

Magnesium

Proper levels of magnesium are important as a preventive of heart diseases.

Magnesium depletion is more common than previously thought. It seems to be especially prevalent in patients with diabetes mellitus. It is usually caused by losses from the kidney or gastrointestinal tract. A patient with magnesium depletion may present with neuromuscular symptoms, hypokalemia, hypocalcemia, or cardiovascular complication. Physicians should maintain a high index of suspicion for magnesium depletion in patients at high risk and should implement therapy early.

Magnesium (Mg) deficiency is a common yet under diagnosed problem in the ICU. Since only 1% of total body Mg is in the extracellular fluid, serum Mg concentrations may not adequately reflect Mg status. Utilizing techniques to measure intracellular Mg concentrations, Mg depletion has been shown to be present in about one half of all ICU patients. These patients have significantly higher morbidity and mortality rates than Mg-replete patients. Accurate identification of patients with Mg depletion requires a knowledge of the risk factors associated with Mg deficiency. These factors include poorly controlled diabetes mellitus, alcohol ingestion, severe diarrhea and steatorrhea, and the use of a number of pharmacologic agents that induce renal Mg wasting. Manifestations of Mg deficiency include hypokalemia, hypocalcemia, neuromuscular hyper-excitability, respiratory muscle weakness, and intractable arrhythmias. Mg deficiency may also play a role in the genesis of myocardial ischemia.

The relationship of hypomagnesemia to digitalis toxicity, congestive heart failure, arrhythmias, and acute myocardial infarction is discussed, as is the clinical interrelationship of Mg and K concentrations, the principal intracellular cations. Although available on order by physicians, the lack of routine serum Mg analysis as part of the "electrolyte panel" impedes the diagnosis of clinical Mg

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deficiency. Renal loss of Mg resulting from the widespread use of loop diuretics is responsible for significant numbers of patients with Mg deficiency and hypomagnesemia. Life-threatening cardiac arrhythmias and seizures represent the most serious manifestations of clinical hypomagnesemia and Mg depletion. In the most critically ill patients, treatment with intravenous Mg is recommended. Oral repletion of Mg is reserved for the less critically ill hospitalized patients and ambulatory patients. Close attention must be paid to optimizing K replenishment in hypokalemic patients by concurrent treatment of any accompanying hypomagnesemia to avoid the problem of refractory K repletion. Hypomagnesemia is one of the most frequent serum electrolyte abnormalities in current clinical practice. Routine inclusion of serum Mg analysis in the electrolyte panel will enhance the clinical recognition and treatment of hypomagnesemia Mg-depleted patients. Failure to respond to treatment of recurrent ventricular tachycardia/fibrillation to usual antiarrhythmic therapy in patients with acute myocardial infarction, idiopathic dilated cardiomyopathy, and congestive heart failure should alert the clinician to consider administering intravenous Mg. Repair of coexisting hypomagnesemia in hypokalemic patients is essential to avoid the problem of refractory K repletion caused by coexisting Mg depletion. More controlled clinical studies of Mg deficiency are necessary to ascertain the cost-effectiveness of Mg replacement therapy.

When given at physiological doses, therapy with magnesium corrects the alterations in cellular function resulting from magnesium deficiency, whereas at higher dosages, which induce hypermagnesaemic levels, magnesium possesses pharmacological effects, such as the inhibition of the calcium influx: this may alter the electrophysiological properties of heart cells, decrease catecholamine secretion, influence the synthesis of prostacyclin and/or alter platelet function. The evidence that magnesium deficiency has untoward effects in patients with ischaemic heart disease is only circumstantial and direct proof that magnesium deficiency causes cardiac disorders is at present lacking. A ubiquitous calcium-channel blockade

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mechanism is the main and well-established way of action whereby magnesium acts at pharmacological levels; other mechanisms may be involved as well but at present remain questionable or unsettled. On the basis of the present knowledge, beneficial effects may thus be expected from high dose intravenous magnesium therapy in the setting of acute myocardial infarction with respect to mortality rates, even when there is concurrent thrombolytic therapy, as recently demonstrated by the large study, although this could not be confirmed. High dose intravenous magnesium is also a first choice therapy for terminating torsade de pointes ventricular tachycardia but cannot be considered an established therapy for other cardiac rhythm disturbances nor for settings other than acute myocardial infarction in the case of ischaemic heart disease. The preliminary evidence that magnesium deficiency has a high prevalence in patients with ischaemic heart disease and that it may have a detrimental influence on the course of ischaemic heart disease needs to be validated by larger prospective and controlled clinical studies. Magnesium therapy in ischaemic heart disease thus proves a promising approach which, however, requires that the respective pharmacological and physiological effects be distinguished and further delineated and that the type and stage of ischaemic heart disease be characterized.

Many years ago, experimental medicine accumulated substantial evidence that magnesium (Mg) balance was important for a stable cardiovascular system. Recent clinical interest was aroused by evidence of decreased mortality in patients with acute myocardial infarction (AMI), treated with Mg infusions. Pharmacologic actions of Mg include its antiarrhythmic, anti-vasospastic and other important cardiovascular effects, substantiating the rationale for its use in AMI. Direct pharmacologic effect of this ion, rather than compensation of hypomagnesemia frequently encountered during acute ischemic injury, has been suggested to account for the above benefits. Several trials studied the efficacy of early Mg therapy in decreasing mortality from AMI while most of the data point to improved survival, a few trials could not demonstrate any benefit of Mg. The reported rate of complications with this therapy is low

though the potential for serious side effects exists. Larger studies of Mg in AMI are expected to resolve the existing controversy.

Magnesium plays a critical role in numerous metabolic functions, including all reactions involving adenosine triphosphate, and is thus essential for the production and use of energy. Magnesium imbalances are common in hospitalized patients, with magnesium deficiency occurring in 20% to 65% of critically ill patients. This article details the homeostatic mechanisms regulating magnesium, the functions of magnesium, and the causes, manifestations, and treatment of both hyper- and hypomagnesemia. Indications and guidelines for the therapeutic uses of magnesium are also reviewed.

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA). A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA metabolism and the endothelium), that are vaso-constrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical (i.e. exertion, heat, cold, trauma--accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may

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account for differences in vulnerability to Mg deficiency and differences in body responses to stress.

Thiazides and loop diuretics facilitate the loss of K and Mg through the kidneys leading to deficiencies that may require treatment with supplements. These losses may be overlooked, however, because serum concentrations may remain normal even when the muscle concentrations are appreciably reduced. In 76 patients who had received diuretics for 1-17 years, the mean concentrations of K, Mg and Na, K-pumps in skeletal muscle biopsies were significantly lower than in those from an age- and sex matched control group, and muscle Mg and K concentrations were significantly correlated. The serum concentrations, however, were only below the control range in a few patients. The fact that Mg, K deficiencies may often be overlooked emphasises the need for data on the contents of skeletal muscle. A recently developed simple biopsy needle procedure permitted the detection of disorders of electrolytes during long-term diuretic treatment despite normal serum concentrations. With the same technique it was possible to detect repletion of the muscle electrolytes after a Mg supplementation period. Oral Mg supplementation could reestablish normal Mg as well as K status in patients in long-term diuretic therapy, provided that the supplementation was maintained for 6 months. Moreover, the normalization of muscle Mg and K was accompanied by a restoration of the concentration of Na, K-pumps measured as the [3H] ouabain binding site capacity in skeletal muscle. Mg and K contents were closely correlated in human muscle biopsies from patients on diuretic treatment, but also in rat muscle which had been moderately Mg depleted in vivo or in vitro. In isolated soleus muscle, which had been moderately Mg-depleted in vitro, reduction in cellular K could not be ascribed to reduced Na, K-pump mediated K-influx. The reduced K content might rather be related to increased K efflux from the muscles. In rats, insufficient dietary supplies of K, Mg and Zn were characterized by inhibition of growth and protein synthesis. These effects could not readily be related to the loss of these elements from muscle tissue, but rather should be seen as a response

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to a general deficiency. The most marked evidence of deficiency was seen in the serum levels, which pointed to the serum concentration as a possible mediator for the regulation of tissue growth. IGF-I is a low molecular weight peptide possessing growth promoting properties in many tissues probably as an interplay of both autocrine/paracrine and endocrine actions. In both animals and man insufficient supplies of energy and protein are accompanied by growth retardation and a decrease in serum IGF-I.

Necrotizing enterocolitis (NEC) is a neonatal disorder of unknown cause characterized by rapid necrosis of the bowel, primarily the ileum and colon. It is a worldwide problem. NEC is the most common gastrointestinal emergency in the neonatal intensive care unit, and ranks second as a cause of neonatal death. The incidence of NEC is inversely proportional to the birth weight and the degree of maturity. Infants born at or before 28 weeks gestational age have not received 80 per cent of the magnesium and 67 per cent of the copper found at term. Congenital deficiencies of these essential minerals may be compounded by high renal or gastrointestinal losses and high metabolic demand during the preterm infant's accelerated growth. Platelet thrombi appear early in the intestinal microvasculature in NEC. Platelet thrombosis and release of vasoconstrictor, platelet aggregating thromboxane A₂ (TXA₂) in human NEC appears to potentiate the intestinal ischaemia and necrosis in neonates who develop NEC. Magnesium and copper deficiency each enhance the synthesis of TXA₂. Plasma levels of the inflammatory cytokines tumour necrosis factor (TNF) and interleukin-6 (IL-6) are increased in NEC and in magnesium deficiency; these experimentally produce shock and tissue injury, especially of the intestine. The synthesis of the potent vasoconstrictor endothelin is increased in magnesium deficiency. NEC has been regarded as a luminal insult that causes local generation of destructive oxygen free radicals. Tissues from animals deficient in magnesium are more susceptible to oxidative injury and lipid peroxidation than tissues from normal animals. Magnesium and copper deficiency impair antioxidant defence through decreased synthesis of glutathione and reduced activity of

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Cu/Zn superoxide dismutase, respectively. Although the aetiology of NEC is unknown, there appears to be sufficient data to implicate magnesium and possibly copper deficiencies in the pathogenesis. Consequences of deficiency of one or both minerals may include increased synthesis or activity of injurious mediators: IL-1, IL-6, TNF, TXA2, endothelin, and oxygen free radicals. A prospective trial of magnesium supplementation, but not copper supplementation, in very premature neonates can be recommended, with NEC as one of the outcome measures.

Electrolyte balance has been regarded as a factor important to cardiovascular stability, particularly in congestive heart failure. Among the common electrolytes, the significance of magnesium has been debated because of difficulty in accurate measurement and other associated factors, including other electrolyte abnormalities. The serum magnesium level represents < 1% of total body stores and does not reflect total-body magnesium concentration, a clinical situation very similar to that of serum potassium. Magnesium is important as a cofactor in several enzymatic reactions contributing to stable cardiovascular hemodynamics and electrophysiologic functioning. Its deficiency is common and can be associated with risk factors and complications of heart failure. Typical therapy for heart failure (digoxin, diuretic agents, and ACE inhibitors) are influenced by or associated with significant alteration in magnesium balance. Magnesium therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving hemodynamics and in treating arrhythmias. Magnesium toxicity rarely occurs except in patients with renal dysfunction. In conclusion, the intricate role of magnesium on a biochemical and cellular level in cardiac cells is crucial in maintaining stable cardiovascular hemodynamics and electrophysiologic function. In patients with congestive heart failure, the presence of adequate total-body magnesium stores serve as an important prognostic indicator because of an amelioration of arrhythmias, digitalis toxicity, and hemodynamic abnormalities.

A rise in intracellular sodium during periods of exposure to calcium free media would seem to be the critical step that predisposes the mammalian heart to the damaging effects of the calcium paradox. The damage which is seen in both single cells and multi cellular preparations, occurs on reperfusion with calcium containing media and results from calcium loading via the sodium/calcium exchanger where the rise in intracellular calcium provokes hyper contraction as well as activating hydrolytic enzymes. Because the rise in intracellular sodium is a critical step in inducing damage, manoeuvres which reduce this rise during calcium depletion are expected to protect the heart against the calcium paradox. Raising extra cellular magnesium concentration is one such manoeuvre which by blocking the influx of sodium through the L-type calcium channels reduces the rise in intracellular sodium during calcium depletion. The beta-amino acid taurine is another agent capable of opposing a rise in intracellular sodium. Taurine is present at high concentration in mammalian heart cells and is maintained against high concentration gradient. During calcium depletion, heart cells use this energy to efflux taurine and sodium via a taurine/sodium symport and therefore protect against the calcium paradox. A similar mechanism may also be used by the ischaemic heart to reduce the rise in intracellular sodium. In contrast to the changes seen during the calcium paradox the ischaemic heart shows a rise in intracellular magnesium concentration. This rise will have several and diverse cellular effects including the modulation of intracellular calcium mobilisation and of several membrane transporters. The potential significance of these effects remains to be evaluated. On the other hand elevated levels of extra cellular magnesium may protect the ischaemic heart by reducing the influx of calcium by suppressing the L-type calcium channels and possibly the sodium/calcium exchanger. Finally evidence suggests that the rat heart may not be identical to that of other species in its response to the calcium paradox and to the protective role of intracellular taurine and extra-cellular magnesium. The reason for this species difference would seem to be due to different metabolic activity and the activity of the sodium, potassium-ATPase.

Magnesium has been reported as an effective medical therapy in an expanding array of conditions. Evidence investigating magnesium's use is presented, with a number of studies suggesting it should be seriously considered in such conditions as ischemic heart disease, cardiac arrhythmias, and asthma. Magnesium balance and metabolism are briefly reviewed, and then various hypotheses are presented that may explain magnesium's physiologic mechanisms of action, most likely involving calcium and potassium flux across cellular membranes in smooth muscle. In a number of the conditions to be discussed, it has been uncertain whether magnesium administration serves the purpose of merely correcting an underlying deficiency state or of utilizing a specific pharmacologic effect of magnesium. Magnesium deficiency is a relatively common condition, and predisposing factors as well as recent methods for assessing total body stores of magnesium are discussed. Physicians should be familiar with the numerous conditions and therapeutics that are risk factors for an underlying magnesium deficiency and in which empiric magnesium replacement should be considered. Guidelines for administration of parenteral magnesium are presented with specific focus on the low risk of adverse effects, as suggested by the large and rapid dosing regimens used in many of the clinical studies.