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IN-DEPTH REVIEW

Magnesium Deficiency: Pathophysiologic and Clinical Overview

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● Magnesium is an essential cation, involved in many enzymatic reactions, as a cofactor to adenosine triphosphatases. It is critical in energy-requiring metabolic processes, as well as protein synthesis and anaerobic phosphorylation. Serum Mg concentration is maintained within a narrow range by the kidney and small intestine since under conditions of Mg deprivation both organs increase their fractional absorption of Mg. If Mg depletion continues, the bone store contributes by exchanging part of its content with extracellular fluid (ECF). The serum Mg can be normal in the presence of intracellular Mg depletion, and the occurrence of a low level usually indicates significant Mg deficiency. Hypomagnesemia is frequently encountered in hospitalized patients and is seen most often in patients admitted to intensive care units. The detection of Mg deficiency can be increased by measuring Mg concentration in the urine or using the parenteral Mg load test. Hypomagnesemia may arise from various disorders of the gastrointestinal tract, conditions affecting Mg renal handling, or cellular redistribution of Mg. The gastrointestinal causes include the following: protein-calorie malnutrition, the intravenous administration of Mg-free fluids and total parenteral nutrition, chronic watery diarrhea and steatorrhea, short bowel syndrome, bowel fistula, continuous nasogastric suctioning, and, rarely, primary familial Mg malabsorption. The renal causes include Bartter's and Gitelman's syndrome, post obstructive diuresis, post acute tubular necrosis, renal transplantation, and interstitial nephropathy. Many therapeutic agents cause renal Mg wasting and subsequent deficiency. These include loop and thiazide diuretics, aminoglycosides, cisplatin, pentamidine, and foscarnet. Magnesium deficiency is seen frequently in alcoholics and diabetic patients, in whom a combination of factors contributes to its pathogenesis. Hypomagnesemia is known to produce a wide variety of clinical presentations, including neuromuscular irritability, cardiac arrhythmias, and increased sensitivity to digoxin. Refractory hypokalemia and hypocalcemia can be caused by concomitant hypomagnesemia and can be corrected with Mg therapy. The dose and route of administration of Mg in the treatment of hypomagnesemia is dictated by the clinical presentation, the degree of Mg deficiency, and the renal function.

INDEX WORDS: Hypomagnesemia; magnesium deficiency; Bartter's syndrome; Gitelman's syndrome.

THE IMPORTANCE of Mg as an essential nutrient in health and disease has been recognized since the studies of Kruse et al[1] in which acute Mg deficiency was induced in rats, as well as in subsequent studies by other investigators.[2,3] Since Mg is present in virtually all food sources, Mg deficiency is rarely encountered in normal individuals and its presence usually indicates underlying disease.[4] Both hypomagnesemic and normomagnesemic Mg deficiency are predisposed to by various pathologic conditions and medications. The functional disturbances resulting from both are readily reversed with Mg therapy. The serum Mg level had the highest prevalence of abnormal values of all ions measured in patients entering the intensive care unit.[5] The reported prevalence of hypomagnesemia in hospitalized patients is variable and ranges from 4.6% to 47%,[6-8] reflecting the type of patient pop-

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ulation studied and the different cut-off levels used to define a low serum Mg in these studies. Lum[7] has reported that the prevalence of hypomagnesemia is higher in acute care (26%) compared with chronic care facilities (3.5%). Hypomagnesemia is most frequent in intensive care settings, occurring in up to 65% of patients with normal serum creatinine,[9] and was associated with an increased mortality rate.[10] Hypomagnesemia usually goes undetected and is identified only by a routine Mg determination. Whang and Ryder[8] measured serum Mg in more than 1,000 specimens submitted for electrolyte determination. Based on physician-initiated requests for serum Mg, these investigators found that 90% of hypomagnesemic patients were not identified if serum Mg was not routinely determined. In our view, serum Mg should be determined routinely in all acute care units and in all patients with conditions or medications that may predispose them to Mg deficiency.

MAGNESIUM METABOLISM

Magnesium Content and Distribution in the Human Body

Magnesium is the fourth most abundant cation in the human body and the second most prevalent intracellular cation, after potassium. The normal human body contains 21 to 28 g of Mg[11]; approximately 53% in the bone, 27% in the muscles, 19% in the nonmuscular soft tissues, and only 1% in the extracellular fluid (ECF).[12] The majority of intracellular Mg is bound to various chelators, such as adenosine triphosphate (ATP), adenosine diphosphate, proteins, RNA, DNA, and citrate. Depending on the cell type, only 5% to 10% of the intracellular Mg^{2+} is free, which is essential for the regulation of intracellular Mg content.[13] The normal total plasma Mg concentration is 1.7 to 2.3 mg/dL, comprising 60% free Mg ions, 33% protein-bound and less than 7% complexed to citrate, bicarbonate, and phosphate.[14]

Magnesium Intake and Absorption

Magnesium is ubiquitous in nature and is especially plentiful in green vegetables that are rich in Mg-containing chlorophyll, as well as coca derivatives, nuts, grains, seafoods, and meats.[4] Drinking water, especially "hard water," contains approximately 30 mg/L of Mg.[15] The optimal Mg-containing diet is the one that leads to zero or positive Mg balance. Seelig[4] had estimated this to be at 6 mg/kg body weight; up to 20% of the western population falls below this recommended dietary allowance.[16]

Under normal conditions Mg is mainly absorbed from the small intestine, only a small fraction being absorbed from the colon.[17] The rectum and sigmoid colon are capable of absorbing Mg, and hypermagnesemia has been reported following administration of rectal enemas containing Mg sulfate.[18] Although the exact mechanism of Mg absorption is not yet determined, substantial evidence suggests the presence of both a transcellular saturable process, mediated by facilitated diffusion, and an intercellular passive process by the electrochemical gradient and the solvent drag.[19] In normal adults 40% to 50% of the dietary Mg is absorbed,[17,20] and the fractional absorption is dependent on the dietary Mg load and the body Mg status. Graham et al[17] demonstrated an increase in absorption to 76% on a low Mg diet, which subsequently decreased to 24% when a high Mg diet was given. A significant amount of Mg is present in the salivary, billiary, pancreatic, and intestinal juices, which are reabsorbed by the bowel.[21]

The effect of vitamin D and parathyroid hormone (PTH) on Mg absorption is disputed. In two clinical studies in uremic patients,[20,22] intestinal Mg absorption was significantly reduced compared with normal subjects. It was postulated that this resulted from the lack of 1,25-dihydroxyvitamin D in uremia. Subsequently, Schmulen et al[23] administered calcitriol to uremic patients and observed normalization of jejunal Mg absorption. However, Mg absorption was found to be normal or minimally reduced in vitamin D-deficient patients and vitamin D repletion resulted in a small, although significant increase in Mg absorption, while the overall Mg balance was not affected due to increased urinary Mg excretion.[24] These data suggest that a substantial fraction of Mg absorption is vitamin D independent, since Mg absorption was normal in the presence of vitamin D deficiency. Coburn et al[25] suggested that the vitamin D-dependent component of Mg absorption may comprise a small fraction of its total net absorption and this fraction is saturable with small doses of vitamin D. Furthermore, while high-dose calcitriol is widely used in patients with end-stage renal disease, Mg absorption is minimally affected in contrast to

that of Ca and phosphate.[25] MacIntyre and Robinson[26] demonstrated increased intestinal Mg absorption following the administration of parathyroid extract to parathyroidectomized rats. It is conceivable that PTH indirectly may enhance intestinal absorption of Mg via renal activation of 25-dihydroxyvitamin D3.

Earlier experimental studies showed that the absorption of Mg or Ca increases in the absence of the other, leading to the suggestion that these cations share a common transport mechanism.[27] Subsequent studies by Brannan et al[22] as well as by Spencer et al[20] did not support this hypothesis. It appears likely that each cation has its own absorptive transport system, and indirect effects of vitamin D and PTH could explain the earlier observations.

Renal Handling of Magnesium

The kidney is responsible for the control of the serum Mg level within a narrow range, and plays an essential role in Mg homeostasis. Approximately 2,400 mg of Mg are filtered per day, of which 5% (120 mg) are excreted in the urine.[28] Renal Mg handling is determined by the combination of glomerular filtration and tubular reabsorption; convincing data for secretory mechanism are lacking.[29] Approximately 70% of the total plasma Mg is filtered in the glomerulus in contrast to 60% of the total plasma Ca.[29] Only 20% to 30% of the filtered Mg is reabsorbed in the proximal tubules, including both convoluted and straight portions. At this segment the tubular fluid Mg increases to more than 1.5 times the ultrafilterable Mg. This is due to the poor permeability of the proximal tubules for Mg in contrast to that of the Na and Ca, in which 70% and 60% of the filtered load, respectively, are reabsorbed. This process delivers to the thick ascending loop of Henle (TAL of Henle), a filtrate that is relatively high in Mg and low in Na and Ca.[30] Micropuncture studies in laboratory animals showed that the TAL of Henle is the principal site for Mg homeostasis, where 60% of the filtered load is reabsorbed.[31] It is also the site where various regulators, hormones, and medications affect the overall Mg balance and excretion. Magnesium reabsorption in the TAL of Henle is closely associated with NaCl transport and is possibly influenced by the tubular fluid flow rate.[29,31] Approximately 25% of the filtered NaCl is reabsorbed, mainly in the medullary and to a lesser extent in the cortical TAL of Henle through the active transcellular transport (Na^+-$2Cl^-$-K^+ transport) and the passive paracellular diffusion.[31] This process creates a favorable luminal positive potential at the cortical TAL of Henle, where most of the delivered Mg and Ca is reabsorbed.[30,31] This passive transport mechanism of Mg has been suggested by the study of Shareghi and Agus,[32] who demonstrated that the movement of Mg from an isolated cortical TAL of Henle to surrounding bath and vice versa is dependent on the tubular transepithelial voltage. Thus, increased Mg transport from the lumen to the bath was seen with elevating the luminal transepithelial voltage and from the bath to lumen with negative luminal potential. On the other hand, active transport may also exist, since Mg movement was enhanced with the addition of glucagon and antidiuretic hormone in the absence of transepithelial potential difference.[31] Magnesium reabsorption is also dependent on tubular fluid flow rate, as low flow rate promotes reabsorption while high flow rate decrease it. This may be caused by the alteration in sodium diffusional gradient and the subsequent attenuation of the positive transepithelial potential, imperative in Mg transport.[29] Consequently, factors that which decrease NaCl reabsorption in the TAL of Henle, such as osmotic diuretics,[33] loop diuretics, and ECF volume expansion, may increase the fractional excretion of Mg.[29] Hypercalcemia or hypermagnesemia are recognized to increase urinary excretion of both Mg and Ca through unknown mechanism. This enhancement of excretion is believed to occur in the peritubular rather than luminal side, as elevating Mg or Ca concentration in the blood inhibits reabsorption while an increase in intraluminal concentration enhances reabsorption.[30-32]

Prolonged phosphate depletion in dogs[34] resulted in functional hypoparathyroidism, transient hypercalcemia, persistent hypercalciuria, and inconsistent hypermagnesuria. Phosphate-depleted rats[35] exhibited marked renal Mg wasting, resulting in hypomagnesemia and negative Mg balance. Experimental phosphate depletion in normal men was shown to significantly increase serum 1,25-$(OH)_2$-vitamin D concentration[36] and led to hypercalciuria and slight, although significant hypermagnesuria and hypomagnesemia. The mechanism for such renal changes is not fully understood and remains speculative. It was postulated that mobilization

of Ca^{34} and Mg^{35} from bone may have had a detrimental effect on the observed renal changes. It is tempting to speculate that the combination of increased calcitriol concentration, hence enhanced intestinal Ca absorption, and increased bone resorption, hence increased Ca mobilization, both lead to mild hypercalcemia, which may inhibit Ca and Mg transport at the TAL of Henle. Induced metabolic acidosis in normal men slightly increased renal Mg excretion[37]; however, the clinical significance of acid base disturbance on overall Mg balance is yet to be defined. Several hormones have been found to enhance Mg transport in the TAL of Henle and distal tubule through cyclic adenosine monophosphate-dependent protein kinase activation. These include PTH, antidiuretic hormone, glucagon, and calcitonin.[30] Recently, insulin has been shown to significantly enhance tubular Mg reabsorption, likely through activation of tyrosine kinase.[30]

Quantitatively, the distal tubules and collecting ducts play a limited role in Mg handling, in which less than 5% of the filtered Mg load is reabsorbed. Most of this reabsorption occurs at the distal tubule and is believed to be load dependent.[30]

The kidney has the ability to conserve Mg in the face of Mg deprivation, in which the fractional excretion may decrease to less than 0.5% (12 mg/d).[28] This adaptation occurs within hours of reduced Mg intake, before any change is observed in the plasma Mg concentration. Micropuncture studies showed that this adaptation occurs in the loop of Henle.[38] Conversely, the kidney is capable of increasing its fractional excretion of Mg to approximate the filtered load if faced with increased intake or excessive Mg administration.[39] The fractional excretion of Mg progressively increases in renal failure, and normal plasma levels are maintained until the later stages, when hypermagnesemia may occur due to loss of nephron mass.[40]

Magnesium Homeostasis

Magnesium homeostasis involves the interaction of three homeostatic systems: the kidney, the small bowel, and the bone. In acute Mg deprivation, tubular reabsorption of Mg and fractional absorption from distal small bowel both increase, maintaining overall balance.[41] If Mg depletion continues, the serum Mg declines and exchangeable bone Mg begins to contribute to maintenance of the ECF Mg level. Alfrey and colleagues[42,43] demonstrated that only 33% of the bone Mg is elutable and readily exchangeable. The largest, nonelutable fraction is intimately complexed to apatite crystals and is deposited during bone formation, thereby equilibrating more slowly with serum Mg.

The intracellular Mg^{2+} concentration is maintained at the expense of ECF and bone reservoirs.[41] The free intracellular Mg2+ [Mg^{2+}]i is in exchanging equilibrium with the bound intracellular Mg^{13} and with ECF Mg.[41] Thus, the free and bound intracellular Mg^{2+} represent the Mg buffer system, which ensures the constancy of the free intracellular Mg^{2+} concentration.[13] The exact mechanism for such regulation of the intracellular Mg^{2+} level is not known. It has been shown that a decrease in [Mg^{2+}]i (eg, by Mg deprivation) results in the movement of Mg^{2+} into the cells, probably through a passive process, while an increase of [Mg^{2+}]i (eg, by Mg administration) causes Mg^{2+} to efflux from the cell, probably by an active process. This process continues until normalization of [Mg^{2+}]i is achieved.[13]

Biologic and Physiologic Effects of Magnesium

Intracellular Mg plays an essential role in energy storage, transfer, and utilization.[11] This function is achieved through the formation of Mg-ATP, which is a substrate for a wide array of enzymes (eg, phosphotases and phosphokinases) located in the plasma membrane, and intracellular compartments. The activation of ATPases by specific ions results in the hydrolysis of ATP, which in turn results in the movement of ions from one compartment to another and, hence, the ultimate control of the intracellular electrolyte content. Recognized Mg^{2} ATPases include Mg^{2+}+(Na^{+}-K^{-}) ATPase, Mg^{2+}($HCO3^{-}$) ATPase, and Ca^{2+}-Mg^{2+} ATPase, which are involved with Na, proton, and Ca transport, respectively. Magnesium has an indirect function in protein synthesis through its action on nucleic acid polymerization, its role in binding of the ribosomes to RNA, and the synthesis and degradation of DNA.[29] Magnesium is also involved, in the anaerobic phosphorylation of glucose and in mitochondrial oxidative metabolism. Adenylate cyclase requires Mg to generate the intracellular second messenger cyclic adenosine monophosphate.[11,29]

On physiologic and clinical grounds, intracellu-

Table 1. Tests Used in Assessing Magnesium Status

Mg concentration in the blood	Physiologic tests
Serum (total and ionized)	Metabolic balance studies
Red blood cells	24-hr urinary excretion of Mg
Mononuclear blood cells (lymphocytes and monocytes)	Parenteral Mg load test
	Isotopes studies (^{26}Mg and ^{28}Mg)
Mg concentration in muscle and bone	Free intracellular Mg^{2+} concentration
Muscle (needle biopsy)	Fluorescent indicators (Furaptra)
Bone (iliac crest biopsy)	NMR spectrometry (^{31}P and ^{25}Mg NMR)
	Ion-selective microelectrode

Abbreviation: NMR, nuclear magnetic resonance.

lar Mg has an important regulatory function on both Ca^{2+} and K^+, which will be discussed in detail under the section on "clinical manifestations." Magnesium is essential in maintaining a low resting level of intracellular-free Ca by competing with Ca for binding sites and by stimulating Ca sequestration by sarcoplasmic reticulum.[44]

Assessment of Magnesium Status

A variety of approaches have been used in an attempt to determine the true Mg status (Table 1). The dilemma of choosing one method over another results from uncertainty as to which tissue best represents the body stores, the invasive nature of some techniques, and the tedious work involved with others. The serum Mg accounts only for 0.3% of total body Mg,[12] and it has been shown on occasion to be normal or elevated in the presence of intracellular Mg depletion.[45-47] Despite that, the serum Mg is the most simple and convenient test and, if significantly low, it denotes substantial Mg deficiency. The serum Mg has been found to correlate best with Mg concentration in the bone,[43,48] while muscle Mg was found to be low in many conditions in the absence of abnormalities in the serum and red blood cell Mg concentration.[45-48] The red blood cell Mg concentration has no advantage over the serum level and did not show significant correlation with other tissue pools.[45,47,48] Red blood cell Mg concentration decreases with the erythrocyte age, as it is higher in reticulocytes than mature red blood cells.[12] The use of leukocyte Mg as an intracellular index has produced conflicting results, which are partly explained by the different cell populations used.[49] Mononuclear blood cell (lymphocyte and monocyte) Mg concentration did not correlate with serum and red blood cell Mg concentration in humans, and variable correlation with the muscle Mg was found.[12,49,50] In two studies,[51,52] lymphocyte Mg was more consistently reduced than the plasma level in conditions known to cause Mg depletion. This was particularly useful if lymphocyte Mg was serially determined.[51,52] However, this test is technically difficult to perform and is considered impractical.

Several recent advances have been made in measuring the intracellular-free Mg $[Mg^{2+}]i$, which were recently reviewed by Murphy[53] and Quamme.[41] Fluorescent indicators such as FURAPTRA allow measurement of the cytosolic-free Mg^{2+} in living cells under physiologic manipulation and permit study of the influence of various effectors on its homeostasis. Nuclear magnetic resonance spectrometry allows the noninvasive determination of free Mg^{2+} in a perfused organ by determining the degree to which Mg is bound to ATP. Based on the knowledge of the dissociation constant (K_D) for Mg ATP, the free Mg^{2+} can be calculated.[41] The accuracy of free Mg^{2+} measurement was particularly enhanced by the introduction and utilization of the ion-selective microelectrode.[53]

Elin[12] has reviewed four tests and called them "physiologic" since they examine the integrity of the homeostatic mechanism. These tests are particularly useful when Mg deficiency is suspected but the serum Mg level is not reduced, and include formal metabolic balance studies, renal excretion and clearance of Mg, the parenteral Mg load test, and isotope studies.

Magnesium balance studies are labor intensive, expensive, and done only in a few research centers. They have been used mostly to determine the nutritional requirements[4,16] and to answer questions regarding Mg absorption and excretion.[54] Balances are measured over a period

Table 2. Suggested Schema for the Clinical Use of Magnesium Tolerance Test in Normomagnesemic Patients

1. Collect baseline urine (spot or timed) for Mg:Cr ratio
2. Infuse 2.4 mg of elemental Mg/kg lean body weight in 50 mL 5% dextrose water over 4 hr
3. Collect urine (starting with infusion) for determination of Mg and creatinine levels for 24 hr
4. Calculate % Mg retained using following formula:

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

5. Criteria for Mg deficiency:
   - >50% retention at 24 hr = definite deficiency
   - >20% retention at 24 hr = probable deficiency

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of days under controlled conditions in which Mg intake and the amount excreted in the feces and urine are estimated. The demonstration of a significant positive balance during Mg repletion suggests recovery from Mg deficiency.[4,12,54]

The most simple, physiological test is the measurement of Mg excretion in a 24-hour urine collection. As has been discussed previously, the kidney is capable of reducing its fractional excretion of Mg to less than 0.5% (12 mg/d) if faced with Mg deprivation. In the presence of hypomagnesemia, the finding of 24-hour urinary excretion in excess of 24 mg is suggestive of renal Mg wasting. On the contrary, a decrease of 24-hour Mg excretion to less than 12 mg/d is convincing evidence of Mg deficiency.[28] The parenteral Mg load tests are used widely by many laboratories owing to their simplicity and the substantial information obtained regarding Mg status. An individual with an adequate Mg balance and normal renal function is capable of excreting most of a parenteral Mg load within 24 hours.[41,55] Different protocols has been advocated,[55,56] including the convenient low-dose infusion described by Ryzen et al[55] (Table 2). A base-line 24-hour urine sample for Mg is collected, immediately followed by 2.4 mg/kg lean body weight of Mg in 50 mL of 5% dextrose, to be infused over 4 hours. A second 24-hour urine collection is started at the time of Mg infusion, and based on the difference of Mg content in both urine collections, the retained Mg fraction is estimated. Retention of more than 20% of the administered dose is suggestive of Mg deficiency. This test is contraindicated in patients with renal insufficiency, and the presence of renal Mg wasting invalidates this test.

Radioactive Mg^{28} and, less commonly, Mg^{26} have been used mostly as a research tools in assessing Mg homeostasis. These isotopes have increased our understanding of Mg absorption, renal excretion, and exchangeable Mg pools.[17,57] Further progress in this field has been hampered by the lack of an isotope with a convenient half-life. The half-life of Mg^{28} is approximately 22 hours.[57]

Clinical Manifestations

Most hypomagnesemia in clinical practice is asymptomatic. Signs and symptoms may be evident when the serum Mg decreases to less than 1.2 mg/dL.[58] The clinical manifestation may depend more on the rate of development of Mg deficiency or on the total body deficit rather than the actual serum Mg level.[59]

Neuromuscular manifestations and hypocalcemia. Experimental Mg deficiency in humans causes neuromuscular irritability, including positive Chvostek and Trousseau signs, tremor, fasciculations, and tetany.[3] Other reported clinical

Table 3. Clinical Manifestations of Magnesium Deficiency

Neuromuscular manifestations	Psychiatric manifestations
Positive Chvosteck's sign	Apathy
Positive Trousseau's sign	Depression
Carpopedal spasm (tetany)	Delirium
Convulsions	Personality changes
Muscle cramps	Cardiac manifestations
Muscle faciculations and tremors	Ventricular arrhythmias
Neurologic manifestations	Supraventricular arrhythmias
Vertigo	Torsade de pointes
Nystagmus	Electrolyte disturbances
Dysphagia	Hypokalemia
Athetoid movements	Hypocalcemia
Hemiparesis and aphasia	

manifestations (Table 3) include convulsions, athetoid movements,[60] nystagmus, dysphagia,[61] apathy,[62] muscle cramps, hyperreflexia, acute organic brain syndrome, depression,[63] generalized weakness,[3,61] anorexia, and vomiting.[3] Recently, hemiparesis and aphasia were reported in a 3-year-old child with severe hypomagnesemia which resolved as the Mg level returned to normal.[64] The presentation in infants is commonly more dramatic, with generalized convulsions, which respond only to Mg therapy.[65,66] Although tetany is well described with Mg deficiency,[3,60,67] it is rare.[58,67] The exact pathogenesis of the tetany and neuromuscular irritability remains obscure, as tetany has been seen in the absence of hypocalcemia or metabolic alkalosis.[1,60,68] It is most likely a manifestation of the interrelated actions of Mg and Ca inside the neuromuscular apparatus. Decreased concentration of either ion will lower the threshold for neuronal stimulation and thereby increase neuronal excitability and enhance transmission at the motor end plate.[11] The low Mg concentration causes liberation of acetylcholine at the nerve ending.[60] Magnesium and Ca have opposite actions in the muscle: low Mg concentration enhances contraction, whereas low Ca concentration causes relaxation.[11,60] Inside the muscle cells Mg acts as a calcium antagonist. A low Mg^{2+} concentration results in a rapid release of Ca from the specialized "Ca+ release channels" in the sarcoplasmic reticulum, while increased Mg^{2+} blocks this process.[69]

Hypocalcemia has been seen in up to one third of hypomagnesemic intensive care unit patients.[9] It is usually refractory to Ca repletion unless Mg is first administered.[9,65,66] This association is explained by several interacting factors, including impaired release of PTH[70] and skeletal end-organ resistance to PTH.[71-73] This resistance could be explained by the low uptake of PTH by bone,[71] as well as the decreased heteroionic exchange of Ca^{2+} for Mg^{2+} at the skeletal surface.[73] Although a low calcitriol level is a common finding in the hypocalcemia of Mg deficiency, it may contribute little to its pathogenesis, as normocalcemia is achieved with Mg therapy before any noticeable increase is observed in the calcitriol level.[74]

Cardiac manifestations and hypokalemia. Refractory cardiac arrhythmias the respond only to Mg therapy have been described in patients with probable Mg deficiency and hypomagnesemia in both digitalized[75,76] and nondigitalized patients.[77,78] In the presence of Mg deficiency, digitalis toxicity develops at slightly elevated or normal serum digoxin levels,[75,76,79] as Mg deficiency increases the myocardial uptake of digoxin,[76] and augments the inhibitory action of digoxin on Na^+-K^+ATPase, causing reduction of intracellular potassium.[75,76] The spectrum of arrhythmias includes ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, junctional rhythm, atrial fibrillation,and supraventricular tachycardia.[76,78,80] Torsade de pointes, a repetitive polymorphous ventricular tachycardia with prolongation of QT interval, has been reported in cases of hypomagnesemia and is successfully suppressed by Mg therapy.[81] Electrocardiographic changes of hypomagnesemia are nonspecific, as other electrolyte abnormalities are often present.[80] The effect of Mg deficiency on cardiac arrhythmias is thought to be related to impairment of the membrane Na^+-K^+ ATPase, which is essential for the transport of potassium and sodium in and out of the cell.[82] More recently, Mg has been found to block the outward movement of K^+ through the distinctive K^+ channels in cardiac cells, and its absence may result in excessive outward movement of K^+ and a reduction of the intracellular K^+ content, causing depolarization of the cells.[83]

Hypomagnesemia is found in 42% of hospitalized patients with hypokalemia,[84] and hypokalemia positively predicts hypomagnesemia.[5] Induced Mg depletion in rats resulted in a low intracellular muscle K^+, despite adequate dietary K, and successful repletion of K was only possible after Mg repletion.[85] In pure experimental Mg depletion in humans, hypokalemia and enhanced kaliuresis were seen. Reinstitution of Mg resulted in a positive potassium balance.[3]

Hypomagnesuria. Excessive extrarenal Mg loss, as with chronic diarrhea, often leads to hypomagnesuria as the kidney attempts to conserve Mg and maintain Mg balance. In certain clinical settings, as in hyperoxaluria, the resulting hypomagnesuria may enhance calcium oxalate stone formation due to a reduction in complexed Mg oxalate and the consequent increase in the urinary saturation of calcium oxalate.[86]

Causes of Mg Deficiency and Hypomagnesemia

Magnesium deficiency may result from one or more of three mechanisms causing Mg loss. These include reduced intestinal Mg absorption,

Table 4. Causes of Magnesium Deficiency

Gastrointestinal causes	Endocrine causes
Nutritional	Hyperaldosteronism
Protein-calorie malnutrition	Hyperparathyroidism
Mg-free fluids and TPN	Hyperthyroidism
Reduced absorption	Inappropriate ADH secretion
Primary infantile hypomagnesemia	Metabolic causes
Malabsorption syndromes	Hypercalcemia
Short bowel syndrome	Hypophosphatemia
Chronic diarrhea	ECF volume expansion
Increased intestinal loss of Mg	Redistribution of Mg
Intestinal fistulas	"Hungry bone syndrome"
Prolonged nasogastric suction	Acute pancreatitis
Renal Mg wasting	Hyperadreneregic states
Intrinsic tubular defect	Massive blood transfusion
Congenital Mg wasting	Acute respiratory alkalosis
Interstitial nephropathy	Insulin therapy and refeeding
Postobstructive diuresis	Miscellaneous
Diuretic phase of ATN	Severe burns
Post-renal transplantation	Excessive sweating
Drug-induced renal Mg wasting	Excessive lactation
Loop and thiazide diuretics	Last trimester of pregnancy
Cisplatin	Cardiopulmonary bypass
Aminoglycosides	Combined causes
Pentamidine and foscarnet	Diabetes mellitus
Cyclosporine A	Chronic alcoholism

Abbreviations: TPN, total parenteral nutrition; ATN, acute tubular necrosis; ADH, antidiuretic hormone.

increased renal Mg loss, and redistribution of Mg from ECF to cells. Rarely, Mg deficiency may arise from other mechanisms, which will be discussed separately (Table 4).

Gastrointestinal causes. Magnesium deficiency is rare in normal subjects, as Mg is widely present in food sources.[4] However, Mg deficiency is well described in protein-calorie malnutrition, although the associated diarrhea and vomiting may play some role in its causation.[87] Prolonged Mg-free total parenteral nutrition and other intravenous fluids may precipitate an acute Mg deficiency syndrome, especially in patients with marginal or reduced Mg stores.[60,63,81] Although uncommon, treatment of nephrolithiasis may result in Mg deficiency. This may occur if a patient is placed on a low oxalate diet that also has a low Mg content. Similarly, cellulose phosphate, prescribed to reduce intestinal Ca absorption in patients with idiopathic hypercalciuria, also binds Mg and may lead to a substantial Mg deficiency.[54]

More than 30 cases of primary infantile hypomagnesemia with secondary hypocalcemia have been reported.[88] Due to the male preponderance, an x-linkage mode of transmission was suggested, but this has been challenged recently and autosomal inheritance proposed.[66,88] The condition usually presents at 4 to 5 weeks of age, with generalized convulsion. There may be associated protein-loosing enteropathy, hypoalbuminemia, and ana sarca, which improve significantly with Mg therapy.[89] A defect in the carrier-mediated transport in the small intestine has been proposed,[65,66,89] which usually can be overcome by increasing the oral Mg intake to approximately five times the normal daily requirement.[88]

Severe Mg deficiency is frequently observed in conditions causing steatorrhea or severe chronic diarrhea, such as Crohn's disease, ulcerative colitis, coeliac disease, Whipple's disease, and short bowel syndrome.[46,60,61,64,68,90-92] Booth et al[91] demonstrated an approximate correlation between the severity of steatorrhea and the degree of hypomagnesemia. There was a similar correlation between stool fat content and fecal Mg concentration, suggesting that the observed Mg malabsorption is secondary to the formation of insoluble Mg soap. The loss of Mg in stool parallels the water content, which explains the frequency of Mg deficiency in many conditions that involve chronic diarrhea.[59] Magnesium deficiency is compounded if Mg in the bowel secretions is lost due to fistula formation or continuous suctioning of the gastrointestinal fluids.[21,93,94]

Renal causes. In the presence of hypomagnesemia, a urinary excretion of Mg in excess of 24 mg/d is indicative of renal Mg wasting.[28] The congenital Mg-losing kidney is a heterogeneous disorder with different modes of presentation.[28,95-100] Bartter's syndrome, first described in 1962,[101] is characterized by chronic hypokalemia with renal potassium wasting, hypochloremic metabolic alkalosis, hyperreninemia, secondary hyperaldosteronism in the presence of low or normal blood pressure, and hyperplasia of the juxtaglomerular apparatus. Characteristically, these patients exhibit decreased vascular responsiveness to the pressor effect of angiotensin II and norepi-

Table 5. Clinical Differences Between Bartter's and Gitelman's Syndrome

Clinical Characteristics	Bartter's Syndrome	Gitelaman's Syndrome
Age at presentation	Infants and children <6 yr of age	Adolescents and adults
History of polyhydramnios and prematurity	Often present	Usually absent
Clinical course	Usually severe	Benign with minimal symptoms
ECF volume status	Contracted (secondary to polyuria)	Normal or slightly reduced
Hypomagnesemia with renal Mg wasting	Present in 39% of cases	Present in all cases
Urinary Ca excretion	Normal or increased	Low in all patients
Putative site of defect	TAL of Henle	Distal convoluted tubules

nephrine and increased renal production of the vasodialatory prostaglandins (PGE_2, PGI_2), which may have a significant role in the pathogenesis of the syndrome and in mediating the vascular unresponsiveness.[102] In 1966, Gitelman et al[95] reported three normotensive patients with primary hypokalemic metabolic alkalosis and hypomagnesemia secondary to renal Mg wasting. Subsequently, more patients with "Bartter's syndrome" and hypomagnesemia were diagnosed. Rudin[97] reviewed 28 patients with "Bartter's syndrome," in whom 22 (78%) were found to have hypomagnesemia. The pathogenesis of the syndrome is a matter of dispute. The prevailing hypothesis attributes the syndrome to a primary defect in NaCl reabsorption at various sites of the renal tubules. This speculation is based on results obtained from renal clearance studies of free water and Cl, and from evaluating the urinary concentrating and diluting capacities.[103] Such studies suggested to some investigators[103,104] that the TAL of Henle is a site of involvement and to others, the distal tubules.[105,106] Bettinelli et al[100] recently categorized two distinct variants of primary tubular hypokalemic metabolic alkalosis based on the urinary calcium excretion (Table 5). The first is the classic Bartter's syndrome, differentiated by normal or increased urinary Ca excretion; hypomagnesemia with evidence of renal Mg wasting was present in 39% of cases. These characteristics usually present before the age of 6 years and have a severe clinical course. The second is the classic Gitelman's syndrome, which is characterized by hypocalciuria and consistent hypomagnesemia secondary to renal Mg wasting in all affected subjects. It is a benign disorder that is usually diagnosed in adults and older children and is commonly discovered incidentally. Bettinelli et al[100] state that " it is tempting to assume that most cases of so-called Bartter's syndrome reported in teenagers or adults may actually represent cases of Gitelman's syndrome." The distinctive difference in Ca excretion between the two syndromes has led many investigators to suggest a different site for tubular involvement.[28,100,107] As has been discussed earlier, Ca and Mg are reabsorbed in parallel at the TAL of Henle, which might implicate it as the site involved in classic Bartter's syndrome to account for the hypercalciuria and (albeit inconsistent) Mg wasting.[28] Furthermore, the laboratory findings of classic Bartter's syndrome are reminiscent of the laboratory findings produced by chronic administration of loop diuretics, which inhibit luminal $Na^+2Cl^-K^+$ channels in the TAL of Henle.[100] On the other hand, because Ca and Mg transport are dissociated at the distal convoluted tubules, as for example with thiazide diuretics, which promote Ca reabsorption and increase Cl and Mg excretion, it is tempting to speculate that this segment is involved in Gitelman's syndrome to account for the striking and consistent hypocalciuria and renal Mg wasting.[107] An apparent problem with this hypothesis lies in the fact that a defect in the distal convoluted tubules is expected to produce insignificant Mg wasting in contrast to that of the loop of Henle, where 60% of the filtered Mg is reabsorbed.[108] An alternative hypothesis that might explain the defect in Gitelman's syndrome is that the permeability of the paracellular channels of the TAL of Henle to Mg might be decreased, leading to significant and consistent Mg wasting, while the permeability to Ca is increased, leading to hypocalciuria.[28] This hypothesis has not yet been substantiated and the possibility of more than one affected segment cannot be ruled out. Another variant of the "congenital Mg-losing kidney" was described by Evans et al[98] in a report of two brothers who presented with hypomagnesemia secondary to a renal Mg leak and associated with azospermia, medullary calcinosis, interstitial fibrosis, and renal calculi. Manz et al[99]

described two siblings with renal Mg wasting associated with hypercalciuria, nephrocalcinosis, and incomplete distal renal tubular acidosis.

Decreased fractional absorption of Mg from the kidney and the intestine in chronic renal failure patients rarely results in hypomagnesemia. Hypomagnesemia and hypocalcemia with renal Mg wasting are reported in patients with tubulointerstitial renal disease.[109] Like wise, Mg wasting is associated with conditions causing tubular abnormalities, such as postobstructive diuresis, the diuretic phase of acute tubular necrosis, and following renal transplantation.[110] A wide range of therapeutic agents has been implicated in the genesis of renal Mg wasting syndromes.

Due to the fact that Mg absorption in the TAL of Henle is dependent on the positive transmembrane potential created by sodium chloride reabsorption, any alteration in sodium chloride transport by loop diuretics, normal saline infusion, and osmotic diuretics will result in increased Mg excretion.[29] Loop diuretics (furosemide, bumetanide, and ethacrynic acid) are potent inhibitors of Mg reabsorption, although with a short duration of action so that deficiency only develops with frequent dosing.[28] Thiazide diuretics act on the distal tubule, where less than 5% of Mg is absorbed. Short-term administration of thiazide does not produce renal Mg wasting, whereas long-term administration may produce substantial Mg deficiency. Factors known to promote magnesuria in patients treated with thiazide include secondary hyperaldosteronism, increased sodium load, and interaction with Ca metabolism.[111]

Cisplatin, an inorganic platinum compound, causes hypomagnesemia in more than 50% of treated patients,[112] and the incidence increases with the cumulative cisplatin dose.[113] The hypomagnesemia is usually mild, although occasionally it may be severe and symptomatic.[112] Hypomagnesemia starts to develop 3 weeks after initiation of chemotherapy and persists for an average of 5 months, but it is occasionally permanent.[112-114] Patients usually present with hypocalciuria, renal Mg wasting, and hypokalemic metabolic alkalosis, a picture comparable to that of Gitelman's syndrome and consistent with a distal tubular defect as the site for Mg wasting.[115,116]

Hypomagnesemia has been reported in 4.5% of patients receiving aminoglycoside treatment and occurs most often in patients with underlying malignancies.[117] Magnesium wasting has been reported with many such agents, including gentamicin, tobramycin, amikacin, and the antituberculous drugs viomycin and capreomycin.[117-119] The hypomagnesemia has been seen in both short-and long-term therapy.[117] It usually occurs with high-dose treatment and is frequently symptomatic.[118,119] The aminoglycosides preferentially accumulate in the proximal tubule, leading to cell necrosis[120]; however, the TAL of Henle is the major site for Mg transport and, in theory, it can reclaim most of the unabsorbed Mg. Juxtaglomerular hyperplasia with hyperreninemia and secondary hyperaldosteronism also has been described with aminoglycoside therapy.[118] Amphotericin B, a highly nephrotoxic agent, has been reported to cause mild and reversible hypomagnesemia.[121] Parenteral pentamidine therapy may cause severe symptomatic hypomagnesemia secondary to Mg wasting. In autopsies of acquired immunodeficiency syndrome patients treated with pentamidine, accumulation of the drug was detected in the kidney up to 1 year following treatment.[122] A high incidence of hypocalcemia (85%) and hypomagnesemia (70%) recently has been reported with the use of foscarnet in the treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. The exact mechanism for this observation is not yet determined, although tubular necrosis is known to be associated with foscarnet.[123]

Cyclosporine is an immunosuppressive agent commonly used in organ transplantation and is recognized for its nephrotoxicity. Its magnesuric effect is well established in animal[124] and clinical[125] studies. In one study,[126] the incidence of hypomagnesemia in cyclosporine-treated heart transplant recipients was found to be exceptionally high (100%) and was associated with myocardial Mg depletion in 94% of the cases. Despite this high incidence, the hypomagnesemia was mild and asymptomatic, and did not necessitate stopping the medication.

Many endocrine conditions may cause renal Mg wasting through various mechanisms. Primary[127] and secondary[47] hyperaldosteronism are associated with Mg wasting, secondary to ECF volume expansion. Severe hypomagnesemia has been reported in patients with inappropriate antidiuretic hormone secretion, and renal Mg loss secondary to water retention was suggested.[128]

Ca^{2+} competes with Mg^{2+} at the basolateral membrane of the TAL of Henle, and Mg deficiency has been reported in hypercalcemia of various etiologies.[29] In primary hyperparathyroidism, the plasma Mg level is usually normal, but occasionally may be either low or high.[129] The enhancing effect of PTH on Mg reabsorption and the opposing magnesuric effect of hypercalcemia may explain these various changes in the Mg level. The plasma Mg level tends to be reduced in hyperthyroidism and slightly elevated in hypothyroidism. Balance studies in hyperthyroid patients, prior to treatment with propylthiouracil, revealed consistent renal Mg wasting.[130]

Magnesium redistribution. Hypomagnesemia may occur secondary to deposition into bone and tissues, formation of circulating Mg complexes, or intracellular Mg shift. "Hungry bone syndrome," precipitated either by parathyroidectomy[131] or by diffuse osteoblastic metastasis,[132] has been reported to cause hypomagnesemic-hypocalcemic tetany. This may result from acute deposition of Ca and Mg in the newly formed bone. Hypomagnesemia has been reported in 20% of patients with acute pancreatitis, probably as a result of Mg deposition in areas of fat necrosis.[133] Conditions with excessive catecholamine release may cause hypomagnesemia. Catecholamines induce lipolysis and increase circulating free fatty acids that bind avidly with plasma Mg.[134] Massive blood transfusion has been reported to cause hypomagnesemia, probably related to the chelating effect of citrate.[135]

The shift of Mg from ECF into the cells may account for the hypomagnesemia seen during treatment of diabetic ketoacidosis,[136] during refeeding of starved patients,[59] and following rapid correction of chronic respiratory acidosis.[137]

Miscellaneous causes. Patients with severe burns may lose Mg through denuded skin. This may account for the hypomagnesemia that was seen in eight of the 20 patients studied by Broughton et al.[138] Excessive sweating[139] and lactation[140] and the last trimester of pregnancy[78] have been associated with Mg deficiency. Transient mild hypomagnesemia may occur following surgical procedures, and is most significant after cardiac surgery.[141,142] In one study,[141] hypomagnesemia was seen in all patients undergoing cardiopulmonary bypass surgery. The proposed mechanisms for the hypomagnesemia are hemodilution due to administering large volumes of Mg-free fluids, removal of Mg by the bypass pump, catecholamine-induced intracellular Mg shift, and binding to free fatty acids.[142]

Combined causes. Diabetes mellitus is one of the common causes of Mg deficiency. Hypomagnesemia is seen in up to 38% of outpatient insulin-treated diabetics, and the serum Mg level is inversely correlated with fasting blood sugar. This is due to the enhanced renal excretion of Mg, since 55% of patients exhibited hypermagnesuria.[143] The renal Mg wasting in diabetic patients is caused by glycosuria, ketoaciduria, and hypophosphatemia.[136,143] Hypomagnesemia was reported in 55% of patients treated for diabetic ketoacidosis, probably as a result of an insulin-mediated intracellular Mg shift.[136]

Significant hypomagnesemia was reported in up to 30% of alcoholics.[144] A higher percentage had normomagnesemic Mg deficiency, which was revealed by the parenteral Mg load test.[55,56] Positive Mg balance on alcohol withdrawal, a low exchangeable ^{28}Mg, and decreased muscle Mg concentration are further pieces of evidence suggesting consistent Mg deficiency in alcoholics.[134] Multiple mechanisms interact to produce hypomagnesemia and Mg deficiency in acute and chronic alcoholics. Poor nutritional status is not uncommon, compounded by the Mg loss through vomiting and diarrhea. Alcoholics are more prone to chronic pancreatitis and liver disease, with resulting steatorrhea and Mg malabsorption.[145]

Heaton et al[146] have demonstrated increased urinary Mg excretion (average 260% of control values) following alcohol ingestion. Recently, De Marchi et al[144] suggested a reversible tubular defect responsible for the enhanced urinary Mg excretion that was seen in 21% of chronic alcoholics. This was accompanied by other tubular dysfunctions, specifically, aminoaciduria, glycosuria, decreased renal threshold for phosphate excretion, and impaired renal acidification ability. All these changes disappeared after 4 weeks of alcohol abstinence.[144] Factors known to contribute to increased renal Mg excretion include alcoholic ketoacidosis, hypophosphatemia and hyperaldosteronism secondary to liver disease.[145] Furthermore, transient hypoparathyroidism was reported during alcohol intoxication and might have a role in enhancing renal Mg wasting.[147]

Magnesium deficiency has been implicated in the alcohol withdrawal syndrome. The simulta-

neous combination of pre-existing Mg depletion, catecholamine-induced Mg redistribution, and respiratory alkalosis (causing intracellular shift of Mg) may suddenly precipitate hypomagnesemia and the alcohol withdrawal syndrome.[134]

Treatment of Hypomagnesemia and Magnesium Deficiency

In most cases, the serum Mg concentration and urinary Mg excretion are sufficient to make the diagnosis of Mg deficiency. The parenteral Mg load test occasionally may be required to assess Mg status (Fig 1). Many protocols have been described for the treatment of Mg deficiency. The dosage and route of administration should be adjusted according to the severity of the Mg deficiency and the clinical presentation. Caution should be exercised in the presence of renal insufficiency since Mg toxicity may rapidly emerge.

The prophylactic addition of 100 to 200 mg/d of Mg to parenteral nutrition is advisable to prevent negative balance and optimize nitrogen retention. Higher doses may be required in malnourished individuals and in patients with ongoing Mg loss.[148] The prophylactic administration of Mg to patients with diabetic ketoacidosis is controversial, although the addition of 60 mg of Mg to each liter of intravenous fluids may be used after the repletion of intracellular losses.[59] The use of Mg-sparing diuretics (amiloride and triamterene) may reduce the occurrence of Mg deficiency.[51] In patient with chronic diuretic therapy, 5 to 10 mg of amiloride may negate the magnesuric effect of 40 mg of furosemide.[44]

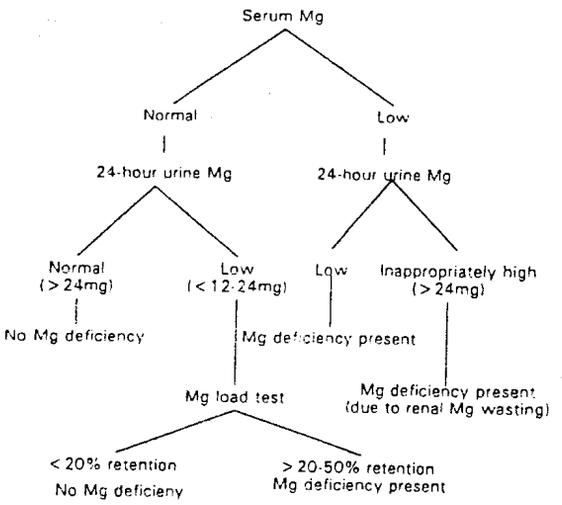

Fig 1. Diagnostic approach to suspected Mg deficiency.

Table 6. The Available Oral Magnesium Salts That May be Used in Magnesium Replacement Therapy

Magnesium Salt	Chemical Formula	Dose (mg/g)	Diarrhea
Sulfate	$MgSO_4 \cdot 7H_2O$	100	++
Oxide	MgO	600	++
Hydroxide	$Mg(OH)_2$	410	++
Citrate	$C_{12}H_{10}Mg_3O_{14}$	53	++
Lactate	$C_6H_{10}MgO_6$	120	+
Chloride	$MgCl_2 \cdot 6H_2O$	120	+
Gluconate	$Cl_2H_{22}MgO_{14}$	58	±

Mild asymptomatic hypomagnesemia can be replenished by a diet rich in Mg.[59] For conditions with chronic Mg loss, oral Mg salts may be used with variable success since large dose may cause diarrhea.[96,98] Oral therapy of Mg deficiency can be achieved with any of the available Mg salts, since comparative controlled data are lacking. Magnesium gluconate is better tolerated than other Mg salts as it tends to cause less diarrhea.[149] Magnesium oxide is supplied as a 600-mg tablet containing 360 mg of elemental Mg. Daily intake of four to six tablets for few a days often is sufficient to replete the Mg store and alleviate hypomagnesemia.[59,150] (For the available oral Mg preparations, see Table 6.)

In symptomatic Mg deficiency, the average deficit of Mg is 12 to 24 mg/kg body weight.[59] This should be replenished by Mg salts ($MgSO_4.7H_2O$ as 50% solution) given in divided doses, bearing in mind that approximately 50% of the administered dose is lost in the urine. Magnesium sulfate is administered intravenously (added to intravenous solutions) or intramuscularly in a total dose of 8 to 12 g (0.8 to 1.2 g of elemental Mg) over the first 24 hours, followed by 4 to 6 g daily for 3 to 4 days.[150] In an emergency situations, such as convulsions, 2 g of $MgSO_4$ (200 mg or 4 mL of 50% $MgSO_4$ in 100 mL solution) may be given intravenously over 5 to 10 minutes followed by continuous intravenous infusion.[50] During treatment, the serum Mg should be frequently monitored and deep tendon reflexes checked, as a significant depression of tendon reflexes indicates a serum Mg level in excess of 4.8 mg/dL.[150] Concomitant administration of potassium and calcium may be necessary

since associated loss of these cations is common in severe Mg deficiency.

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