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REVIEW

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Magnesium in critical illness: metabolism, assessment, and treatment

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Introduction

Magnesium is the second most abundant intracellular cation and the fourth most common cation in the body [1]. Its importance as an essential nutrient has been recognized since 1932, when Kruse et al. [2] reported the effects of acute Mg deficiency in rats. Even recently Mg was considered the "forgotten cation" in clinical practice [3]; however, this is no longer the case [4]. Estimates of Mg deficiency range from 20% to 61% [5, 6, 7], while a recent study found that reductions in total serum Mg on admission are associated with increased mortality [8].

Nonetheless, the relevance of such data to intensive care is problematic. Controlled data are lacking on how circulating total Mg concentrations are related to levels of biologically active ionized Mg (Mg^{2+}). Data are likewise sparse concerning the interplay between serum total and ionized Mg levels during specific critical illnesses and their treatment. In particular, the efficacy of therapeutic Mg supplementation on Mg^{2+}, organ function, inflammatory events, and mortality are poorly understood. This lack of information on the biology of Mg contrasts with well established correlations between serum total and ionized calcium (Ca^{2+}) concentrations, manifestations of acute Ca^{2+} deficiency, and the physiological effects of correcting ionized hypocalcemia [9, 10, 11, 12].

This review summarizes key aspects of Mg metabolism in adult intensive care patients, emphasizing the interdependence of Mg homeostasis with that of other cations such as Ca^{2+} and K^{+}. Thereafter we examine the justification for the trend of increasingly frequent measurements of serum total Mg in the critically ill, and how this information is related to emerging data concerning circulating Mg^{2+}. In this context, the limitations of current treatment recommendations for hypomagnesemia in the ICU are analyzed as well as research developments likely to alter our diagnostic and therapeutic algorithms in the near future. The use of therapeutic doses of Mg independent of hypomagnesemia or titration to serum total Mg levels to treat conditions such as preeclampsia and asthma are covered since this is beyond the scope of this review.

Compartmental distribution and metabolism of Mg

The body normally contains 21–28 g Mg [13]. Approximately 53% of total Mg stores are in bone, 27% in muscle, 19% in soft tissues, 0.5% in erythrocytes, and 0.3% in serum [14]. The Mg in muscle, soft tissues, and erythrocytes is considered to be intracellular [1], and mostly bound to chelators such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), proteins, RNA, DNA, and citrate [14]. Although only 5–10% of intracellular Mg is ionized, this fraction is essential for regulating intracellular Mg homeostasis [15] (Fig. 1).

Traditionally, extracellular Mg in serum was considered to be 33% protein bound, 7% complexed to citrate, PO_4^{2-}, and HCO_3^{-} [16], and 55% circulating in the diva-

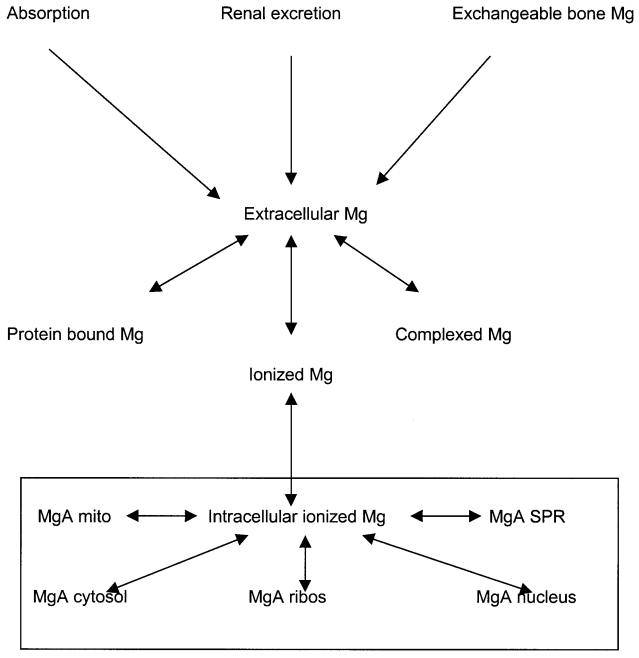

Fig. 1 Mg homeostasis. Extracellular Mg levels are maintained via absorption, renal excretion, and bone contribution. Extracellular Mg comprises protein-bound, complexed, and ionized fractions. Ionized extracellular Mg is in exchanging equilibrium with the intracellular ionized Mg fraction. *MgA cytosol*, *MgA ribos*, *MgA nucleus*, *MgA SPR*, *MgA mito* refer to Mg bound in the cytosol, ribosomes, nucleus, sarcoplasmic reticulum, and mitochondria, respectively

lent ionized form (Mg^{2+}). However, the newer methods of ion-selective Mg electrodes, atomic absorption spectroscopy, and ultrafiltration indicate that serum Mg is 67% ionized, 19% protein bound, and 14% complexed [17]. Standard clinical determinations of serum total Mg reflect all three forms. Of note, protein-bound and complexed Mg are unavailable for most biochemical processes [1]. The important issue of the dynamics of equilibration among the various states of extracellular Mg has not been extensively studied. Since serum contains only 0.3% of total body Mg stores, serum total Mg measurements poorly reflect total body status. Serum total Mg concentrations normally average 1.7–2.3 mg/dl (1.4–2.1 mEq/l) [13], depending on the laboratory and measurement technique. Mg concentrations are commonly expressed in units of milligrams, millimoles, or milliequivalents; for conversion one can use the following formula: 1 g Mg sulfate contains 98 mg= 4.06 mmol=8.12 mEq elemental Mg.

Daily Mg intake in adults normally averages 6–10 mg/kg [18]. Absorption occurs primarily in the jejunum and ileum [19]. Several lines of evidence suggest that absorption involves a transcellular, saturable process involving facilitated diffusion and a passive intercellular mechanism mediated by cationic electrochemical gradients and solvent drag [20]. Although 30–40% of dietary Mg is absorbed [19, 20], factors controlling intestinal absorption are unclear. An inverse curvilinear relationship was shown in healthy volunteers between Mg intake and its fractional absorption ranging from 65% absorption at low intake to 11% at high intake [21]. Thus, estimating the amount of oral Mg salts to correct hypomagnesemia in ICU patients who commonly have ileus and other forms of gastrointestinal dysfunction is problematic. The effects of vitamin D and parathyroid hormone (PTH) on enteral Mg absorption are minor [22].

Renal function is central to Mg homeostasis. Of the approx. 2.4 g Mg filtered per day (i.e., the 77% of total serum Mg that is not protein bound), 5% (120 mg) is normally excreted in the urine [23]. Glomerular filtration and tubular reabsorption both influence renal Mg handling [24]. Specifically, 20–30% of filtered Mg is reabsorbed in the proximal tubule and 60% in the thick ascending loop of Henlé [25]. This is where ionic regulators, hormones, and medications affect Mg excretion. Mg reabsorption in the thick ascending loop of Henlé is linked with NaCl transport and is therefore influenced by tubular flow [24, 25]. Conservation of Mg by normal kidneys during Mg deprivation may decrease fractional excretion to less than 0.5% (12 mg/day) [23]. Conversely, the kidneys increase excretion of Mg to approximate the filtered load during increased intake or excessive Mg administration [26]. During renal failure the fractional excretion of Mg progressively increases, and normal serum total Mg levels are maintained until the later stages when hypermagnesemia supervenes [27].

Mg homeostasis and compensatory mechanisms

Mg homeostasis involves interaction between three organ systems: kidneys, small bowel, and bone (Fig. 1). Acute Mg deprivation increases tubular reabsorption and intestinal absorption [28]. The mechanisms for such compensatory alterations in Mg transport are not fully understood. Several reports indicate a lack of correlation of these alterations with serum total Mg concentrations [29, 30, 31]. In Mg deficient rats a fall in urinary Mg excretion was found to occur without changes in plasma total Mg concentrations [28]. This adaptation was rapid (within 5 h) and specific (without changes in Na^+ or Ca^{2+} reabsorption). If Mg deprivation continues, exchangeable bone Mg starts contributing to extracellular Mg levels [32]. Up to 30% of bone Mg is rapidly exchangeable [33].

The threshold of negative Mg balance that triggers compensatory mechanisms is not known. Even so, ionized intracellular Mg $[Mg^{2+}]_i$ appears to be the ultimate regulatory signal [28]. $[Mg^{2+}]_i$ and intracellular bound Mg are exchangeable and are in equilibrium with extracellular Mg^{2+} [34]. Thus, ionized and bound intracellular

Mg represent buffers whose chief function appears to be maintaining constancy of the intracellular concentration of free $[Mg^{2+}]_i$. In human erythrocytes and other cells an increase in $[Mg^{2+}]_i$ by Mg loading is associated with Mg efflux via the Na^{2+}/Mg^{2+} antiport until $[Mg^{2+}]_i$ is normalized. Furthermore, reductions in $[Mg^{2+}]_i$ stimulate cationic diffusion down a concentration gradient from higher levels of extracellular Mg^{2+} [35, 36]. Consequently, Mg homeostasis is regulated chiefly by $[Mg^{2+}]_i$ which is in equilibrium with both intracellular bound Mg and extracellular Mg^{2+}. Neither the magnitude nor the efficiency of these compensatory mechanisms is known for critically ill patients, in whom counterregulatory hormone release, insulin administration, and de novo renal and gastrointestinal dysfunction are common.

Biochemical, biological, and physiological effects of Mg

Mg is important in physiological processes involving energy storage, transfer, and utilization [13, 37]. Mg complexed to ATP is a substrate for signal-transducing enzymes including phosphatases and phosphokinases on the plasma membrane and within intracellular compartments. Enzymatic reactions involving ATP require Mg^{2+}, which neutralizes the negative charge on ATP to facilitate binding to enzymes and assists hydrolysis of the terminal PO_4^{2-} bond [38]. Intracellular Mg^{2+} regulates intermediary metabolism by activating rate-limiting glycolytic and tricarboxylic acid cycle enzymes [39]. Mg^{2+}-ATPases include Mg^{2+}-(Na^+-K^+) ATPase, Mg^{2+}-(HCO_3^-) ATPase, and Ca^{2+}-Mg^{2+} ATPase, which are involved in Na^+, proton, and Ca^{2+} transport, respectively [40]. Mg indirectly affects protein synthesis by four mechanisms: (a) facilitation of nucleic acid polymerization, (b) enhanced binding of ribosomes to mRNA, (c) acceleration of the synthesis and degradation of DNA, and (d) regulation of protein:DNA interactions and thus transcriptional activity [41, 42]. Adenylate cyclase also requires Mg to generate the intracellular second messenger cAMP [40].

Intracellular Mg^{2+} significantly affects Ca^{2+} and K^+ metabolism. As a divalent cation Mg^{2+} competes with Ca^{2+} for membrane-binding sites and modulates Ca^{2+} binding and release from the sarcoplasmic reticulum [43]. Complementary effects include maintenance of low resting levels of intracellular Ca^{2+}, thereby modulating muscle contraction by noncompetitive inhibition of inositol 1,4,5-triphosphate gated Ca^{2+} channels [44]. Calcium metabolism is controlled chiefly through PTH; substantial evidence indicates that Mg modulates Ca balance by its actions on PTH itself [45]. For example, impaired PTH secretion associated with hypomagnesemia results in hypocalcemia. This is attributed to reduced Mg-dependent activation of adenylate cyclase in parathyroid tissue [46, 47]. Whether Mg deficiency also contributes to skeletal muscle resistance to PTH is controversial [48].

Mg^{2+} regulates K^+ transport via the Na^+-K^+-ATPase system as a cofactor. This action influences Na^+ and K^+ extracellular fluxes, which determine the electrical potential across cell membranes [49]. $[Mg^{2+}]_i$ blocks outward movement of K^+ through K^+ channels in cardiac cells. Decreases in $[Mg^{2+}]_i$ cause excessive outward movement of K^+ even as intracellular K^+ falls, thereby inducing depolarization [50]. This critical role of Mg^{2+} to maintain intracellular K^+ concentrations is termed "inward rectification" [51]. Mg^{2+} deficiency also impairs K^+-Na^+-Cl^- cotransport [52].

In the nervous system Mg has a depressant effect at the synapses; this is related to competition with calcium in the stimulus-secretion coupling processes in transmitter release. The best described of these is presynaptic inhibition of acetylcholine release at the neuromuscular junction [53]. The action of Mg as an anticonvulsant is related to noncompetitive blockade of *N*-methyl-D-aspartate receptors. These are a group of glutamate receptors, stimulation of which leads to excitatory postsynaptic potentials causing seizures [54].

Overall, Mg^{2+} deficiency has the potential to impair oxidative phosphorylation, protein metabolism, and transmembrane electrolyte flux in cardiac and neural tissues.

Assessment of Mg status

Assessing Mg status in the critically ill beyond serum total Mg levels is difficult. No single laboratory test tracks total body Mg stores. In all, three groups of tests are available: (a) estimates of tissue Mg using concentrations in serum, red blood cells, blood mononuclear cells, or muscle; (b) metabolic assessments of Mg balance encompassing isotopic analyses and evaluation of renal Mg excretion and retention, and (c) determination of Mg^{2+} levels which utilize fluorescent probes, nuclear magnetic resonance spectroscopy, or ion-selective electrodes (ISE).

Measuring total Mg concentrations in serum rather than plasma has been preferred because additives such as anticoagulants may be contaminated with Mg or otherwise affect the assay. For example, citrate binds Ca^{2+} as well as Mg^{2+} to affect fluorometric (8-hydroxyquinoline) and colorimetric procedures for Mg estimation [55]. As indicated above, serum total Mg levels reflect Mg^{2+}, the protein-bound Mg fraction, and Mg complexed to anions, and each component of the total value may change independently and in a nonlinear manner with respect to the other Mg fractions.

Most clinical laboratories report serum total Mg concentrations using colorimetric methods with calmagite or methylthymol blue as the chromophore [56]. As men-

tioned above, the chief limitation is that serum concentrations represent only 0.3% of total body Mg content [14]. Moreover, with the exception of bone, serum total Mg concentrations are not correlated with other tissue pools of Mg [57]. As for Ca, normal total Mg levels may coexist with ionized hypomagnesemia and vice versa [58]. Red blood cell Mg determinations have no advantage over serum levels and also are not correlated with other tissue fractions [57]. In normal subjects there is no correlation among Mg levels in mononuclear cells compared with serum or erythrocytes [59]. In a prospective controlled study measuring skeletal muscle Mg concentrations in 32 ICU patients with respiratory failure no correlation was found between serum total and muscle Mg concentrations [60]. Lower muscle Mg levels were associated with reduced intracellular K^+ levels, a higher incidence of ventricular extrasystoles, and a longer ICU stay.

Physiological assessments of Mg balance require steady-state conditions for accurate results, conditions that are infrequent in the critically ill. A 24-h urine collection for renal Mg excretion takes into account the circadian rhythm of cationic urinary losses [61]. However, existence of this rhythm during critical illness is unknown. Even so, a 24-h Mg excretion rate of less than 12 mg/day is acceptable evidence of Mg deficiency in the presence of serum total hypomagnesemia and normal renal function [23]. The Mg tolerance test has been used for many years as a fairly reliable means of assessing total body Mg status in patients at risk of hypomagnesemia [62]. Subjects with normal Mg balance and renal function excrete most of a parenterally administered Mg load within 24 h [28, 62]. A generally accepted protocol includes: (a) a baseline 24-h urine collection for Mg, followed immediately by (b) an infusion of 2.4 mg Mg per kilogram of lean body weight in 50 ml 5% dextrose over 4 h, and (c) a second 24-h urine collection. Differences in Mg content between the two urine collections represent the retained Mg fraction. Retention of more than 20% of administered Mg is suggestive of Mg deficiency, whereas retention of more than 50% is confirmatory [40]. This test is contraindicated when serum creatinine exceeds 200 µmol/l. Furthermore, drugs or conditions producing renal Mg wasting invalidate the results. Using the Mg loading test, serum ionized Mg levels were found to be insensitive markers of Mg deficiency in 44 ICU patients without renal insufficiency [63]. However, confounding variables, such as the use of diuretics, prevent any firm conclusions to be drawn.

A major advance in evaluating Mg deficiency is the ability to measure Mg^{2+}. In 1989 Raju et al. [64] modified the calcium fluoroprobe fura-2 to improve selectivity for Mg^{2+}. The resulting compound furaptra (mag fura-2) exhibits a shift in the peak excitation wavelength for fluorescence when bound to Mg^{2+} or Ca^{2+}. The change in fluorescence corresponds to Mg^{2+} and Ca^{2+} concentrations weighted by their respective dissociation constants. For Mg^{2+}, these probes work well within the cell. Other fluorescent probes for Mg^{2+} have been described [65]. Nuclear magnetic resonance spectroscopy estimates Mg^{2+} noninvasively. Although several isotopes ($^{19}F^-$, $^{25}Mg^{2+}$, and $^{31}P^{-2}$) have been used to estimate Mg^{2+}, the α- and β-phosphate moieties of ATP have been used most frequently [66].

Three ISEs for Mg^{2+} determination are currently available: (a) the NOVA 8 analyzer (NOVA, Waltham, Mass., USA); (b) the Microlyte 6 analyzer (Kone, Espoo, Finland); and (c) the AVL 988/4 analyzer (AVL, Schaffhausen, Switzerland). In May 1993 the United States Food and Drug Administration approved the NOVA 8 electrode for clinical use, and most studies of Mg^{2+} have used the NOVA 8 instrument. These ISEs employ ionophores and neutral carrier-based membranes designed to function in the presence of Ca^{2+} and other cations. Mg^{2+}-specific ISEs yield rapid results on whole blood, plasma, and serum using samples between 100–200 µl. Ionized Mg concentrations in healthy subjects using the NOVA 8 average 0.54–0.67 mmol/l [58, 67]. Serum reference intervals for the Kone and AVL analyzers are 0.47–0.57 mmol/l and 0.55–0.63 mmol/l, respectively [68]. No gender-related differences in Mg^{2+} have been described [67]. To date ISEs have been found to be selective for Mg^{2+}; physiological concentrations of Ca^{2+}, Na^+, K^+, H^+ and NH_4^+ have negligible effects. Therefore the precision of these analyzers is suitable for determining Mg^{2+} in intensive care [67].

The NOVA 8 and AVL analyzers correct signals from the Mg^{2+} electrode for concurrent Ca^{2+}. Calculations of Mg^{2+} and Ca^{2+} are normalized to a pH of 7.4 in the NOVA 8 instrument, which also estimates Na^+, K^+, Ca^{2+}, hematocrit, and pH [69]. The binding capacity and affinity of albumin for Mg^{2+} and Ca^{2+} varies with pH [70]; hence the Mg^{2+} and Ca^{2+} levels are pH dependent. Because of pH changes during specimen storage, measured Mg^{2+} can be reported as the Mg^{2+} at the pH of the blood sample (preferably) or as Mg^{2+} normalized to a pH of 7.4.

Mg deficiency in intensive care

Ideally, Welt and Gitelman's [71] definition of hypomagnesemia as "a reduction in total body magnesium content" defines true Mg deficiency. Unfortunately, this definition of Mg deficiency is not in keeping with commonly available laboratory technology. In spite of its imperfections serum total Mg is still used as the standard for defining hypomagnesemia in intensive care patients.

Clinical manifestations of hypomagnesemia

Most hypomagnesemia in intensive care is asymptomatic. In theory, symptoms and signs occur when the serum total Mg concentrations fall below 1.2 mg/dl (0.5 mmol/l) [72], as summarized below:

- Neuromuscular manifestations
  - Positive Chvostek's sign
  - Positive Trousseau's sign
  - Carpopedal spasm (tetany)
  - Muscle cramps
  - Muscle fasciculations and tremor
  - Muscle weakness
- Neurological manifestations
  - Convulsions
  - Nystagmus
  - Athetoid movements
  - Apathy
  - Delirium
  - Coma
- Cardiac manifestations
  - Supraventricular arrhythmias
  - Ventricular arrhythmias
  - Torsades de pointes
  - Enhanced sensitivity to digitalis intoxication
- Electrolyte disturbances
  - Hypokalemia
  - Hypocalcemia

However, manifestations of hypomagnesemia may depend more on the rate of development of the deficiency, on serum ionized rather than total hypomagnesemia, or on tissue Mg deficits rather than on circulating levels [73]. Consequently symptoms and signs ascribed to Mg deficiency may be absent even with severe hypomagnesemia (serum total Mg levels <0.8 mg/dl) [72]. Such dissociations between serum total Mg levels and clinical findings make it difficult to infer total body Mg deficiency, the need for correction of hypomagnesemia, and the physiological benefit of such correction in individual patients.

Neuromuscular manifestations of hypomagnesemia: relationship to hypocalcemia

Serum total hypomagnesemia is usually corrected because of concerns over neuromuscular irritability (e.g., positive Chvostek's and Trousseau's signs, tremors, fasciculations, and tetany) or weakness [74]. In particular, the possibility of weakness and resultant delays in ventilatory weaning attributable to hypomagnesemia have resulted in the widespread practice of frequent measurements and vigorous normalization of serum total Mg levels in ventilated patients. However, no controlled data support this practice, and its putative physiological benefit to respiratory muscle function remains obscure. Indeed, neuromuscular manifestations of serum total hypomagnesmia may be due more to concomitant hypocalcemia, even though tetany attributable solely to hypomagnesemia can occur independently of reduced serum total Ca levels [75]. Overall, neuromuscular irritability and weakness appear to be related to the combined actions of ionized hypomagnesemia and ionized hypocalcemia on the neuromuscular apparatus. Hypocalcemia does not usually develop until serum total Mg is below 1.2 mg/dl; serum total hypocalcemia occurs in one-third of hypomagnesemic medical ICU patients [76]. Hypocalcemia is usually refractory to Ca repletion unless Mg is first administered [76, 77].

Neurological manifestations of hypomagnesemia

Reported neurological manifestations of hypomagnesemia include convulsions, athetoid movements, nystagmus, apathy, delirium, and coma [40]. As mentioned above, the anticonvulsant effect of Mg appears to be via a voltage-gated antagonist action at the *N*-methyl-D-aspartate receptor [54].

Cardiac electrophysiology, hypomagnesemia, and hypokalemia

The frequency and pathogenesis of cardiac arrhythmias during hypomagnesemia [78] are hard to establish because coexisting hypokalemia is common. Whang et al. [79] reported hypokalemia in 42% of hypomagnesemic patients. Such hypokalemia is also refractory to treatment unless Mg is first repleted [74]. Although Mg per se does not participate in the production of the cardiac action potential [80], Watanabe and Dreifus [81] showed that Mg's effects on cardiac transmembrane potentials varied in perfused rat hearts according to extracellular K^+ levels. Increases or decreases in Mg levels with normal extracellular K^+ concentrations causes minor electrophysiological changes. Alterations in serum total Mg concentrations are unlikely to destabilize sinus rhythm unless accompanied by changes in other cations [80].

Serum total Mg levels below 0.7 mmol/l are associated with electrocardiographic changes indistinguishable from hypokalemia-related effects, including ST segment depression, flattened T waves, and prolongation of PR and QT/QTc intervals [38]. Arrhythmias associated with serum total hypomagnesemia include premature atrial contractions, atrial fibrillation, multifocal atrial tachycar-

dia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation [82, 83]. Hypomagnesemia promotes digitalis-induced arrhythmias [84]. The mechanisms are unclear but include: (a) increased myocardial uptake of digoxin, (b) augmented inhibitory action of digoxin on Na^+-K^+-ATPase causing a reduction in intracellular K^+ [82], and (c) loss of the membrane-stabilizing effect Mg^{2+} on the myocardial cell membranes [84]. Mg therapy is recommended for torsades de pointes [85]. Despite these associations of low serum total Mg levels with cardiac electrophysiological changes, purported links between low Mg and arrhythmias do not confirm a cause and effect relationship. Lack of a standard by which to define a Mg-deficient state, coexistence of other electrolyte abnormalities, varying methods of arrhythmia monitoring, and inability to distinguish between spontaneous and drug-induced arrhythmia termination are all factors [80]. Moreover, a prospective uncontrolled study of 23 heart failure patients found no correlation between serum total Mg and myocardial Mg concentrations [86].

Causes of Mg deficiency in intensive care

Singly or combined, Mg deficiency in intensive care has three main causes – (a) reduced intestinal absorption, (b) increased renal losses, and (c) compartmental redistribution, as detailed below.

Gastrointestinal causes include:

- Nutritional disturbances
  - Inadequate intake
  - Mg-free fluids and total parenteral nutrition
  - Refeeding syndrome
- Reduced absorption
  - Malabsorption syndromes
  - Short bowel syndrome
  - Chronic diarrhea
- Increased intestinal losses
  - Intestinal and biliary fistulae
  - Prolonged nasogastric suction
- Pancreatitis

Causes related to renal Mg wasting include:

- Intrinsic tubular defect
  - Interstitial nephropathy
  - Postobstructive diuresis
  - Diuretic phase of ATN
  - Postrenal transplantation
- Drug-induced renal Mg wasting
  - Loop and thiazide diuretics
  - Cisplatin
  - Cyclosporine A
  - Aminoglycosides
  - Amphotericin B
  - Pentamidine and foscarnet
  - Colony-stimulating factor therapy
- Hypophosphatemia
- Hypercalcemia/hypercalciuria

Endocrine causes include:

- Hyperaldosteronism
- Hyperparathyroidism
- Hyperthyroidism
- Syndrome of inappropriate antidiuretic hormone
- Diabetic ketoacidosis
- Alcoholic ketoacidosis

Causes related to the redistribution of Mg include:

- Acute pancreatitis
- Administration of epinephrine
- “Hungry bone” syndrome
- Massive blood transfusion
- Acute respiratory alkalosis

Other causes include:

- Cardiopulmonary bypass
- Severe burns
- Excessive sweating
- Chronic alcoholism and alcoholic withdrawal

Nearly all data concerning hypomagnesemia during critical illness comes from measurements of circulating total Mg. These do not shed light on the causes of Mg deficiency and likely underestimate ionized hypomagnesemia and total body Mg depletion.

Gastrointestinal causes

Prolonged administration of Mg-free parenteral nutrition formulae and other intravenous fluids can precipitate Mg deficiency, especially in patients with preexisting marginal stores of Mg [87]. Vomiting and nasogastric suctioning further contribute to Mg depletion [48], since the Mg content of upper intestinal fluids is about 1 mEq/l. Diarrheal fluids and fistula drainage contain up to 15 mEq/l total Mg ions [88]. Hemorrhagic pancreatitis is an additional cause of acute hypomagnesemia with hypocalcemia due to formation of Mg and Ca fatty acid soaps in sites of tissue necrosis [89].

Renal causes

Renal Mg wasting is traditionally diagnosed when the 24 h urinary Mg excretion exceeds 24 mg in the presence of hypomagnesemia as assessed by serum total Mg levels [23]. Random or "spot" urinary tests for Mg are interesting albeit unvalidated diagnostic tests. Renal Mg wasting has been reported with tubulointerstitial renal diseases, postobstructive diuresis, the diuretic phase of acute tubular necrosis, and following renal transplantation [90]. Since Mg absorption in the thick ascending loop of Henlé depends on the positive transmembrane potential created by NaCl absorption, alterations in NaCl transport by loop diuretics, 0.9% NaCl infusion, or osmotic diuresis promote Mg excretion. Loop diuretics (furosemide, bumetamide, and ethacrynic acid) are potent inhibitors of Mg reabsorption and are a common cause of hypomagnesemia in the ICU. Thiazide diuretics act on the distal tubule, where less than 5% of Mg is absorbed. Short-term administration of thiazides does not produce significant renal Mg wasting, whereas long-term administration may produce substantial Mg deficiency [40].

Several drugs cause excessive renal losses of Mg. Cisplatin causes hypomagnesemia in more than 50% of treated patients [91]; the incidence increases with the cumulative dose. Likewise, aminoglycosides induce magnesuria; 4.5% of 200 patients treated with 400 courses of aminoglycosides developed hypomagnesemia [92]. The total dose of aminoglycoside treatment in these studies varied from 1.3–40 g and recovery from hypomagnesemia varied from 2–8 weeks. A recent prospective study showed ionized hypomagnesemia secondary to renal Mg wasting in cystic fibrosis patients treated with a 2-week course of 33 mg/kg amikacin daily and 250 mg/kg ceftazidime daily [93], although no clinical correlation with ionized hypomagnesemia was performed. Amphotericin B causes mild and reversible hypomagnesemia [94]. Barton et al [94]. reported that reversal of amphotericin B-induced renal Mg wasting could take as long as 1 year following treatment. As with amphotericin B, cyclosporine A causes Mg deficiency secondary to defects in renal tubular function [95]. Parenteral pentamidine has also been implicated in hypomagnesemia secondary to renal Mg wasting [96].

Hypophosphatemia is common during intensive care, particularly in insulin-dependent diabetics and during Gram-negative bacterial sepsis [97]. Although hypophosphatemia promotes magnesuria, the mechanism is unclear [79]. Serum total Mg levels are inversely correlated with the fasting blood sugar level in diabetics in whom glycosuria, ketoaciduria, and hypophosphatemia contribute to renal Mg wasting [98]. Primary [99] and secondary [100] hyperaldosteronism are associated with renal Mg wasting secondary to volume expansion, causing increased tubular flow rates and decreased NaCl reabsorption [99]. The exact mechanism, however, remains controversial. Other hormonal conditions associated with hypomagnesemia are the syndrome of inappropriate antidiuretic hormone secretion [101] and hyperthyroidism [102].

Redistribution of Mg

"Hungry bone syndrome" after parathyroidectomy [103] or diffuse osteoblastic metastasis [104] can result in hypomagnesemic, hypocalcemic tetany from osseous deposition of Mg and Ca. Epinephrine and other β-agonists (e.g., salbutamol) cause transient hypomagnesemia in healthy subjects [105]. This is thought to occur from uptake of Mg into adipose tissue as fatty acids are released. Release of fatty acids into the blood may also lead to the formation of insoluble fatty acid–Mg^{2+} and fatty acid–Ca^{2+} complexes [40]. Massive blood transfusion (>10 U/24 h) may cause hypomagnesemia from the chelating effects of citrate [106]. Hypomagnesemia occurs during and after cardiopulmonary bypass surgery [84, 107]. Potential mechanisms include hemodilution from large-volume infusion of Mg-free fluids, removal of Mg by the bypass pump, and catecholamine-induced intracellular Mg shifts, and binding to free fatty acids [107]. A retrospective study of 30 patients undergoing elective cardiopulmonary bypass surgery demonstrated ionized hypomagnesemia in 73% [108]. Of note, the relationship between Mg^{2+} and Ca^{2+} during CPB was variable, and Ca^{2+} levels did not predict Mg^{2+} levels [108]. Significant hypomagnesemia (i.e., serum total Mg level <1.40±0.15 mEq/l) occurs in up to 30% of alcoholics. Multiple mechanisms are likely, including decreased Mg intake accompanying poor nutritional status, vomiting, chronic pancreatitis-induced steatorrhea, and Mg malabsorption [109].

Collectively, the above data indicate that hypomagnesemia (serum total Mg level <1.5 mEq/l) may have multiple causes in the ICU patient. Even so, three critical questions remain: (a) to what extent does ionized hypomagnesemia parallel reductions in serum total Mg levels and in total body Mg stores? (b) Does Mg replacement to correct levels of serum total Mg also correct ionized hypomagnesemia? (c) Is correction of serum total or ionized hypomagnesemia associated with definable clinical changes in biochemistry, electrophysiology, inflammatory responses or organ function? Until the answers to these questions are forthcoming, we may be spending considerable effort and expense merely to make serum total Mg levels "look better."

Mg, sepsis, and shock

Novel immunoregulatory effects of Mg deficiency and supplementation are increasingly reported [110, 111,

112]. Such data suggest that reductions in circulating and intracellular Mg have important, albeit clinically occult immunomodulatory consequences during severe sepsis and shock states. By enhancing generation of reactive O_2 species [111] and cytokine biosynthesis, hypomagnesemia can promote inflammatory tissue injury [112].

Altura et al. [113] proposed that circulating free Mg^{2+} ions are "natural" Ca^{2+} antagonists that modulate lethal cellular Ca^{2+} entry during shock. Lower Mg^{2+} concentrations have been found to be correlated with efflux of Ca^{2+} from the sarcoplasmic reticulum of frog myocytes over a 0.3- to 3-mmol concentration range of Mg^{2+} [114]. A direct effect of low $[Mg^{2+}]_i$ to increase the voltage-gated calcium current (I_{Ca}) was implicated. Based on this and other reports [115], Mg^{2+} deficiency may promote abnormal cellular Ca^{2+} entry during sepsis; this may in turn increase free cytosolic and mitochondrial Ca^{2+} to cause cell death. In support of this, intracellular Ca^{2+} has been reported to increase as tissue Mg^{2+} levels decline in a rat endotoxic shock model [116]. Concomitant depression of mitochondrial respiration was restored after Mg^{2+} supplementation.

Since considerable intracellular Mg^{2+} is complexed to ATP, sepsis, or ischemia/reperfusion-induced ATP hydrolysis or falls in ATP production release intracellular Mg^{2+} ions. Subsequently $[Mg^{2+}]_i$ concentrations rise, and Mg^{2+} effluxes from cells [115, 117]. Three negative consequences may result: (a) impaired Na^+-K^+ ATPase pump activity, (b) reduced inwardly rectifying K^+ ion channels, and (c) dysfunctional cell membrane and sarcolemmal Ca^{2+} ion channels [61]. These changes may partly account for the increased lethality of endotoxemia seen in rats during hypomagnesemia as well as the protective effects of Mg replacement from endotoxin challenge [118].

Mg^{2+} ions modulate key immunological functions, including macrophage activation, leukocyte adherence, and bactericidal activity [119], granulocyte oxidative burst, lymphocyte proliferation, and endotoxin binding to monocytes [118]. In Mg-deficiency models time-dependent increases are seen in circulating interleukin-1, tumor necrosis factor-α, interferon-γ, substance P, and calcitonin gene related peptide [110, 112, 120]. Such effects may result from altered DNA binding of transcription factors notable for their suppression of inflammatory cytokine gene activation, including the cyclic AMP response element binding protein [42]. Likewise, Mak et al. [121] reported overproduction of nitric oxide in an Mg-deficient rat model. In that report increased nitric oxide production was considered secondary to Mg deficiency-related stimulation of inducible nitric oxide synthase and activation of Ca-sensitive nitric oxide synthase from increased intracellular Ca^{2+}. Cytotoxic effects of NO include those resulting from its combination with superoxide to form peroxynitrite [121]. Inhibition of mitochondrial respiration, interference with the O_2 carrying ability of hemoglobin and myoglobin due to interaction with heme proteins, and inhibition of enzymes containing heme and nonheme iron-sulfur centers all contribute to toxicity [122]. Overall, emerging data showing interrelated links among biochemical, physiological, and immunoregulatory effects of Mg deficiency during sepsis and shock suggest the corollary thesis that titrated Mg supplementation can alter outcomes. Further experimental and clinical data are needed to confirm this notion.

Ionized Mg and intensive care

Serum total Mg levels are not correlated with serum Mg^{2+} in the critically ill because of accompanying variations in plasma protein concentrations, acid-base balance, metabolic derangements, and drugs that affect Mg balance [58, 123]. Külpmann et al. [123] showed that reduced serum total Mg concentrations maymight reflect "pseudohypomagnesemia" from hypoalbuminemia when concomitant Mg^{2+} concentrations are normal. Such findings have led to the suggestion that the terms hypo-, normo-, and hypermagnesemia should be restricted to Mg^{2+} levels. Of note, $[Mg^{2+}]_i$ levels are correlated well with serum Mg^{2+} by ^{31}P-nuclear magnetic resonance spectroscopy [124]. In aortic endothelium $[Mg^{2+}]_i$ levels change within 5 min of increasing extracellular Mg^{2+}, suggesting that extracellular Mg^{2+} dynamically equilibrates with $[Mg^{2+}]_i$ [125]. Additional studies are needed to confirm whether extracellular Mg^{2+} accurately tracks total body Mg balance. In spite of in vitro studies demonstrating the superiority of ionized Mg measurements over total Mg estimations; few studies have attempted to demonstrate the importance of measuring ionized Mg levels in the critical care setting and to examine the correlation of ionized hypomagnesemia with clinical manifestations and outcomes.

Salem et al. [126] measured Mg^{2+} and serum total Mg concentrations in 180 critically ill patients. Serum total Mg values were sensitive (75%) but not specific (38%) in predicting ionized hypomagnesemia. Increased supraventricular and ventricular dysrhythmias, seizures, hypotension, and death were associated with ionized hypomagnesemia (normal range 0.52–0.60 mmol/l). Recently, Huijgen and colleagues [127] evaluated the relationships between serum Mg^{2+}, total body Mg estimated by Mg content in blood mononuclear cells and erythrocytes, serum albumin, and 30-day mortality in 115 critically ill patients. A normal serum Mg^{2+} was found in 71% of patients with total serum hypomagnesemic values. Moreover, neither total nor ionized Mg measurement was correlated with cellular Mg levels or with outcome. With respect to the cardiovascular effects of hypomagnesemia, Kasaoka et al. [128] found that supraventricular and ventricular extrasystoles decreased by 50% and ventricular

tachycardia was abolished by a 0.15 mmol/kg intravenous bolus of Mg sulfate ($MgSO_4$) over 10 min, which increased serum Mg^{2+} from 0.35±0.06 mmol/l to 0.54±0.09 mmol/l. $MgSO_4$ had no effect in patients with a normal serum Mg^{2+}. The ratio of Mg^{2+} to Ca^{2+} as a modulator of vascular tone also increased after intravenous $MgSO_4$ and was thought to contribute to the antiarrhythmic effect. Bertschat et al. [129] determined serum Mg^{2+} levels on days 1, 2, 3, 5, and 7 after myocardial infarction in 42 patients, in addition to concomitant serum total Mg, free fatty acids, Ca^{2+}, and total Ca. Compared with serum total Mg concentrations, Mg^{2+} levels fell on the 1st day of myocardial infarction and were inversely correlated with serum free fatty acids. The ionized hypomagnesemia was attributed to β-adrenergic induced lipolysis and binding of Mg^{2+} by fatty acids. Since the benefit of intravenous $MgSO_4$ during acute myocardial infarction is not established, the authors suggest that serum Mg^{2+} rather than total Mg be measured in coronary care patients, and that those with ionized hypomagnesemia be treated [129].

Frankel et al. [130] noted a poor correlation between serum total and Mg^{2+} values in 113 trauma patients, although injury severity or blood ethanol levels did not predict ionized hypomagnesemia. It has been hypothesized that decreased serum Mg^{2+} levels after trauma result from increases in circulating catecholamines and corticosteroids, and to Mg redistribution within injured tissues [131]. Ionized hypomagnesemia occurs after experimental head trauma [132] and in brain-injured patients [133]. In vivo animal studies have shown that pre- or posttreatment with $MgCl_2$ 15 min after cerebral injury restores brain Mg^{2+} levels, improves motor function [134], attenuates cognitive deficits [135], and reduces cerebral edema [136]. In a traumatic brain injury rat model Bareyre et al. [137] studied serum Mg^{2+} levels 24 h postinjury and neuromotor outcome after 1 and 2 weeks. Supplemental Mg treatment given to rats with ionized hypomagnesemia reduced posttraumatic impairments. No such correlation was found using blood total Mg levels, which did not change postinjury. In other in vivo animal studies Mg treatment has been shown to reduce posttraumatic edema and cortical damage, in association with concomitant changes in gene expression for c-fos, heat shock protein-70, neurotrophins, and cyclooxygenase-2 [136, 138]. In addition to Mg's multiple effects on intermediary metabolism, oxidative phosphorylation, protein synthesis, regulation of membrane permeability to Ca^{2+} and K^+ ions, and potential anti-inflammatory effects, it has also been recently shown in murine cortical cell cultures to be a potent antioxidant to iron-dependent oxidative injury [139]. By increasing the physiologically active ionized Mg fraction, $MgCl_2$ possibly restores the ability of cells to maintain homeostasis [137]. Available data therefore suggest that early measurement of blood ionized Mg levels and supplementation when indicated may be of value in reducing morbidity after head injury or cerebral infarction. The positive data correlating neuromotor outcomes after head injury and correcting ionized hypomagnesemia are currently limited to animal studies only; more investigation needs to be carry out to determine whether the same holds true in human head-injured patients in prospective randomized controlled trials.

Treatment of hypomagnesemia

Treatment recommendations for hypomagnesemia in intensive care are confounded by the lack of controlled clinical data regarding the directional changes in time-matched serum total and ionized Mg levels, particularly in relation to concomitant ionized Ca^{2+}, K^+, and PO_4 concentrations. In addition, renal insufficiency, administration of drugs which promote renal Mg wasting, and varying recommendations for Mg repletion are problematic [140, 141]. An ideal ICU study to clarify these issues would therefore have to first attempt to define the measure of true Mg deficiency (total body, extracellular ionized, etc.) that is correlated with clinical manifestations. The study would further need to control for disturbances in other cations and drugs that interfere with Mg balance and renal function and determine the clinical, biochemical, and hemodynamic effects of correcting Mg deficiency with the ultimate goal of determining patient outcomes.

Nonetheless, several generalizations are appropriate regarding the treatment of Mg deficiency:

- Emergency (intravenous route):
  - 8–12 mmol Mg over 1–2 min
  - 40 mmol Mg over next 5 h
- Severely ill (intravenous or intramuscular route)
  - 40 mmol Mg on day 1
  - 16–24 mmol Mg on days 2–5
- Oral maintenance
  - 12–24 mmol per day

Kidney function must be assessed prior to the initiation of Mg therapy. Since the major route of Mg excretion is via the kidney, significant hypermagnesemia can occur in the setting of compromised renal function. In general, when rapid Mg administration is needed, as for cardiac arrhythmias, the intravenous route is safe. It should, however, be performed with hemodynamic and electrocardiographic monitoring as there may be significant prolongation of intra-atrial and atrioventricular nodal conduction times [142] as well as hypotension. Davies et al. [143] noted hypotension in three patients during

Gram-negative bacteremic sepsis when Mg sulfate ($MgSO_4$) was given using a rapid regimen (8 mmol intravenously over 5 min). The authors did not mention the degree of hypotension that occurred, nor the baseline blood pressure and the use of vasopressors (if any) prior to Mg administration. No hypotension occurred when 48 mmol $MgSO_4$ was infused over 24 h. Such hypotensive responses may reflect the combined effects of sepsis-induced myocardial dysfunction together with Mg infusion-induced reductions in systemic vascular resistance. In the critical care setting treatment recommendations must therefore be tempered with the urgency of replacing Mg deficits. Slower infusions (mentioned below) are appropriate unless cardiac arrhythmias or seizures are present. Slow replacement can be achieved by giving 8–12 g $MgSO_4$ intravenously over 24 h, followed by 4–6 g daily for another 3–4 days [40]. Since up to 50% of administered Mg may be lost in the urine, continuous infusions of Mg or repeated doses may be preferable. However, there are no controlled data with regard to the efficacy of this approach in critically ill patients. Oral Mg salts can be used as maintenance therapy in conditions associated with chronic Mg loss, for example, short or long-term use of diuretics. An initial daily dose of 300–600 mg elemental Mg may be used. The Mg is given in divided doses to decrease its cathartic effect. Significant hypermagnesemia can complicate Mg replacement when the glomerular filtration rate is less than 30 ml/min [13]. Elevation in serum total Mg to levels higher than 2 mmol/l are usually accompanied by symptoms. The effects of increasing rise in serum total Mg levels include hypotension (1.5–2.5 mmol/l), electrocardiographic changes (2.5–5 mmol/l), areflexia (5 mmol/l), respiratory paralysis (7.5 mmol/l), and cardiac arrest (>12.5 mmol/l) [38]. Physiological antagonism of hypermagnesemia with intravenous calcium gluconate can be used until dialysis can be initiated.

With respect to cardiac arrhythmias and ventricular arrhythmias in particular, recommended protocols for Mg treatment are unclear as no large-scale controlled studies comparing replacement regimens, their effects on total vs. ionized Mg levels, and clearcut physiological endpoints have been performed. In general, 2 g $MgSO_4$ constituting 8 mmol intravenously over 1–2 min, followed by an additional 40 mmol over the next 5 h is considered safe and probably effective [141]. As discussed above, an antiarrhythmic dose of 0.15 mmol/kg $MgSO_4$ given as an intravenous bolus over 10 min was used by Kasaoka et al. [128] to correct ionized hypomagnesemia (<0.40 mmol/l). Simultaneous administration of K^+ and Ca may be necessary because concomitant losses of these cations are common in Mg deficiency. Emerging data underscore the lack of a predictable relationship between serum total and ionized Mg levels, either before or after intravenous Mg supplementation. Barrera et al. [144] were unable to predict serum Mg^{2+} levels from serum total Mg values in 33 ICU patients, in whom intravenous treatment with 4.1 mmol (1 g) had no effect on ionized Ca^{2+} or K^+ concentrations, although both serum ionized and total Mg levels were increased.

Summary

Mg metabolism and the important physiological roles of Mg as they relate to the critically ill have been reviewed. However, fundamental aspects of Mg metabolism, assessment of Mg deficiency, and efficacy of treatment of hypomagnesemia, whether total or ionized, remain poorly understood. Although serum total Mg continues to be the most frequently used tool for diagnosing and treating hypomagnesemia, randomized clinical studies are needed to determine whether newer methods of Mg assessment, including the measurement of Mg^{2+}, are superior. Newer insights into the immunomodulatory roles of Mg in vivo, improvements in estimating whole-body and compartmental Mg concentrations, and clearer documentation of the biochemical and physiological effects of correcting hypomagnesemia will undoubtedly assist the intensivist in determining the the rationale and the mode for correcting a low Mg value.

References

1. Elin RJ (1994) Magnesium: the fifth but forgotten electrolyte. Clin Chem 102:616–622
2. Kruse HD, Orent ER, McCollum EV (1932) Studies on magnesium deficiency in animals. I. Symptomatology resulting from Mg deprivation. J Biol Chem 96:519–539
3. Whang R (1987) Routine serum magnesium determination: a continuing unrecognized need. Magnesium 6:1–4
4. Toffaletti J (1995) Physiology and regulation: ionized calcium, magnesium and lactate measurements in critical care settings. Am J Clin Pathol 104 [Suppl 1]:S88–S94
5. Reinhart RA, Desbiens NA (1985) Hypomagnesemia in patients entering the ICU. Crit Care Med 13:506–507
6. Ryzen E, Wagers PW, Singer FR, Rude RK (1985) Magnesium deficiency in a medical ICU population. Crit Care Med 13:19–21
7. Chernow B, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellrich V, Warshaw AL (1989) Hypomagnesemia in patients in postoperative intensive care. Chest 95:391–397
8. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW (1993) Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 21:203–209

9. Drop LJ (1985) Ionized calcium, the heart, and hemodynamic function. Anesth Analg 64:432–451
10. Kost GJ (1993) The significance of ionized calcium in cardiac critical care. Arch Pathol Lab Med 117:890–896
11. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA (1988) A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. Crit Care Med 16:578–582
12. Broner CW, Stidham GL, Westenkirchner DF, Tolley EA (1990) Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. Crit Care Med 18:921–928
13. Wacker WEC, Parisi AF (1968) Magnesium metabolism. N Engl J Med 278:658–663
14. Elin RJ (1987) Assessment of magnesium status. Clin Chem 33:1965–1970
15. Günther T (1993) Mechanisms of regulation of Mg efflux and Mg influx. Miner Electrolyte Metab 19:259–265
16. Speich M, Bousquet B, Nicolas G (1981) Reference values for ionized, complexed and protein-bound plasma magnesium in men and women. Clin Chem 27:246–248
17. Altura BT, Altura BM (1994) A method for distinguishing ionized, complexed and protein-bound Mg in normal and diseased subjects. Scand J Clin Lab Invest 54, Suppl 217:83–87
18. Seelig MS (1981) Magnesium requirements in human nutrition. Magnesium Bull 3 [Suppl 1A]:26–47
19. Graham LA, Caessar JJ, Burgen ASV (1960) Gastrointestinal absorption of Mg28 in man. Metabolism 9:646–659
20. Kayne LH, Lee DBN (1993) Intestinal magnesium absorption. Miner Electrolyte Metab 19:210–217
21. Fine KD, Santa Ana CA, Porter JL, Fordtran JS (1991) Intestinal absorption of magnesium from food and supplements. J Clin Invest 88:396–402
22. Hodgkinson A, Marshall DH, Nordin BEC (1979) Vitamin D and magnesium absorption in man. Clin Sci (Colch) 57:121–123
23. Sutton RAL, Domrongkitchaiborn S (1993) Abnormal renal magnesium handling. Miner Electrolyte Metab 19:232–240
24. Quamme GA, Dirks JH (1986) The physiology of renal magnesium handling. Renal Physiol 9:257–269
25. Quamme GA (1989) Control of magnesium transport in the thick ascending limb. Am J Physiol 256:F197–F210
26. Wong NLM, Dirks JH, Quamme GA (1983) Tubular reabsorptive capacity for magnesium in the dog kidney. Am J Physiol 244:F78–F83
27. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR (1969) The physicochemical state and renal handling of divalent ions in chronic renal failure. Arch Intern Med 124:302–311
28. Quamme GA (1993) Laboratory evaluation of magnesium status. Renal function and free intercellular magnesium concentration. Clin Lab Med 13:209–223
29. Dunn MJ, Walser MR (1964) Magnesium depletion in normal man. Metabolism 15:884–895
30. Fitzgerald MG, Fourman P (1956) An experimental study of magnesium deficiency in man. Clin Sci (Colch) 15:635
31. Rude RK, Bethune JR, Singer FR (1980) Renal tubular maximum for magnesium in normal, hypoparathyroid and hyperparathyroid man. J Clin Endocrinol Metab 51:1425
32. Alfrey AC, Miller NL, Trow R (1974) Effect of age and magnesium depletion on bone magnesium pools in rats. J Clin Invest 54:1074–1081
33. Alfrey AC, Miller NL (1973) Bone magnesium pools in uremia. J Clin Invest 52:3019–3027
34. Günther T (1990) Functional compartmentation of intracellular magnesium. In: Sigel H, Sigel A (eds) Metal ions in biological systems, vol 26. Dekker, New York, pp 193–213
35. Quamme GA (1997) Renal magnesium handling: new insights in understanding old problems. Kidney Int 52:1180–1195
36. Beyenbach KW (1990) Transport of magnesium across biological membranes. Magnes Trace Elem 9:223–254
37. Aikawa JK (1981) Magnesium: its biological significance. CRC, Boca Raton
38. Reinhart RA (1988) Magnesium metabolism: a review with special reference to the relationship between intracellular content and serum levels. Arch Intern Med 148:2415–2420
39. Garfinkel L, Garfinkel D (1985) Magnesium regulation of the glycolytic pathway and the enzymes involved. Magnesium 4:60–72
40. Al-Gamadi SMG, Cameron EC, Sutton RAL (1994) Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis 24:737–752
41. Vernon WB (1988) The role of magnesium in nucleic acid and protein metabolism. Magnesium 7:234–248
42. Schumacher MA, Goodman RH, Brennan RG (2001) The structure of a CREB bZIP.somatostatin CRE complex reveals the basis for selective dimerization and divalent cation-enhanced DNA binding. J Biol Chem 10:35242–35247
43. Ryan MF (1991) The role of magnesium in clinical biochemistry: an overview. Ann Clin Biochem 28:19–26
44. Volpe P, Vezu L (1993) Intracellular magnesium and inositol 1:4,5 triphosphate receptor: molecular mechanisms of interaction, physiology and pharmacology. Magnes Res 6:267–274
45. Rude RK, Oldham SB, Sharpe CF, Singer FR (1978) Parathyroid hormone secretion in magnesium deficiency. J Clin Endocrinol Metab 47:800–806
46. Rude RK, Singer FR (1981) Magnesium deficiency and excess. Annu Rev Med 32:245–259
47. Targovnik JH, Rodman JS, Sherwood LM (1971) Regulation of parathyroid hormone secretion in vitro: quantitative aspects of calcium and magnesium ion control. Endocrinology 88:1477–1482
48. Nadler JL, Rude RK (1995) Disorders of magnesium metabolism. Endocrinol Metab Clin North Am 24:623–641
49. Dyckner T, Wester PO (1984) Intra-/extracellular shifts of potassium after administration of Mg in patients with cardiovascular diseases. Magnesium 3:339–345
50. White RE, Hartzell HC (1989) Magnesium ions in cardiac function. Regulator of ion channels and second messengers. Biochem Pharmacol 38:859–867
51. Vandenberg CA (1987) Inward rectification of a potassium channel in cardiac ventricular cells depends on internal magnesium ions. Proc Natl Acad Sci USA 84:2560–2564
52. Whang R, Whang DD, Ryan MR (1992) Refractory potassium repletion. Arch Intern Med 152:40–45
53. Borzeix MG, Akimjak JP, Charles P, Lenfant M, Cahn R (1994) Effect of magnesium on GABA inhibition-induced convulsions in mice. Effect of three salts. In: Golf S, Dralle D, Vecchiet L (eds) Magnesium 1993. Libbey, London, pp 177–180
54. Mason BA, Standley CA, Irtenkauf SM, Bardicef M, Cotton DB (1994) Magnesium is more efficacious than phenytoin in reducing N-methyl-D-aspartate seizures in rats. Am J Obstet Gynecol 171:999–1002
55. Caddell JL, Erickson M, Byrne PA (1974) Interference from citrate using the titan yellow method and two fluorometric methods for magnesium determination in plasma. Clin Chim Acta 41:435–438
56. Elin RJ (1991) Determination of serum magnesium concentration by clinical laboratories. Magnes Trace Elem 10:60–66
57. Alfrey AC, Miller NL, Butkus D (1974) Evaluation of body magnesium stores. J Lab Clin Med 84:153–162
58. Altura BT, Altura BM (1992) Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. Magnes Trace Elem 10:90–98

59. Elin RJ (1988) Status of the determination of magnesium in mononuclear blood cells in humans. Magnesium 7:300–305
60. Fiaccadori E, Del Canale S, Coffrini E, Melej R, Vitali P, Guariglia A, Borghetti A (1988) Muscle and serum magnesium in pulmonary intensive care unit patients. Crit Care Med 16:751–760
61. Luce GG (1970) Biological rhythms in psychiatry and medicine. Publication no 2088. Public Health Service, Washington
62. Ryzen E, Elbaum N, Singer FR, Rude RK (1985) Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. Magnesium 4:137–147
63. Hébert P, Mehta N, Wang J, Hindmarsh T, Jones G, Cardinal P (1997) Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. Crit Care Med 25:749–755
64. Raju B, Murphy E, Levy LA, Hall RD, London RE (1989) A fluorescent indicator for measuring cytosolic free magnesium. Am J Physiol 256:C540–C548
65. Illner H, McGuigan JAS, Lüthi D (1992) Evaluation of Mag-fura-5, the new fluorescent indicator for free magnesium measurements. Pflugers Arch 422:179–184
66. London RE (1991) Methods for measurement of intracellular magnesium: NMR and fluorescence. Annu Rev Physiol 53:241–258
67. Altura BT, Shirey TL, Young CC, Hiti J, Orfano KD, Handwerker M, Altura BM (1992) A new method for the rapid determination of ionized Mg in whole blood, serum and plasma. Methods Find Exp Clin Pharmacol 14:297–304
68. Huijgen HJ, Sanders R, Cecco SA, Rehak NN, Sanders GT, Elin RJ (1999) Serum ionized magnesium: comparison of results obtained with three ion-selective analyzers. Clin Chem Lab Med 37:465–470
69. Anonymous (1997) NOVA 8 reference manual. Nova Biomedical, Waltham
70. Fogh-Andersen N, Bjerrum PJ, Siggaard-Andersen O (1993) Ionic binding, net charge, and Donnan effect of human serum albumin as a function of pH. Clin Chem 39:48–52
71. Welt LG, Gitelman H (1965) Disorders of magnesium metabolism. DM 11:1–32
72. Kingston ME, Al-Siba'i MB, Skooge WC (1986) Clinical manifestations of hypomagnesemia. Crit Care Med 14:950–954
73. Sutton RL, Dirks JH (1991) Disturbances of calcium and magnesium metabolism. In: Brenner BM, Rector FR (ed) The kidney, vol 1, 4th edn. Saunders, Philadelphia, pp 841–887
74. Shills ME (1969) Experimental human magnesium depletion. Medicine (Baltimore) 48:61–85
75. Wacker WEC, Moore FD, Ulmer DD, Vallee BL (1962) Normocalcemic magnesium deficiency tetany. JAMA 180:161–163
76. Ryzen E, Wagers PW, Singer FR, Rude RK (1985) Magnesium deficiency in a medical ICU population. Crit Care Med 13:19–21
77. Abdulrazzaq YM, Smigura FC, Wettrell G (1989) Primary infantile hypomagnesemia; report of two cases and review of literature. Eur J Pediatr 148:459–461
78. Iseri LT, Allen BJ, Brodsky MA (1989) Magnesium therapy of cardiac arrhythmias in critical care medicine. Magnesium 8:299–306
79. Whang R, Oei TO, Aikawa JK, Vannatta J, Fryer A, Markanich M (1984) Predictors of clinical hypomagnesemia. Arch Intern Med 144:1794–1796
80. Keller P, Aronson R (1990) The role of magnesium in cardiac arrhythmias. Prog Cardiovasc Dis 32:433–448
81. Watanabe Y, Dreifus LS (1972) Electrophysiological effects of magnesium and its interaction with potassium. Cardiovasc Res 6:79–88
82. Iseri LT, Freed J, Bures AR (1975) Magnesium deficiency and cardiac disorders. Am J Med 58:837–844
83. Burch GE, Giles TD (1977) The importance of magnesium deficiency in cardiovascular disease. Am Heart J 94:649–657
84. Fawcett WJ, Haxby EJ, Male DA (1999) Magnesium: physiology and pharmacology. Br J Anaesth 83:302–320
85. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S (1988) Treatment of torsade de pointes with magnesium sulfate. Circulation 77:392–397
86. Ralston MA, Murnane MR, Kelley RE, Altschuld R, Unverferth DV, Leier CV (1989) Magnesium content of serum, circulating mononuclear cells, skeletal muscle, and myocardium in congestive heart failure. Circulation 80:573–580
87. Hall RCW, Joffre JR (1973) Hypomagnesemia: physical and psychiatric symptoms. JAMA 224:1749–1751
88. Booth CC, Babouris N, Hanna S, MacIntyre I (1963) Incidence of hypomagnesemia in intestinal malabsorption. BMJ 2:141–144
89. Edmondson HA, Berne CJ, Homann RE, Wertman M (1952) Calcium, potassium, magnesium and amylase disturbances in acute pancreatitis. Am J Med 12:34–42
90. Davis BB, Preuss HG, Murdaugh HV Jr (1975) Hypomagnesemia following the diuresis of post-renal obstruction and renal transplant. Nephron 14:275–280
91. Schilsky RL, Anderson T (1979) Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med 90:929–931
92. Shah GM, Kirschenbaum MA (1991) Renal magnesium wasting associated with therapeutic agents. Miner Electrolyte Metab 17:58–64
93. Von Vigier RO, Truttmann AC, Zindler-Schmocker K, Bettinelli A, Aebischer CC, Wermuth B, Bianchetti MG (2000) Aminoglycosides and renal magnesium homeostasis in humans. Nephrol Dial Transplant 15:822–826
94. Barton CH, Pahl M, Vaziri ND, Cesario T (1984) Renal magnesium wasting associated with amphotericin B therapy. Am J Med 77:471–474
95. Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S (1987) Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. Am J Med 83:693–699
96. Shah GM, Alvarado P, Kirschenbaum MA (1990) Symptomatic hypocalcemia and hypomagnesemia with renal magnesium wasting associated with pentamidine therapy in a patients with AIDS. Am J Med 89:380–382
97. Knochel JP (1977) The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 137:203–220
98. Martin HE, Smith K, Wilson ML (1958) The fluid and electrolyte therapy of severe diabetic acidosis and ketosis. Am J Med 24:376–389
99. Delva P, Pastori C, Degan M, Montesi G, Brazzarola P, Lechi A (2000) Intralymphocyte free magnesium with primary aldosteronism. Hypertension 35:113–117
100. Lim P, Jacob E (1972) Magnesium deficiency in liver cirrhosis. Q J Med 41:291–300
101. Hellman ES, Tschudy DP, Bartter FC (1962) Abnormal electrolyte and water metabolism in acute intermittent porphyria. The transient inappropriate secretion of antidiuretic hormone. Am J Med 32:734–746
102. Jones JE, Desper PC, Shane SR, Flink EB (1966) Magnesium metabolism in hyperthyroidism and hypothyroidism. J Clin Invest 45:891–900
103. Davies DR, Friedman M (1966) Complications after parathyroidectomy. Fractures from low calcium and magnesium convulsions. J Bone Joint Surg Br]48:117–126
104. Navarro J, Oster JR, Gkonos PJ, Ruiz JP, Rhamy RK, Perez GO (1991) Tetany induced on separate occasions by administration of potassium and magnesium in a patient with hungry-bone syndrome. Miner Electrolyte Metab 17:340–344

105. Whyte KF, Addis GJ, Whitesmith R, Reid JL (1987) Adrenergic control of plasma magnesium in man. Clin Sci (Colch) 72:135–138
106. McLellan BA, Reid SR, Lane PL (1984) Massive blood transfusion causing hypomagnesemia. Crit Care Med 12:146–147
107. England MR, Gordon G, Salem M, Chernow B (1992) Magnesium administration and dysrhythmia after cardiac surgery. JAMA 268:2395–2402
108. Aziz S, Haigh WG, Van Norman GA, Kenny RJ, Kenny MA (1996) Blood ionized magnesium concentrations during cardiopulmonary bypass and their correlation with other circulating cations. J Card Surg 11:341–347
109. Shane SR, Flink EB (1992) Magnesium deficiency in alcohol addiction and withdrawal. Magnes Trace Elem 10:263–268
110. Weglicki WB, Phillips TM (1992) Pathobiology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis. Am J Physiol 32:R734–737
111. Weglicki WB, Freedman AM, Bloom S, Atrakchi AH, Cassidy MM, Dickens BF (1992) Antioxidants and the cardiomyopathy of Mg-deficiency. Am J Cardiovasc Pathol 4:210–215
112. Weglicki WB, Phillips TM, Freedman AM, Cassidy MM, Dickens BF (1992) Magnesium-deficiency elevates circulating levels of inflammatory cytokines and endothelin. Mol Cell Biochem 110:169–173
113. Altura BM, Altura BT (1990) Role of magnesium in the pathogenesis of hypertension: relationship to its actions on cardiac and vascular smooth muscle. In: Laragh JH, Brenner BM (ed) Hypertension: pathophysiology, diagnosis and management. Raven, New York, pp 1003–1025
114. White RE, Hartzell HC (1988) Effects of intracellular free magnesium on calcium current in isolated cardiac myocytes. Science 239:778–780
115. Murphy E, Steenbergen C, Levy LS, Raju B, London RE (1989) Cytosolic free magnesium levels in ischemic rat heart. J Biol Chem 264:5622–5627
116. Sayeed MM, Zhu M, Maitra SR (1989) Alterations in cellular calcium and magnesium during circulatory/septic shock. Magnesium 8:179–189
117. Günther T, Ebel H (1990) Membrane transport of magnesium. Metal Ions Biol Syst 26:216–225
118. Salem M, Kasinski N, Munoz R, Chernow B (1995) Progressive magnesium deficiency increases mortality from endotoxin challenge: protective effects of acute magnesium replacement. Crit Care Med 23:108–118
119. Johnson JS, Hand WL, King-Thompson NL (1980) The role of divalent cations in interactions between lymphokines and macrophages. Cell Immunol 53:236–245
120. Weglicki WB, Mak IT, Stafford RE, Dickens BF, Cassidy MM, Philliips TM (1994) Neurogenic peptides and the cardiomyopathy of Mg-deficiency: effects of substance P receptor inhibition. Mol Cell Biochem 130:103–109
121. Mak IT, Komarov AM, Wagner TL, Stafford RE, Dickens BF, Weglicki WB (1996) Enhanced NO production during Mg deficiency and its role in mediating red blood cell glutathione loss. Am J Physiol 271:C385–C390
122. Schmidt HH, Walter U (1994) NO at work. Cell 78:919–925
123. Külpmann WR, Gerlach M (1996) Relationship between ionized and total magnesium in serum. Scand J Clin Lab Invest 56 [Suppl 224]:251–258
124. Altura BM, Altura BT (1996) Role of magnesium in patho-physiological processes and the clinical utility of magnesium ion selective electrodes. Scand J Clin Lab Invest 56 [Suppl 224]:211–234
125. Zhang A, Cheng TPO, Altura BT, Altura BM (1992) Extracellular magnesium regulates intracellular free Mg in vascular smooth muscle cells. Pflugers Arch 421:391–393
126. Salem M, Stacey J, Chernow B (1993) Ionized magnesium values in critically ill patients – a novel ion selective electrode for determining free extracellular magnesium concentrations. Crit Care Med:S256
127. Huijgen HJ, Soesan M, Sanders R, Mairuhu WM, Kesecioglu J, Sander GT (2000) Magnesium levels in critically ill patients: what should we measure? Am J Clin Pathol 114:688–695
128. Kasaoka S, Tsuruta R, Nakashima K, Soejima Y, Miura T, Sadamitsu D, Tateishi A, Maekawa T (1996) Effect of intravenous magnesium sulfate on cardiac arrhythmias in critically ill patients with low serum ionized magnesium. Jpn Circ J 60:871–875
129. Bertschat F, Ising H, Günther T, Jeremias A, Jeremias E (1995) Changes of ionized magnesium and free fatty acids in serum after myocardial infarction. Eur J Clin Chem Clin Biochem 33:553–558
130. Frankel H, Haskell R, Lee SY, Miller D, Rotondo M, Schwab CW (1999) Hypomagnesemia in trauma patients. World J Surg 23:966–969
131. Sawyer RB, Drew MA, Gesink MH, Sawyer KC Jr, Sawyer DC (1970) Post-operative magnesium metabolism. Arch Surg 100:343–348
132. Heath DL, Vink R (1998) Blood-free magnesium concentration declines following graded experimental traumatic brain injury. Scand J Clin Invest 58:161–166
133. Altura BM, Memon ZS, Altura BT, Cracco RQ (1995) Alcohol-associated acute head trauma in human subjects is associated with early deficits in serum ionized Mg and Ca. Alcohol 12:433–437
134. Heath DL, Vink R (1998) Neuroprotective effects of $MgSO_4$ and $MgCl_2$ in closed head injury: a comparative phosphorous NMR study. J Neurotrauma 15:183–189
135. Smith DH, Okiyama K, Gennarelli TA, McIntosh TK (1993) Magnesium and ketamine attenuate cognitive dysfunction following experimental brain injury. Neurosci Lett 157:211–214
136. Kinoshita Y, Ueyuama T, Senba E, Terada T, Nakai K, Itakura T (2001) Expression of c-fos, heat shock protein 70, neurotrophins, and cyclooxygenase-2 mRNA in response to focal cerebral ischemia/reperfusion in rats and their modification by magnesium sulfate. J Neurotrauma 18:435–445
137. Bareyre FM, Saatman KE, Helfaer MA, Sinson G, Weisser JD, Brown AL, McIntosh TK (1999) Alterations in ionized and total blood magnesium after experimental traumatic brain injury: relationship to neurobehavioral outcome and neuroprotective efficacy of magnesium chloride. J Neurochem 73:271–280
138. Feldman Z, Gurevitch B, Artru A, Oppenheim A, Shohami E, Reichenthal E, Shapira Y (1996) Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. J Neurosurg 85:131–137
139. Regan RF, Jasper E, Guo Y, Panter SS (1998) The effect of magnesium on oxidative neuronal injury in vitro. J Neurochem 70:77–85
140. James MFM (1991) Magnesium in critical care medicine. Care Crit Ill 7:233–237
141. Iseri LT, Freed J, Bures AR (1975) Magnesium deficiency and cardiac disorders. Am J Med 58:837–846
142. Rasmussen HS, Thomsen PEB (1989) The electrophysiological effects of intravenous magnesium sulfate on human sinus node, atrioventricular node, atrium, and ventricle. Clin Cardiol 12:85–90
143. Davies GE, Cudworth P, Lawler PG (1992) Intravenous magnesium in critically ill patients. Anaesthesia 47:1104
144. Barrera R, Fleischer M, Miletic J, Groeger J (2000) Ionized magnesium supplementation in critically ill patients: comparing ionized and total magnesium. J Crit Care 15:36–40