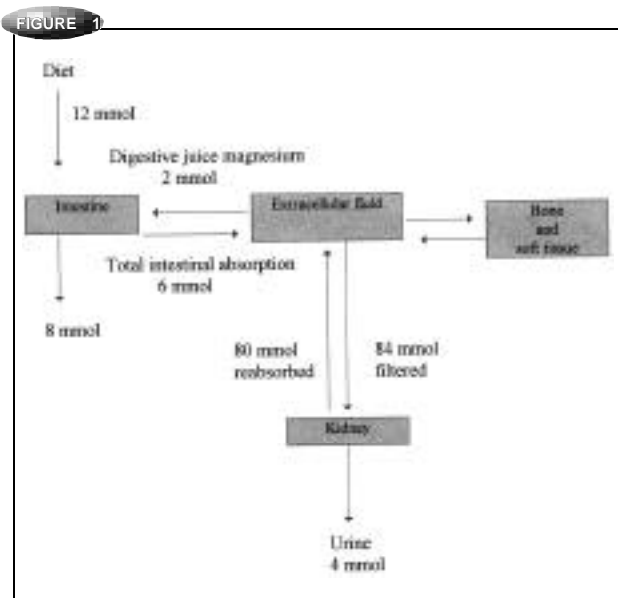


Fig. 1: Magnesium turnover in an adult male.

FIGURE 2

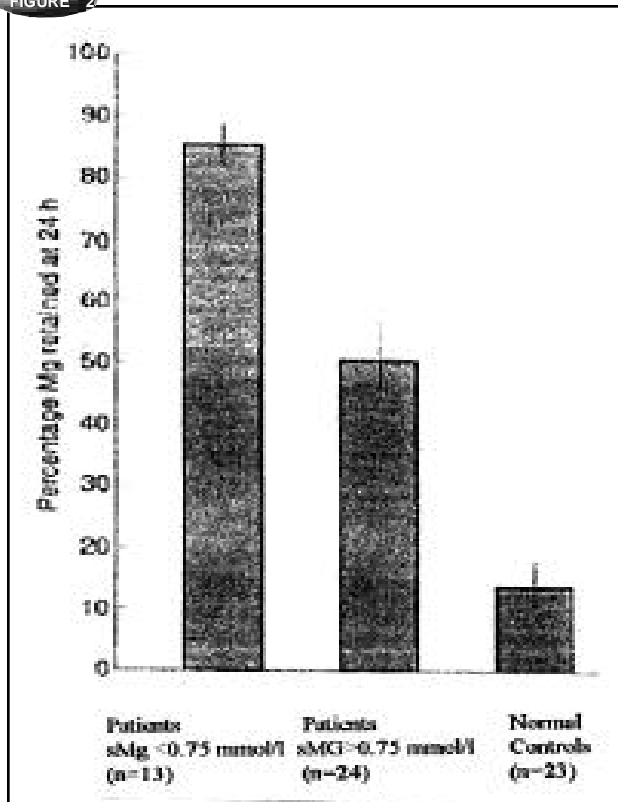


Fig. 2: Percentage magnesium retained after infusion of 0.1 mmol of magnesium/kg body weight in normal subjects, hypomagnesemic subjects, and normomagnesemic subjects at high risk of magnesium deficiency (adapted from Ryzen et al (1989) with permission).

this are not fully understood. Fig. 1 shows the metabolism of magnesium in a normal adult. In normal individuals consuming a balanced diet, about 30-50% of dietary magnesium is absorbed but fractional absorption can vary from 65-11% depending on the intake.⁵ Until recently it was thought that magnesium was absorbed mainly and uniformly in the small intestine, but recent studies suggest that the large intestine may be an important site of magnesium absorption.⁶ At normal intakes, absorption is primarily passive and at low intakes it is active. Other dietary constituents such as phytate, fibre, oxalate, and phosphate can influence magnesium absorption. The exact role of hormonal factors such as PTH and vitamin D (1,25 dihydroxy vitamin D) on magnesium absorption is not fully understood.⁷

The kidneys play a major role in the regulation of magnesium homeostasis. Under normal circumstances when 80% of the total plasma magnesium is ultrafiltrable, 84 mmol of magnesium is filtered and about 3-5 mmol appears in the urine in 24 hours following about 95% reabsorption. Of the filtered magnesium only about 25-30% is reabsorbed in the proximal tubular segments including both the convoluted and the straight portions.⁸ Approximately 60-65% of filtered magnesium is reabsorbed in the thick ascending limb of the loop of Henle (TALH) and the rest (about 5%) is reabsorbed in the distal segments. There is no evidence for secretion of magnesium along the renal tubules.

Of the many factors affecting renal magnesium excretion, the plasma magnesium concentration is a major determinant of urinary magnesium excretion.⁸ Hypermagnesemia is associated with an increase in magnesium excretion that approaches 100% of the filtered load. No single hormone has been shown to be specifically related to magnesium homeostasis. Many hormones including PTH, antidiuretic hormone (ADH), calcitonin, glucagon, and insulin have been shown to affect mag-

FIGURE 3

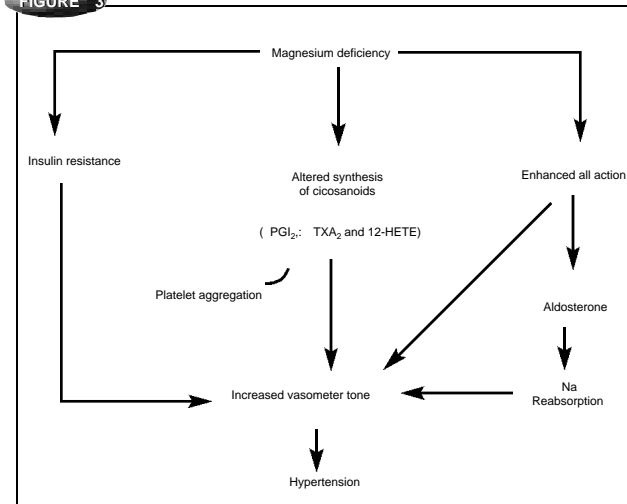


Fig. 3: Hypothesis linking magnesium deficiency to altered vascular function and insulin resistance. AIT angiotensin II, PGI₂, prostaglandin I₂, TXA₂, thromboxane A₂, 12-HETE 12, hydroxyeicosatetraenoic acid (adapted from Nadler & Rude (1995) with permission).

nesium reabsorption and of these PTH is thought to play a significant role. Although PTH increases the reabsorption of magnesium, magnesium excretion is higher in hyperparathyroid subjects due to the concomitant effect of hypercalcaemia which opposes the action of PTH.

Assessment of magnesium status

As magnesium is mainly an intracellular ion, assessing its status is difficult. At present, there is no simple, rapid, and accurate laboratory test to indicate the total body magnesium sta-

Table 1. Physiologic functions of magnesium.

<p>▷ Enzyme function</p>	
<p>à Enzyme substrate (ATPmg, GTPmg)</p> <ul style="list-style-type: none"> • Kinases B <ul style="list-style-type: none"> - Hexokinase - Creatine kinase - Protein kinase 	
<p>à ATPases or GTPases</p> <ul style="list-style-type: none"> • Cyclases <ul style="list-style-type: none"> - adenylate cyclase - Guanylate cyclase 	
<p>à Direct enzyme activation</p> <ul style="list-style-type: none"> • Phosphofructokinase • Creatine kinase • 5-phosphoribosyl-pyrophosphate synthetase • Adenylate cyclase • Na⁺,K⁺-ATPase 	
<p>▷ Membrane function</p>	
<p>à Cell adhesion</p>	
<p>à Transmembrane electrolyte flux</p>	
<p>▷ Calcium antagonist</p>	
<p>à Muscle contraction/relaxation</p>	
<p>à Neurotransmitter release</p>	
<p>à Action potential conduction in nodal tissue</p>	
<p>▷ Structural function</p>	
<p>à Protein</p>	
<p>à Polyribosomes</p>	
<p>à Nucleic acids</p>	
<p>à Multiple enzyme complexes</p>	
<p>à Mitochondria</p>	

Table 2. Distribution of magnesium in the adult human.

Tissue	Weight (kg wet wt)	Concentration (mmol/kg wet wt)	Content (mmol)	% of total body magnesium
Serum	3.0	0.85	2.6	0.3
Red blood cells	2.0	2.5	5.0	0.5
Soft tissue	22.7	8.5	193.0	19.3
Muscle	30.0	9.0	270.0	27.0
Bone	12.3	43.2	530.1	52.9
Total	70.0		1000.7	100

tus⁹ (see Table 3). The most commonly used method is serum magnesium concentration and there are several methods available for this. Of these colorimetric methods, xylydyl blue is the most widely used in many laboratories.¹⁰ Magnesium concentration is preferably measured in serum rather than plasma as the anticoagulant used for collection of plasma could be contaminated with magnesium or could affect the assay procedure. For instance, citrate binds not only calcium but also magnesium and affects the fluorometric and colorimetric methodology. It is also important to avoid hemolysis because the magnesium concentration in red cells is approximately three times greater than that of serum and it has been estimated that serum magnesium concentration will increase by 0.05 mmol/l for each gram/l of hemoglobin produced by haemolysis. Measurement of serum total magnesium concentration can also be affected by high bilirubin concentration, lipemic serum, and high phosphate concentration. Delay in separating cells will artificially elevate serum magnesium concentration. In adults, serum magnesium concentration is not influenced by sex or age, except in the very elderly where it may be slightly higher. Variation in serum magnesium concentration between individuals (interindividual) is between 5.9–7.5% and within individuals (intraindividual) is 3.4–4.7%. Colorimetric methods commonly used for the measurement of magnesium have relatively poor analytic perfor-

Table 3. Tests used in assessing magnesium status.

↳ Serum magnesium concentration
↳ Total magnesium
↳ Ultrafiltrable magnesium
↳ Ionized magnesium
↳ Intracellular magnesium content
↳ Red cells
↳ Mononuclear blood cells
↳ Skeletal muscle
↳ Physiologic test
↳ Metabolic balance studies
↳ 24-hour urinary excretion of magnesium
↳ Magnesium loading test
↳ Intracellular free magnesium ion concentration
↳ Fluorescent dye
↳ Nuclear magnetic resonance spectroscopy
↳ Others
↳ Magnesium balance
↳ Isotope studies
↳ Hair or tooth magnesium
↳ Functional assays

mance in relation to the biologic variation.¹⁰

The total serum magnesium concentration is not the best method to evaluate magnesium status for several reasons.⁹ As about 30% of serum magnesium is bound to proteins, changes in serum protein concentrations may affect serum total magnesium concentration without necessarily affecting the physiologically active ionized fraction or showing any change in total body magnesium status. Furthermore, serum concentration can be acutely affected by exogenous and endogenous catecholamines, which may cause a fall of approximately 0.2 mmol/l. It may also be normal or even elevated in the presence of intracellular magnesium deficiency if there is associated volume contraction or rhabdomyolysis. Ionized, together with the complexed, fraction can be measured as ultrafiltrable magnesium, and this measurement may be more meaningful than that of the total magnesium as it is likely to reflect ionized magnesium concentration. In the last few years ion-selective electrodes for magnesium have been developed and several commercial analyzers are now available for the measurement of ionized magnesium concentration.¹⁰ However, results from different instruments do not agree as a correction must be applied because there is difficulty in producing an ionophore and membranes specific for magnesium and free from interference by calcium.

Total red blood cell magnesium concentration can be determined directly or indirectly using total magnesium concentration of whole blood and hematocrit.⁹ This indirect method is reproducible, reliable, accurate and easy to perform. However, it does not seem to correlate well with total body or other measures of magnesium status. The magnesium content of mononuclear cells is a better predictor of total magnesium, but the method is technically more difficult than either red cell magnesium or serum magnesium and intraindividual variation at 12–22% is high. Platelet total magnesium and ionized magnesium can be measured, but the value of this test against other methods has not yet been properly evaluated. As muscle contains nearly 30% of the total body magnesium, it is logical to conclude that it is an appropriate tissue for the assessment of magnesium status. However, this is an invasive procedure and requires special expertise. The 24-hour urine excretion of magnesium reflects intestinal absorption of magnesium, and for accurate assessment, the urine should be collected with acid to prevent precipitation of magnesium salt due to high pH. It is of value in determining whether magnesium wasting is by the renal route. In the presence of hypomagnesemia, a 24-hour urine magnesium excretion higher than 1 mmol/day is suggestive of renal magnesium wasting.

Magnesium tolerance test has been used for many years and appears to be an accurate means of assessing magnesium status.⁹ In this test, 0.1 mmol magnesium/kg body weight in 50 ml of 5% dextrose is infused intravenously over 4 hours; the urinary excretion of magnesium over the next 24 hours (starting with the infusion) is determined and the percentage of magnesium retained is calculated. Percentage of magnesium retained that is greater than 25% is indicative of magnesium deficiency. As shown in Fig. 2, this test is a very sensitive method to detect magnesium deficiency. However, it depends on normal renal function and it may be of limited value in patients with poor renal function or those in whom there is increased magnesium loss through the kidneys.

As magnesium is important for many enzymes, the activation of magnesium-containing enzymes such as creatine kinase and alkaline phosphatase have been examined as indices of magnesium, but they are not satisfactory.⁹

In summary, no single method is satisfactory to assess magnesium status. The simplest, most useful and readily available methods are serum total magnesium concentration and magnesium tolerance test. These together with full clinical evaluation will be adequate in most clinical situations.

Magnesium deficiency and hypomagnesemia

The terms hypomagnesemia and magnesium deficiency are

Table 4. Causes of hypomagnesaemia.

↳ Redistribution of magnesium
↳ Refeeding and insulin therapy
↳ Hungry bone syndrome
↳ Correction of acidosis
↳ Catecholamine excess
↳ Massive blood transfusion
↳ Gastrointestinal causes
↳ Reduced intake
• Mg-free intravenous fluids
• Dietary deficiency
§ low oxalate diet
§ cellulose phosphate
↳ Reduced absorption
• Malabsorption syndrome
• Chronic diarrhea
• Intestinal resection
• Primary infantile hypomagnesemia
↳ Renal loss
↳ Reduced sodium reabsorption
• Saline infusion
• Diuretics
↳ Drugs
• Diuretics
• Cytotoxic drugs
§ Cisplatin
§ Carboplatin
§ Gallium nitrate
§ Deoxyspergualin
• Antimicrobial agents
§ Aminoglycosides
◦ Gentamicin
◦ Tobramycin
◦ Amikacin
◦ Antituberculous drugs
- Viomycin
- Caproxyimycin
§ Immunosuppressants
◦ Cyclosporine
◦ FK 506
§ Beta adrenergic agonists
◦ Theophylline
◦ Salbutamol
◦ Rimiterol
§ Other drugs
◦ Amphotericin B
◦ Pentamidine
◦ Foscarnet
◦ Pamidronate
◦ Anascrine
↳ Renal disease
• Postobstructive nephropathy
• Postrenal transplantation
• Dialysis
• Diuretic phase of acute renal failure
↳ Inherited disorders
• Bartter's syndrome
• Gitelman's syndrome
↳ Endocrine causes
↳ Hypercalcemia
• Primary hyperparathyroidism
• Malignant hypercalcemia
↳ Hyperthyroidism
↳ Hyperaldosteronism
↳ Diabetes mellitus
↳ Alcoholism
↳ Miscellaneous

commonly used interchangeably, although total body magnesium depletion can be present with normal serum magnesium concentrations and there can be significant hypomagnesemia without total body deficit.

Magnesium deficiency can be divided into (a) those in which there is a general loss of cell mass, for example starvation, and in which the serum magnesium concentration is usually normal and (b) those in which there is selective magnesium deficiency, when hypomagnesemia is usually present. Loss of cell mass as in starvation, trauma, and protein-calorie malnutrition is accompanied by intracellular magnesium loss as well as loss of potassium, phosphate, and protein and the ratio of magnesium to nitrogen in muscle will remain normal.⁷ Selective magnesium deficiency usually causes hypomagnesemia, although intracellular free magnesium concentration is maintained at the expense of bound intracellular magnesium and extracellular magnesium.

With the introduction of routine colorimetric methods for measurement of serum magnesium concentration, it has been possible to measure magnesium more readily in clinical laboratories and hypomagnesemia is now recognized as more prevalent than was previously realized.¹¹ It may be the single most underdiagnosed electrolyte abnormality in current clinical practice. In large surveys, prevalence of hypomagnesemia has been found to range from 6.9%–11% of hospitalized patients. Hypomagnesemia is more common in critically ill patients ranging from 20% to as high as 65% in medical intensive care units and in patients with other electrolyte abnormalities. Hypomagnesemia is not detected clinically in about 90% of hypomagnesemic patients and is identified only by routine measurement of serum magnesium concentration.¹¹

Magnesium deficiency may result from one or more of the following mechanisms: reduced intake, reduced intestinal magnesium absorption, increased gastrointestinal loss, increased loss though the kidneys or redistribution of magnesium from extracellular or intracellular fluid. Causes of magnesium deficiency are listed in Table 4.

Hypomagnesemia may result during refeeding of starved patients, so-called refeeding syndrome; due to redistribution of magnesium from extracellular fluid into cells or bone. Similar redistribution of magnesium into cells accounts for hypomagnesemia seen during correction of metabolic acidosis, during rapid correction of respiratory acidosis, in hungry bone syndrome, precipitated either by parathyroidectomy or by diffuse osteoblastic metastases. Hypomagnesemia has been reported in up to 20% of patients with acute pancreatitis, probably due to deposition of magnesium in areas of necrosis. Hypomagnesemia seen during treatment of diabetic ketoacidosis is due to retention of magnesium in cells during treatment with insulin and may be predisposed by pre-existing magnesium deficiency, correction of acidosis, and phosphate administration. Catecholamines decrease magnesium concentration due to a shift of magnesium into cells as a result of stimulation of beta adrenergic receptors. High catecholamines may be one of the contributing factors for the hypomagnesemia seen during and after cardiac surgery and in congestive heart failure. Massive blood transfusion may cause low ionized magnesium due to chelation of magnesium by citrate.

Magnesium deficiency entirely due to reduced dietary intake in otherwise healthy subjects is very uncommon because the kidney has a remarkable capacity to conserve magnesium. Nevertheless, magnesium deficiency and hypomagnesemia may occur in patients who are maintained on magnesium-free intravenous fluids or total parenteral nutrition, especially in those patients who have marginal or reduced magnesium at the start.¹² Occasionally, magnesium deficiency is seen in patients during treatment of nephrolithiasis due to low magnesium content of the low oxalate diet and due to the use of cellulose phosphate.

Hypomagnesemia and magnesium deficiency are common in patients with gastrointestinal disorders, in conditions causing steatorrhea or severe chronic diarrhea such as Crohn's dis-

Table 5. Clinical features of hypomagnesemia.

- ↳ **Electrolyte disturbance**
 - ↳ Hypokalemia
 - ↳ Hypocalcemia
- ↳ **Neuromuscular and central nervous system**
 - ↳ Carpopedal spasm
 - ↳ Convulsions
 - ↳ Muscle cramps
 - ↳ Muscle weakness, fasciculations, tremors
 - ↳ Vertigo
 - ↳ Nystagmus
 - ↳ Depression, psychosis
 - ↳ Athetoid movements and choreiform movements
- ↳ **Cardiovascular**
 - ↳ Atrial tachycardias, fibrillation
 - ↳ Supraventricular arrhythmias
 - ↳ Ventricular arrhythmias
 - ↳ Torsade de pointes
 - ↳ Digoxin sensitivity
- ↳ **Complications of magnesium deficiency**
 - ↳ Altered glucose homeostasis
 - ↳ Atherosclerotic vascular disease
 - ↳ Hypertension
 - ↳ Myocardial infarction
- ↳ **Osteoporosis**
- ↳ **Miscellaneous**
 - ↳ Migraine
 - ↳ Asthma
 - ↳ Chronic fatigue syndrome
 - ↳ Athletic performance

ease, ulcerative colitis, coeliac disease, Whipple's disease, and short-bowel syndrome.¹² Hypomagnesemia is a frequent complication in patients with short-bowel syndrome, including patients who have had intestinal bypass surgery for obesity. Magnesium deficiency in bowel disease is exacerbated if there is loss of intestinal secretions due to fistula formation or by continuous suction of gastrointestinal fluids. Patients with chronic diarrhea or fistula may develop magnesium deficiency, especially if they are maintained on intravenous fluids devoid of magnesium because the secretions from the lower intestinal tract contain more magnesium than the upper intestinal tract. Hypomagnesemia has also been found with excessive use of laxatives and in some a pseudo-Bartter's syndrome has been described. An inherited disorder causing isolated magnesium malabsorption associated with hypocalcemia, tetany, and seizures has been described in infants as well as in older individuals.¹² Children usually present at 4-5 weeks of age with generalized convulsions and there may be associated protein losing enteropathy, hypoalbuminemia, and anasarca. The lesion is likely to be a defect in the carrier-mediated transport system in the small intestine and treatment is to increase the oral intake of magnesium to approximately 5 times the normal daily requirement.

As proximal tubular magnesium reabsorption is proportional to the tubular fluid flow and sodium reabsorption chronic intravenous fluid therapy, particularly sodium-containing fluids, and osmotic diuresis may result in magnesium deficiency created by sodium chloride reabsorption. Loop diuretics (frusemide, bumetanide, and ethacrynic acid) inhibit magnesium transport in the TALH and magnesium depletion can result from long-term use of loop diuretics. Thiazide diuretics act on the distal convoluted tubule and short-term administration of thiazide does not produce magnesium wasting, whereas long-term administration may produce substantial magnesium depletion. Secondary hyperaldosteronism, increased sodium load, and interaction with calcium metabolism are all factors that contribute to magnesium loss in long-term thiazide therapy. However, in conventional doses, thiazides do not cause significant magnesium deficiency.

A variety of drugs including antibiotics and chemotherapeutic agents can cause magnesium wasting.¹³ Cisplatin, an inorganic platinum based chemotherapeutic agent used in the treatment of certain tumors, causes hypomagnesemia in a large percentage of patients and the incidence increases with cumulative cisplatin dose. Hypomagnesemia during cisplatin therapy may be acute or chronic. During the acute phase, apart from cisplatin, other factors contributing to magnesium wasting are the use of diuretics and poor dietary intake of magnesium. Chronic hypomagnesemia starts to develop 3 weeks after initiation of chemotherapy and persists usually for several months. Occasionally hypomagnesemia may persist for several years after completion of treatment. In chronic magnesium wasting, patients usually present with hypocalcemia, renal magnesium wasting, and hypokalaemic metabolic alkalosis—a picture similar to Gitelman's syndrome, features consistent with a distal tubular defect. In addition, there may be a lesion in the proximal tubule as shown by increased excretion of B₂ microglobulin and N-acetyl-B-glucosaminase (NAG), which are markers of tubular cell damage. Carboplatin, an analogue of cisplatin, causes less nephrotoxicity and only 10% of patients develop hypomagnesemia. Hypomagnesemia due to renal magnesium loss is seen with high doses of aminoglycosides including gentamicin, tobramycin, amikacin, viomycin, and capreomycin.¹³ Hypomagnesemia is seen both in short-term and long-term therapy and symptomatic hypomagnesemia is seen especially in the elderly or if there are other associated conditions causing magnesium loss. Cyclosporine causes increased magnesium excretion.¹³ The hypomagnesemia is usually mild, asymptomatic, and does not necessitate stopping the medication, but occasionally severe symptomatic magnesium deficiency is seen. Although serum total magnesium concentration during cyclosporine treatment is variable ionized magnesium concentration is low. Short-term cyclosporine treatment causes hypomagnesemia due to intracellular shift of magnesium whereas long-term treatment causes magnesium deficiency as a result of renal magnesium wasting. The newer immunosuppressive agent, FK506, can also produce hypomagnesemia. Overdose with theophylline causes hypomagnesemia and patients on theophylline are at increased risk of developing hypomagnesemia.¹³ The hypomagnesemia is accompanied by other metabolic abnormalities including hypokalemia, hyponatremia, hypophosphatemia, and hyperglycemia, and there is a linear relationship between plasma drug concentration and the metabolic abnormalities. Adrenaline and other beta-2 agonists, salbutamol and rimiterol, causes a decrease in plasma magnesium concentration due to shift of magnesium into the cells. Amphotericin B, a highly nephrotoxic agent, can cause mild but reversible hypomagnesemia.¹³ Pentamidine may cause severe symptomatic hypomagnesemia due to renal magnesium wasting. Up to 70% of patients treated with foscarnet for cytomegalovirus retinitis in patients with AIDS has been shown to have hypomagnesemia. The exact mechanism for this is not clear. Pamidronate used in the treatment of hypercalcemia and malignancy has been found to cause significant hypomagnesemia, and patients treated with ansacrine can develop transient hypomagnesemia possibly due to transcellular shift.

Hypomagnesemia is occasionally observed in chronic renal failure probably due to an obligatory renal magnesium loss. Renal magnesium wasting may also occur during the diuretic phase of acute renal failure, in postobstructive diuresis and after renal transplantation. Hypocalcemia, hypomagnesemia, and hypocalcemia with renal magnesium wasting have been reported in patients with tubular interstitial renal disease. Patients on continuous ambulatory peritoneal dialysis develop hypomagnesemia when low magnesium dialysis fluid is used.

Hypokalemia and magnesium depletion has also been described in a variety of endocrine metabolic disorders.⁷ Although parathyroid hormone (PTH) has been shown to

Table 6. Causes of hypermagnesemia.

- ▷ **Redistribution**
 - Acute acidosis
- ▷ **Excessive intake**
 - Oral
 - Antacids
 - Cathartics
 - Swallowing salt water
 - Rectal
 - Purgation
 - Parenteral
 - Urethral irrigation
- ▷ **Renal failure**
 - Chronic renal failure
 - Acute renal failure
 - Rhabdomyolysis
- ▷ **Others**
 - Lithium infection
 - Familial hypocalciuric hypercalcemia
 - Hypothyroidism
 - Addison's disease
 - Milk alkali syndrome
 - Depression

increase the reabsorption of magnesium, hypomagnesemia has been described in primary hyperparathyroidism, and this is thought to be due to the opposite effect of hypercalcemia on renal tubular magnesium reabsorption. Hypomagnesemia may develop in the postoperative period after parathyroidectomy due to the entry of magnesium into cells as part of the 'hungry bone syndrome.' Hypercalcemia of malignancy may also cause hypomagnesemia due to increase renal magnesium excretion. Plasma magnesium concentrations tend to be lower in hyperthyroidism due to increased magnesium excretion. Hypomagnesemia seen in primary and secondary hyperaldosteronism is due to volume expansion and the consequent increased delivery of sodium, calcium, and magnesium to the distal tubules. A similar volume-related mechanism might also explain hypomagnesemia that occurs in patients with the syndrome of inappropriate antidiuretic hormone secretion. Phosphate depletion is commonly associated with hypomagnesemia due to renal magnesium wasting.

Diabetes mellitus, both insulin-dependent and noninsulin-dependent, is one of the most common^{7,11} causes of magnesium deficiency, with an incidence of hypomagnesemia between 25-39%. Magnesium depletion of diabetes mellitus is thought to be due to increased excretion brought about by osmotic diuresis, but there may also be a specific tubular defect. The decrease in serum magnesium concentration is correlated with fasting blood sugar, glycated hemoglobin, and with the duration of diabetes. The magnesium depletion/hypomagnesemia of diabetes mellitus may be of pathogenic significance in the development of diabetic complications such as retinopathy and hypertension via its effects on inositol transport.

The incidence of hypomagnesemia may be as high as 30% in acute and chronic alcoholics.¹⁴ In many patients, magnesium deficiency can be detected using the magnesium loading test, even when the magnesium concentration in the blood is normal. Multiple mechanisms interact to produce magnesium depletion and these include poor nutritional status, magnesium loss through vomiting and diarrhea, malabsorption produced as a result of steatorrhea due to chronic pancreatitis or liver disease, phosphate depletion, vitamin D deficiency, acute alcoholic ketoacidosis, hyperaldosteronism secondary to liver disease, and a renal tubular dysfunction.⁷

Bartter's syndrome, a congenital disorder, is characterized by chronic hypokalemia with renal potassium wasting, hyperchloraemic metabolic alkalosis, hyperreninemia, secondary hyperaldosteronism, and renal magnesium wasting.¹⁵ The

Table 7. Clinical manifestations of hypermagnesemia.

- ▷ **Neuromuscular**
 - Confusion
 - Lethargy
 - Respiratory depression
 - Absent tendon reflexes
 - Paralytic ileus
 - Bladder paralysis
 - Muscle weakness/paralysis
- ▷ **Cardiovascular**
 - Hypotension
 - Bradycardia
 - Inhibition of AV and interventricular conduction
 - Heart block
 - Cardiac arrest
- ▷ **Others**
 - Nausea, vomiting

abnormality in this syndrome lies within the epithelial cells of the medullary thick ascending limb of the nephron, where mutations of the bumetanide-sensitive sodium-potassium-chloride cotransporter (KCC2) or the ROMK1 channel leads to impairment of sodium and chloride reabsorption.¹⁵ Gitelman's syndrome is characterized by renal tubular hypokalemic alkalosis, hypomagnesemia, and hypocalciuria. Urinary calcium excretion is normal or increased in Bartter's syndrome. In Bartter's syndrome, hypomagnesemia is present in 39% of cases whereas in Gitelman's syndrome hypomagnesemia is a consistent finding. Gitelman's syndrome is usually a benign disorder diagnosed in adolescence and adults, whereas Bartter's syndrome is usually seen in infants and children under the age of 6 years. Gitelman's syndrome is due to mutations in the thiazide-sensitive sodium-chloride cotransporter (NCCT) in the distal convoluted tubule.¹⁵

Hypomagnesemia is seen in 40% of patients with severe burns and is due to loss of magnesium through the burns area, topical application of antibiotic spray, and catecholamine release. Prolonged exercise in humid conditions may lead to excessive magnesium loss.

Clinical manifestation of hypomagnesemia and magnesium deficiency

Many patients with magnesium deficiency and hypomagnesemia remain asymptomatic. As magnesium deficiency is usually secondary to other disease processes or drugs, the features of the primary disease may complicate or mask magnesium deficiency. Signs and symptoms of magnesium deficiency are usually not seen until the magnesium concentration decreases to 0.5 mmol/l or lower. Furthermore, the clinical manifestations may depend more on the rate of development of magnesium deficiency and/or the total body deficit rather than the actual serum magnesium concentration. Long-term magnesium deficiency may have a role in chronic diseases such as atherosclerosis, myocardial infarction, hypertension, and renal calculi. Clinical manifestations of severe or moderate magnesium deficiency are listed in Table 5.

Biochemical manifestations

Hypokalemia. Magnesium and potassium are closely related and hypokalemia is a frequent finding in patients with hypomagnesemia.¹⁶ Intracellular magnesium deficiency causes a low intracellular potassium and an inability of the kidney to conserve potassium. The potassium depletion cannot be corrected until the magnesium depletion is corrected. The exact mechanism underlying this interrelationship is not clear. It may be related to the dependence of Na,K-ATPase, Na,K-Cl cotransport, potassium channels and other transport processes on magnesium. The hypokalemia of magnesium deficiency contributes to the cardiac manifestations of hypomagnesemia,

but may delay the onset of tetany.

Hypocalcemia. Hypocalcemia is a common manifestation in hypomagnesemia. Up to one-third of patients with hypomagnesemia in intensive care units may have hypocalcemia.⁷ Symptomatic hypocalcemia is usually seen in moderate to severe magnesium deficiency and there is a positive correlation between serum magnesium and calcium concentrations in these patients. Hypocalcemia of magnesium deficiency like hypokalemia cannot be corrected by treatment with calcium, vitamin D, or both. Magnesium therapy alone will restore serum calcium concentration to normal. Several factors contribute to the hypocalcemia of magnesium deficiency and these are: (a) a decrease in PTH secretion, (b) resistance to the action of PTH, (c) decrease in serum concentration of 1,25 dihydroxy vitamin D due to decreased production, causing reduced intestinal calcium absorption, and (d) resistance to 1,25 dihydroxy vitamin D.^{7,17}

In acute situations, low magnesium concentration increases PTH secretion. However, in magnesium deficiency, there is impairment of PTH release. End organ resistance is suggested by the presence of decreased osteocalcin concentration and the failure of serum calcium concentration to rise despite an increase in PTH when hypomagnesemic patients are treated with magnesium. Administration of exogenous PTH to hypocalcemic hypomagnesemic patients has little effect on serum calcium concentrations. The urinary excretion of cyclic adenosine monophosphate (AMP) and phosphate in response to administration of exogenous PTH is impaired in severe magnesium depletion. In magnesium deficiency, serum concentration 1,25 dihydroxy vitamin D is low or low/normal and does not rise in response to low calcium diet. There is also evidence for increased clearance of 1,25 dihydroxy vitamin D. Endorgan resistance to vitamin D and its metabolites in magnesium deficiency is shown by reduced binding of 1,25 dihydroxy vitamin D to bone tissue and the reduced intestinal response to exogenous 1,25 dihydroxy vitamin D.

Neuromuscular and central nervous system manifestations

The earliest manifestations of symptomatic magnesium deficiency are usually neuromuscular and neuropsychiatric disturbances.¹⁷ The most common clinical manifestation is hyperexcitability manifested as positive Chvostek and Trousseau signs, tremor, fasciculations, and tetany. Other manifestations include convulsions, athetoid movements, nystagmus, dysphagia, apathy, muscle cramps, hyperreflexia, acute organic brain syndrome, depression, generalized weakness, reversible psychiatric manifestations, anorexia, and vomiting. Occasionally hemiparesis, aphasia, and reduced respiratory muscle power have also been found. Several mechanisms contribute to these features. The threshold of axon stimulation is decreased and nerve conduction velocity is increased when serum magnesium concentration is low. By competitively inhibiting the entry of calcium into the presynaptic nerve terminals, magnesium influences the release of neurotransmitters at the neuromuscular junction and causes hyperresponsive neuromuscular activity. The release of calcium from the sarcoplasmic reticulum in muscle is increased and the reuptake of calcium is reduced in magnesium deficiency. The net effect is a muscle that is more readily contractible to a given stimulus and that is less able to recover from the contraction, i.e., prone to tetany.¹⁷ The effect of magnesium deficiency on the central nervous system is even more complicated and less well understood.

Cardiovascular manifestations

Cardiovascular manifestations of acute magnesium deficiency include effects on electrical activity, myocardial contractility, potentiation of digoxin toxicity and on vascular tone.⁷ Various ECG changes have been described, which include slight prolongation of conduction and depression of ST segment, but

these are non-specific. Magnesium depletion also increases the susceptibility to arrhythmogenic effects of drugs such as isoproterenol and cardiac glycosides. The effects of magnesium deficiency on the heart are further complicated by intracellular potassium depletion and hypokalemia. The spectrum of arrhythmias includes supraventricular arrhythmias such as premature atrial complexes, atrial tachycardia, atrial fibrillation, junctional arrhythmias, ventricular premature complexes, ventricular tachycardia, and ventricular fibrillation. Torsade pointes, a repetitive polymorphous ventricular tachycardia with prolongation of QT interval, has been reported in cases of hypomagnesemia, and this and other arrhythmias have been successfully treated with magnesium. However, this effect of magnesium may be a pharmacologic one and independent of the underlying magnesium deficiency. Hypomagnesemia and magnesium depletion may contribute to digoxin toxicity, even in the presence of apparently therapeutic concentration of serum digoxin and routine monitoring of serum magnesium concentration in digitalized patients has been recommended.⁷ Digoxin is thought to act via its inhibitory effect on the Na⁺,K⁺-ATPase, which is a magnesium-dependent enzyme. A low magnesium state causes a reduction in intracellular potassium and enhances the inhibitory effect of digoxin.⁷

Hardness of drinking water and the incidence of cardiovascular disease are inversely correlated as are the magnesium content of drinking water and death from ischemic heart disease.¹⁸ It has been suggested that long-term magnesium deficiency may contribute to the progression of atherosclerosis by increased peroxidation of lipoproteins, increased platelet aggregation, and by the development of hypertension (see the following).

Patients after myocardial infarction retain abnormally high amounts in a magnesium loading test and patients in cardiac intensive care have lower lymphocyte magnesium content. Because of these relationships and the fact that magnesium depletion may worsen or precipitate acute myocardial infarction and precipitate arrhythmias, intravenous magnesium therapy has been given to patients with acute myocardial infarction in an attempt to reduce morbidity and mortality. Meta-analysis of trials evaluating such intravenous therapy showed that mortality was reduced by 55%.¹⁹

Epidemiologic studies show an inverse relationship between magnesium intake and blood pressure.^{17,20} Possible mechanisms linking magnesium deficiency and hypertension are illustrated in Fig. 3.¹¹ In magnesium deficiency, angiotensin II-induced plasma aldosterone concentrations and production of thromboxane are increased. Insulin resistance of magnesium deficiency further increases the vascular tone. There is a reduction in the vasodilatory prostaglandin I₂ and an increase in vasoconstrictive prostaglandins, thromboxane A₂ and the lipo-oxygenase product 12-hydroxy-eicosatetraenoic acid. These changes lead to an increase in platelet aggregation and release in growth factors causing vasoconstriction. Changes in cytosolic free calcium produced by magnesium deficiency may further increase vascular reactivity. Magnesium may also have an effect on the endothelium-derived relaxing factor—nitric oxide.

Magnesium and bone

The magnesium content of trabecular bone and magnesium intake are lower in osteoporotic subjects²¹ and magnesium tolerance studies show increased retention of magnesium in osteoporotics.¹⁷ Magnesium intake is frequently below the recommended dietary intake in many groups, especially in the elderly. The mechanism whereby reduced magnesium status exacerbates osteoporosis is not clear but is probably multifactorial. As the hydrogen/potassium-ATPase pump in the cells of the periosteum and endosteum is magnesium-dependent; the pH of bone extracellular fluid in magnesium deficiency may fall resulting in demineralization. In addition, the formation of 1,25 dihydroxy vitamin D₃ involves a magnesium-

dependent hydroxylase enzyme, and serum 1,25 dihydroxy vitamin D concentrations are lower in magnesium deficiency.

Other manifestations

Magnesium is involved in many of the enzyme systems regulating glucose homeostasis and deficiency therefore may give rise to alteration in glucose metabolism. Magnesium deficiency inhibits the acute phase of insulin release in response to glucose challenge and reduces glucose disposal and/or insulin sensitivity.

Management of hypomagnesemia

Patients who present with signs and symptoms of deficiency should be treated promptly with magnesium. As oral magnesium is poorly absorbed and causes gastrointestinal side effects in large doses, parenteral nutrition is preferable. In critically ill patients with ventricular tachycardia or convulsions, 8 mmol of magnesium as magnesium sulfate should be given over one minute followed by 40 mmol of magnesium over the next 5 hours, and if necessary, another 40 mmol may be administered over the next 10 hours. In less urgent situations, 0.5 mmol/kg/24 hrs may be given by continuous intravenous infusion or 4 mmol (2 mls of 50% magnesium sulfate) may be given by intramuscular injection every 3 or 4 hours for the first day, but intramuscular injections are painful. Therapy should be continued for approximately 3-7 days and in patients continuing to lose magnesium from the intestines or kidneys, therapy may have to be continued for a longer duration. If patient is unable to eat normally, a daily maintenance dose of 4 mmol of magnesium should be given parenterally.¹¹

Mild asymptomatic hypomagnesemia can be treated by a diet rich in magnesium and/or by oral magnesium supplementation as gluconate, an initial dose of 12 mmol per day increasing to 48 mmol in divided doses (3 or 4 times a day) is recommended to avoid diarrhea.¹² Administration of potassium and calcium together with magnesium may be necessary since associated loss of these cations is common in severe magnesium deficiency. Assessment of renal function before replacement therapy and monitoring of serum concentrations of magnesium, potassium, and other major cations during therapy is recommended.

Hypermagnesemia

Hypermagnesemia is seen less frequently than hypomagnesemia due to the capacity of the normally functioning kidney to eliminate excess magnesium. Incidence of hypermagnesemia varies from 5.7-9.3% in hospital populations.²²

Causes of hypermagnesemia are listed in Table 6. Hypermagnesemia commonly occurs due to the excessive administration of magnesium salts or magnesium-containing drugs, especially in patients with reduced renal function. Hypermagnesemia due to redistribution from cells has been described in acute acidosis, e.g., in acidosis after massive theophylline overdose.

Magnesium-containing medications are commonly used as laxatives, antacids, and as rectal enemas, and hypermagnesemia has often been described with the use of magnesium-containing cathartics, especially during treatment of drug overdose.^{7,23} In patients with bowel disorders, the risk of hypermagnesemia is higher. The use of multiple doses of magnesium-containing cathartics is especially liable to cause hypermagnesemia, and serum magnesium concentrations as high as 9.5 mmol/l has been reported.²³

Hypermagnesemia frequently results from oral or intravenous therapy with magnesium salts such as in the treatment of eclampsia, some dysrhythmias and myocardial ischemia.²⁴ Hypermagnesemia may occur in the mother and occasionally in the infant following treatment of eclampsia. Urethral irrigation with hemiacidrin has been reported to cause symptomatic hypermagnesemia in patients with or without renal failure. Severe hypermagnesemia followed swallowing of salt

water in patients drowning in the Dead Sea.²⁵

Renal failure is the most common clinical disorder associated with hypermagnesemia. In acute renal failure, administration of exogenous magnesium during the oliguric phase can result in severe hypermagnesemia, especially in the acidotic patient. In chronic renal failure, severe hypermagnesemia may result especially if magnesium-containing medications are used and in patients undergoing regular dialysis, the serum magnesium concentration is directly related to the dialysate magnesium concentration.

Lithium therapy causes hypermagnesemia, the mechanism of which is not fully understood. Modest elevations in serum magnesium concentrations have been reported in familial hypocalciuric hypercalcemia, which is an autosomal dominant disorder characterized by very low urinary excretion of magnesium and calcium. The increased magnesium reabsorption is thought to be due to abnormal sensitivity of the loop of Henle to magnesium ions. Mild elevation of serum magnesium concentration has been seen in hypothyroidism, Addison's disease, and milk alkali syndrome.⁷

Effects of hypermagnesemia

Signs and symptoms of hypermagnesemia (see Table 7) are not usually apparent until the serum concentration is in excess of 2 mmol/l.⁷ Neuromuscular symptoms are the most common presentation of magnesium intoxication, as a result of blockage of neuromuscular transmission and depression of the conduction system of the heart and sympathetic ganglia.⁷ Clinically, one of the earliest effects of magnesium intoxication is the disappearance of deep tendon reflexes, often seen at magnesium concentrations of 2-4.5 mmol/l. Somnolence may be observed at concentrations of 2 mmol/l or above. Other manifestations include muscle weakness proceeding to flaccid paralysis of voluntary and/or respiratory muscles, leading to depressed respiration at concentration in excess of 5 mmol/l. The effects on the neuromuscular junctions are antagonized by calcium, and therefore the effects of hypermagnesemia are exaggerated in the presence of hypocalcemia.

Moderate increase in serum magnesium concentrations of 2-3 mmol/l results in mild reduction in supine as well as erect blood pressure, and higher concentrations may cause severe symptomatic hypotension. The negative inotropic effect of hypermagnesemia may contribute to the hypotension.²³ Other potential factors contributing to the hypotension include the effect of magnesium on the central nervous system, skeletal muscle paralysis, and depression of the carotid-baro receptor. Magnesium is also cardiotoxic. At serum concentrations greater than 3 mmol/l, ECG findings include prolonged PR intervals, increased QRS duration and QT intervals. Mild bradycardia is observed and occasionally complete heart block as well as cardiac arrest may occur at concentrations greater than 7 mmol/l. Electrophysiologic studies have shown prolonged conduction through the AV node.

Magnesium intoxication causes a fall in serum calcium concentration. This has been most commonly reported in patients with pregnancy-induced hypertension treated with magnesium and is due to suppression of PTH secretion by hypermagnesemia.⁷ Hypermagnesemia may cause paralytic ileus due to smooth muscle paralysis²⁶ and may impair blood clotting due to interference with platelet adhesiveness, thrombin generation time and clotting time. Other nonspecific manifestations of magnesium intoxication include nausea, vomiting, and cutaneous flushing.

Management of hypermagnesemia

Most cases of hypermagnesemia can be prevented. The possibility of hypermagnesemia should be anticipated in any patient receiving magnesium treatment, especially if the patient has reduced renal function; serum magnesium concentration should be monitored daily. When hypermagnesemia is found, magnesium therapy should be withdrawn and 1 gm of intravenous calcium gluconate should be given.⁷ This usually

causes a dramatic improvement in the patient's clinical condition. Administration of glucose and insulin may also help to promote magnesium entry into the cells. Occasionally, exchange transfusion has been used in severe neonatal hypermagnesemia and in patients with renal failure, peritoneal or hemodialysis against a low dialysis magnesium fluid will be required.

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