MAGNESIUM IN CLINICAL MEDICINE

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1. ABSTRACT

Until recently the physiological role of magnesium was essentially ignored. However, with the development of new technologies to measure the intracellular free concentration of magnesium ([Mg²⁺]), the biologically important fraction, there has been an explosion of interest in the molecular, biochemical, physiological and pharmacological functions of magnesium. In addition, improved methods for assessing magnesium status in the clinic have contributed to the further understanding of magnesium regulation in health and disease. Magnesium deficiency is now considered to contribute to many diseases and the role for magnesium as a therapeutic agent is being tested in numerous large clinical trials. This review focuses on clinical manifestations associated with magnesium deficiency and highlights the clinical significance of hypermagnesemia. Specific clinical conditions in which magnesium deficiency has been implicated to play a pathophysiological role, namely hypertension, ischemic heart disease, arrhythmias, pre-eclampsia, asthma and critical illness will be discussed and the possible therapeutic role of magnesium will be considered. Although there is still much to be learnt regarding the exact role of magnesium in clinical medicine, there are two conditions where magnesium is now considered the therapeutic agent of choice, pre-eclampsia and torsades de pointes. Future research, both at the fundamental and clinical levels, will certainly facilitate our understanding of how magnesium contributes to pathological processes and under what circumstances it should be used therapeutically.

2. INTRODUCTION

Although the medicinal use of magnesium in the form of magnesium-rich minerals has been known for centuries, the physiological and pharmacological properties of this essential ion have only recently been investigated in detail. Data from experimental and epidemiological studies suggest an important role for magnesium deficiency in many diseases. However, findings from clinical studies have been not been conclusive. Consequently, it is still unclear exactly how magnesium contributes to pathological processes and what the pharmacological role of magnesium is in clinical medicine. Reasons for this are attributable, in part, 1) to the paucity of controlled clinical data on how circulating total magnesium levels relate to levels of biologically active ionized Mg²⁺, and 2) to a lack of data on the efficacy of therapeutic magnesium to alter ionized Mg²⁺ concentrations and to affect organ function.
Magnesium is absorbed mainly in the jejunum and ileum (9). Absorption seems to involve at least two transport systems neither of which is yet identified at the molecular level (9,10). The major portion of magnesium is absorbed across the paracellular route, which is nonsaturable and determined by the electrochemical gradient and by solvent drag (11,12). Although not yet confirmed, it may be possible that a paracellular protein, such as paracellin, a member of the claudin family found in epithelial tissue, may play a role in this process (13). Saturable transcellular uptake processes also contribute to intestinal magnesium uptake. Uptake into brush border cells may occur via a Mg\(^{2+}\)/anion complex (14) and efflux of magnesium across the basolateral membrane may involve Na\(^+\)/Mg\(^{2+}\) antiport systems (9). In addition a recently identified transcellular transporter TRPM6 (accession number NM_017662) may play a role in intestinal magnesium absorption (15). TRPM6 a member of the long transient receptor potential channel family is located in intestinal epithelia and kidney tubules and is a Mg\(^{2+}\)-permeable cation channel with protein kinase activity. Patients with mutations in TRPM6 have decreased magnesium absorption and associated hypomagnesemia (15), further confirming the potentially important role of this transporter in gastrointestinal magnesium absorption. Another member of the long transient receptor potential channel family, TRPM7 (Accession number NM_017672), has recently been identified to play an important role in transcellular magnesium transport in vertebrate cells (16). Whether TRPM7 plays a role in gastrointestinal magnesium uptake is unclear and awaits clarification.

3.2. Renal magnesium handling

Regulation of magnesium homeostasis occurs primarily within the nephron of the kidney (17). Approximately 80% of the total serum magnesium is...
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filtered through the glomerulus, with 15% of this amount reabsorbed in the proximal tubule, 70% reabsorbed in the cortical thick ascending limb of the loop of Henle, and 15% in the distal convoluted tubule. The thick ascending limb of the loop of Henle and the distal convoluted tubule are the sites where hormones, such as parathyroid hormone, insulin, aldosterone and prostaglandins and drugs such as diuretics, affect magnesium excretion (17). Other factors that influence magnesium transport include hypermagnesemia and hypercalcemia (18,19). In experimental animals elevated extracellular magnesium or calcium inhibits fractional magnesium transport leading to increased urinary magnesium excretion (20-22). Because there is little magnesium reabsorption beyond the distal convoluted tubule, this is considered the site of major importance for renal magnesium homeostasis. Magnesium conservation in the normal kidney during magnesium deprivation may decrease fractional excretion to less than 0.5% (23). Conversely, kidneys increase magnesium excretion during increased dietary intake or excessive magnesium administration. In renal failure, the fractional excretion of magnesium progressively increases to maintain normal serum magnesium levels until the later stages when hypomagnesemia occurs.

Cellular mechanisms whereby magnesium is reabsorbed in the kidney have recently been shown to involve paracellular transport through paracellin-1, a membrane protein of the claudin family of proteins, integral constituents of tight junctions between epithelial cells (24,25). Loss-of-function mutations in paracellin-1 (Accession number AF 152101) (claudin 16) reduce magnesium permeability, causing profound renal magnesium wasting, a clinical syndrome termed familial hypomagnesemia with hypercalciuria and nephrocalcinosis (24).

3.3 Bone magnesium

The major reservoir for body magnesium is bone (26). Part of this magnesium is in equilibrium with extracellular magnesium. When serum magnesium decreases, magnesium is rapidly released from the bone surface (26). Conversely when serum levels are elevated increased magnesium binds to the bone surface. Up to 30% of bone magnesium is rapidly exchangeable (27). Thus bone magnesium functions as a buffer regulating extracellular magnesium concentration.

4. BIOCHEMICAL AND PHYSIOLOGICAL ROLE OF MAGNESIUM

Magnesium is a cofactor in hundreds of enzymatic reactions, particularly in those involved in transfer, storage and utilization of energy (28-30). Magnesium is necessary for reactions involving hydrolysis and transfer of a phosphate group and when complexed to ATP is a substrate for signal transducing enzymes including phosphokinases and phosphatases (28,29). Reactions involving ATP require magnesium, which positions the terminal ATP-phosphate bond allowing phosphate transfer. Magnesium is an intrinsic component of Na⁺,K⁺-ATPase, HCO₃⁻ ATPase and Ca²⁺,Mg²⁺-ATPase and as such regulates Na⁺/K⁺, proton and Ca²⁺ transport respectively (30,31). Magnesium is also necessary for protein and nucleic acid synthesis, regulation of the cell cycle, control of mitochondrial processes, membrane stability and maintenance of cytoskeletal integrity (32,33). Emerging evidence indicates that magnesium plays an important role in oxidative phosphorylation processes and in the regulation of signalling kinases such as PI3 kinase, MAP kinase and tyrosine kinases (34-36).

Magnesium functions as a Ca²⁺ antagonist and directly influences Ca²⁺ uptake, distribution and content in cardiovascular cells (30,31,37). It competes with Ca²⁺ for membrane-binding sites, modulates Ca²⁺-binding release from reticular stores and thereby influences Ca²⁺-dependent signaling events. Decreased concentrations of intracellular free magnesium ([Mg²⁺]) are associated with increased [Ca²⁺], which in vascular smooth muscle cells, results in enhanced contractility (38). Magnesium also regulates Na⁺/K⁺ transport via the Mg²⁺-(Na⁺,K⁺)-ATPase system, which influences Na⁺ and K⁺ fluxes, a major determinant of the electrical potential across the cell membrane (39,40). Intracellular magnesium blocks outward K⁺ movement through K⁺ channels in cardiac cells (41). Decreased [Mg²⁺], results in increased outward K⁺ movement, thereby inducing depolarization. In the nervous system, magnesium has a depressant effect. This is mediated in part, by the inhibition of acetylcholine release at the neuromuscular junction and by non-competitive blockade of N-methyl-D-aspartate (NMDA) glutamate receptors (42). Clinical effects of magnesium deficiency typically manifest as cardiac, neuromuscular and neurological disorders (see section 5).

5. CLINICAL ASSESSMENT OF MAGNESIUM STATUS

Clinical evaluation of magnesium status is associated with numerous difficulties. First, serum ionized Mg²⁺, the biologically significant fraction of magnesium, is not routinely measured. Second, no single laboratory test tracks total body magnesium stores. Finally, changes in extracellular (serum) magnesium levels may not necessarily reflect intracellular levels. In the clinic, three major groups of tests are currently available: 1) estimates of tissue magnesium using concentrations in serum, erythrocytes, leukocytes or muscle; 2) metabolic assessments of magnesium balance utilizing isotopic analyses and evaluation of renal magnesium and retention, and 3) determination of free magnesium levels with fluorescent probes, nuclear magnetic resonance spectroscopy or ion selective electrodes.

The most frequently used test for assessing magnesium status in patients is total serum magnesium levels. Measuring total magnesium in serum rather than in plasma is preferred because additives such as anticoagulants may be contaminated with magnesium (43). The total serum magnesium level comprises free Mg²⁺, the protein-bound magnesium fraction and magnesium complexed to anions and phosphates. Each component of
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<table>
<thead>
<tr>
<th>Table 1. Causes of magnesium deficiency</th>
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<td>1. Decreased dietary intake</td>
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<td>2. Gastrointestinal malabsorption</td>
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<td>3. Increased gastrointestinal loss</td>
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<td>- diarrhoea</td>
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<td>- vomiting</td>
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<td>- laxative abuse</td>
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<td>4. Increased renal loss</td>
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<tr>
<td>- Congenital or acquired tubular defects</td>
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<td>- Drug-induced</td>
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<td>- diuretics</td>
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<td>- angiotensin converting enzyme inhibitors</td>
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<td>- aminoglycosides</td>
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<td>- amphotericin</td>
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<td>- cyclosporin</td>
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<td>- cisplatin</td>
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<td>- pentamidine</td>
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<td>5. Endocrine causes</td>
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<td>- Hyperaldosteronism</td>
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<td>- Hyperparathyroidism</td>
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<td>- Syndrome of inappropriate antidiuretic hormone</td>
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<td>- Diabetes mellitus</td>
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<td>6. Other causes</td>
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<td>- Alcoholism</td>
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<td>- Excessive sweating</td>
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<tr>
<td>- Severe burns</td>
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<td>- Cardiopulmonary bypass surgery</td>
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the total value may change independently and in a non-linear fashion with respect to the other fractions. Despite the fact that serum levels of magnesium represent only 0.3% of total body magnesium content and that serum magnesium concentrations do not correlate with other tissue pools, the total serum magnesium concentration is still used as the standard for evaluating magnesium status in patients (43-45).

The magnesium tolerance test is used as a physiological assessment of magnesium balance (43,46). The test involves a baseline 24 hour urine magnesium collection, followed immediately by an infusion of 0.1 mmol (2.4 mg) magnesium per kilogram body weight in 50 ml 5% dextrose over 4 hours and then a second 24 hour urine collection. Differences in magnesium content between the two urine collections represent the retained magnesium fraction. Retention of > 20% of administered magnesium suggests magnesium deficiency, whereas retention of > 50% is confirmatory (46). This test should not be undertaken if serum creatinine >200 µmol/l. Also, drugs producing renal magnesium wasting will invalidate the results.

One of the most significant advances in evaluating magnesium deficiency has been the development of assays to measure ionized Mg^{2+}. Three major techniques are used to measure free magnesium levels; 1) magnesium fluoroprobes, 2) nuclear magnetic resonance (NMR) spectroscopy and 3) ion-selective electrodes. Fluorescent probes and NMR spectroscopy have the advantage that they can be used to assess [Mg^{2+}]. Using these techniques in multiple cell types, normal [Mg^{2+}] is about 0.5 mmol/l (47-49). However, these techniques are used primarily in research environments and are not yet available in clinical laboratories.

Since the early 1990s, ion-selective electrodes became commercially available to measure ionized Mg^{2+} (50). In 1993, the United States Food and Drug Administration approved the NOVA 8 electrode for clinical use. Mg^{2+}-specific electrodes yield rapid results on whole blood, plasma and serum using 100-200 µl. The NOVA 8 normalizes values to a pH of 7.4 and can also estimate Na^+, K^+, Ca^{2+}, hematocrit and pH. Reference values for ionized Mg^{2+} concentrations in healthy subjects using the NOVA 8 are 0.54-0.67 mmol/l. This system is gaining popularity, especially in the intensive care setting, where rapid assessment of magnesium status in critically ill patients is important. These assays may become good substitutes for or complements to the determination of total magnesium status in patients.

In addition to the NOVA 8 system, other analyzers equipped with a magnesium ion-selective electrode, specifically the AVL 988/4 and KONE Microlyte 6 systems, are currently available (51-53). However there are significant intermethod differences between the three analyzers, which limit comparison of results obtained from the different systems. Accordingly, until there is improved specificity and standardization of calibrators between systems, results should be interpreted using reference values for the specific analyzer used (51-53).

6. CLINICAL MANIFESTATIONS OF HYPMAGNESEMIA

In spite of its imperfections, serum total magnesium is currently used as the standard for defining hypomagnesemia. Symptoms and signs of hypomagnesemia usually occur when serum total magnesium levels fall below 0.5 mmol/l (54). However, manifestations of magnesium deficiency may be influenced more by the rate of development of the deficiency and/or by serum ionized rather than total serum levels. Accordingly, clinical features of magnesium deficiency may be absent in the presence of very severe hypomagnesemia or they may occur with only modestly reduced serum concentrations. This dissociation between serum total magnesium levels and clinical findings makes it difficult to infer total body magnesium deficiency, to determine the need for correction of hypomagnesemia and to document any physiological benefit of such correction in patients. The common causes for magnesium deficiency are disturbances in intestinal magnesium absorption and/or increased renal magnesium excretion (Table 1).

Based on the physiological actions of magnesium in cardiovascular and neural tissue, it is easy to understand why magnesium deficiency manifests primarily as cardiac and neuromuscular disorders (Table 2). The coexistence of secondary electrolyte disturbances, particularly related to
Table 2. Clinical manifestations of magnesium deficiency

Cardiac manifestations
- Atrial fibrillation
- Ventricular arrhythmias
- Torsades de pointes
- Hypersensitivity to cardiac glycosides (eg. Digoxin)

Neurological manifestations
- Convulsions
- Nystagmus
- Athetoid movements
- Apathy
- Delirium
- Coma (severe hypomagnesemia)

Neuromuscular manifestations
- Positive Chvostek’s sign
- Positive Trousseau’s sign
- Tetany
- Muscle cramps
- Muscle fasciculations and tremor
- Muscle weakness

Electrolyte disturbances
- Hypokalemia
- Hypocalcemia

Table 3. Clinical conditions in which magnesium deficiency has been implicated to play a pathophysiological role

Cardiovascular conditions
- Hypertension
- Acute myocardial infarction
- Cardiac arrhythmias
- Atherosclerosis
- Cardiopulmonary bypass surgery

Neurological conditions
- Stroke
- Migraines
- Epilepsy

Endocrine conditions
- Diabetes mellitus
- Phaeochromocytoma

Obstetric conditions
- Pre-eclampsia
- Eclampsia

Other conditions
- Osteoporosis
- Asthma
- Cancer

Calcium and potassium, also plays a key role in the clinical features of magnesium deficiency.

6.1 Cardiovascular manifestations
Increases or decreases in magnesium levels with normal extracellular K⁺ concentrations leads to minor electrophysiological changes. However, in the presence of coexisting hypokalemia, which is not uncommon with hypomagnesemia, cardiac arrhythmias are frequent (54,55). Electrocardiographic changes of hypomagnesemia are indistinguishable from hypokalemia-related effects, including ST segment depression, flattened T waves and prolongation of PR and QT/QTc intervals. Arrhythmias associated with hypomagnesemia include premature atrial contractions, atrial fibrillation, multifocal atrial tachycardia, premature ventricular contractions, ventricular tachycardia and ventricular fibrillation (55). In addition, hypomagnesemia promotes digitalis-induced arrhythmias (55). Although, it is still unclear whether these magnesium-associated electrophysiological changes are causal or whether they are due to changes in potassium concentrations, it is evident that hypokalemia is refractory to treatment unless magnesium is repleted first (56,57).

6.2. Neural manifestations
Magnesium seems to play an important role in conduction in the nervous system by acting as a voltage-gated antagonist at the NMDA receptor and by inhibiting catecholamine release (58,59). Severe hypomagnesemia is usually associated with neuromuscular irritability and weakness, manifesting as tremors, fasciculations, tetany and positive Chvostek’s and Trousseau’s signs (60). Some of these features may be due to concomitant hypocalcemia. Similar to hypokalemia associated with hypomagnesemia, hypocalcemia is usually refractory to calcium repletion unless magnesium is administered before (60,61). Neurological manifestations of severe hypomagnesemia include convulsions, athetoid movements, nystagmus, apathy, delirium and coma (62).

7. CLINICAL CONDITIONS ASSOCIATED WITH HYPMAGNESEMIA
As indicated in table 3, numerous clinical conditions are associated with magnesium deficiency. Major conditions include cardiovascular, neurological and obstetric conditions.

7.1. Hypertension
Epidemiological studies have linked hypertension, hypertensive heart diseases and ischemic heart diseases, with 'soft water', low in magnesium, and protection against cardiovascular disease with 'hard water', high in magnesium (63). The best epidemiological evidence linking magnesium and blood pressure comes from the Honolulu Heart study (64), in which the relationships of various dietary variables with blood pressure were examined. Of all the nutrients, dietary magnesium intake had the strongest relationship with blood pressure. Numerous subsequent epidemiological and clinical investigations further supported the view that increased magnesium intake contributes to prevention of hypertension and cardiovascular disease (65-70).

Clinical studies have shown, for the most part, some form of hypomagnesemia (serum and/or tissue) in hypertensive patients, with significant negative correlations between magnesium concentration and blood pressure (71-73). A relationship has also been described between the renin-angiotensin system, magnesium and blood pressure. High renin hypertensive patients have lower serum magnesium levels than normotensive subjects (74,75) and...
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Serum magnesium is inversely associated with plasma renin activity. Recent studies have also reported a negative dependency between Mg2+, and arterial compliance in humans, the lower the [Mg2+], the stiffer the blood vessels and the greater the blood pressure (76). In earlier investigations, total magnesium levels were determined. Today, with the availability of selective fluorescent Mg2+ probes and Mg2+-specific ion-selective electrodes, which measure [Mg2+], in living cells, it is evident that many cell types from hypertensive patients have significantly lower [Mg2+], than cells from normotensive subjects, even if total magnesium levels are within the normal range (77).

Underlying causes for altered magnesium metabolism in hypertension are unclear, but an unknown combination of genetic, dietary, hormonal factors or drugs presumably plays a role. Inadequate dietary intake of magnesium or errors in magnesium metabolism leads to dyslipidemias, insulin resistance, vasospasm and endothelial damage, characteristic features of small arteries in hypertension. At the cellular level, aberrant regulation of magnesium is important. Changes in magnesium buffering, influx, mobilization or efflux all contribute to reduced [Mg2+]. Recent studies reported that activity of the Na+-Mg2+ exchanger, which induces magnesium efflux, is increased in erythrocytes from essential hypertensive patients, in lymphocytes from patients with hyperaldosteronism and in vascular smooth muscle cells from spontaneously hypertensive rats (SHR), a model of genetic hypertension, suggesting that this transporter may be pivotal in abnormal intracellular magnesium status in hypertension (78-80).

Not all clinical investigations have reported magnesium depletion in hypertension. Some studies found no differences in serum magnesium levels or in [Mg2+] in hypertensive patients (81,82), while others reported increased erythrocyte [Mg2+], in patients with essential hypertension (83). A few epidemiological studies have also failed to show an association between magnesium intake and blood pressure (65). It is evident that not all hypertensive patients are hypomagnesemic, and not all patients with magnesium deficiency are hypertensive. Despite the inconsistencies in the literature regarding magnesium status in hypertension, there are subgroups of hypertensive patients who consistently demonstrate altered magnesium metabolism. These include patients with obesity, insulin resistance, hypertriglyceridemia, severe or malignant forms of hypertension and of African-American descent (84-86).

The therapeutic value of magnesium in the treatment of clinical hypertension was suggested in 1925 when magnesium infusion was found to improve malignant hypertension (87). Since then many investigations have supported a putative role for magnesium in the treatment of hypertension. Considering the inexpensive nature of magnesium and the fact that it is easy to handle, magnesium is theoretically an excellent contender for a place in the routine management of hypertension. However, this is not so in clinical practice. In general, data from clinical trials of magnesium therapy in hypertension have been disappointing. Some studies reported significant blood pressure-lowering effects of oral or intravenous magnesium treatment (88,89), and magnesium supplementation to patients already receiving diuretics or other antihypertensive agents appears to reduce blood pressure further (90,91). However other trials have failed to demonstrate any hypotensive action of magnesium supplementation (92,93) and results from the Trial of Hypertension Prevention (TOHP) study showed no benefit of magnesium therapy in 698 patients followed for 6 months (94). The inconsistency in results may be due to the number of studies that were small or of short duration, differing treatment protocols, variable forms of magnesium salts used, different concentrations of magnesium supplemented and the heterogeneity of the population of hypertensives investigated. Nonetheless, studies have consistently shown a beneficial effect of magnesium treatment in African-American patients, those with established hypomagnesemia, those with diuretic-associated hypertension, and in patients where magnesium was supplemented long term (95,96). In addition, magnesium is therapeutically effective in lowering blood pressure in secondary hypertension and in pre-eclampsia, (97,98). Taken together, these data suggest magnesium is at best weakly hypotensive. Thus, although magnesium may not be a universally effective antihypertensive agent, it does seem to benefit a subgroup of hypertensive patients.

Before making definitive therapeutic recommendations on the use of magnesium in the management of hypertension, well-controlled, long-term therapeutic trials, in carefully characterized hypertensive patients are need. However, the potential benefits of magnesium are currently recognized and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) has included maintenance of adequate dietary magnesium intake as a recommendation for lifestyle modifications for hypertension prevention management (99).

7.2. Cardiac Disease
7.2.1. Acute Myocardial Infarction

Results from autopsy studies demonstrated lower myocardial and muscle total magnesium in subjects who died from ischemic heart disease as compared to those who died from non-cardiac causes (100). Gasser (101) reported that during myocardial ischemia, free ionized intracellular magnesium increases, while total intracellular magnesium decreases. The reduction in free magnesium in ischemia has been attributed, in part, to decreased ATP content (102,103). Furthermore, ischemia leads to intracellular calcium overload, which is exacerbated during reperfusion. Magnesium administration may confer cellular protection during ischemia by acting as a calcium antagonist, thereby reducing calcium overload, by conserving cellular ATP as the magnesium salt and thereby preserving energy-dependent cellular activity, by improving myocardial contractility and by limiting infarct size (104). Furthermore magnesium may prevent arrhythmias associated with ischemia, decrease catecholamine release and protect against oxidative stress-induced cardiac damage (55,104).
Given the above magnesium effects, it is not surprising that magnesium therapy has been studied extensively in the context of acute myocardial infarction. Numerous small clinical trials reported that magnesium administration is a safe and effective method of reducing arrhythmias and mortality in acute myocardial infarction. The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT2) was the first randomized, double-blind, placebo-controlled study demonstrating that intravenous magnesium therapy has a protective effect during the treatment of acute myocardial infarction (105). 2316 patients with acute myocardial infarction were allocated randomly to receive magnesium or placebo. Treatment consisted of magnesium 8 mmol over 5 minutes before thrombolytic therapy, followed by 65 mmol as an infusion over the following 24 hours. There was a 24% relative reduction in mortality after 28 days and a 25% lower incidence of left ventricular failure. The reduction in left ventricular failure was associated with a corresponding reduction in mortality from ischemic heart disease over a mean follow-up period of 2.7 years. The conclusion from LIMIT 2 was that early intravenous magnesium is a useful addition to standard therapy in acute myocardial infarction.

However, findings from two recent mega-trials, the Fourth International Study of Infarct Survival (ISIS 4) (106) and the Magnesium in Coronaries (MAGIC) trial (107), failed to demonstrate a beneficial effect of magnesium therapy in acute myocardial infarction. In ISIS 4, effects of early intervention with oral captopril, isosorbide-5-mononitrate or intravenous MgSO4 were assessed in 58 050 patients with suspected acute myocardial infarction. Results showed a trend towards increased mortality at 35 days with an excess incidence of cardiogenic shock and cardiac failure in the magnesium group, although there was a significant reduction in the early occurrence of ventricular fibrillation. No benefit was observed in the treatment group across all major subgroups, whether they were treated early or late and whether or not they received thrombolysis. The aim of the MAGIC trial was to compare short-term mortality in patients with ST-elevation myocardial infarction who received either intravenous MgSO4 or placebo. 6213 patients were randomly assigned to a 2 g intravenous bolus of MgSO4 (8 mmol elemental magnesium) administered over 15 minutes, followed by a 17 g infusion of MgSO4 (68 mmol elemental magnesium) over 24 hours (n=3113) or matching placebo (n=3100). At 30 days 15.3% patients in the magnesium group and 15.2% in the placebo group had died. No benefit or harm of magnesium was observed.

Differences in results between LIMIT 2, ISIS 4 and MAGIC have led to confusion as to whether or not magnesium should be administered routinely as first-line therapy during the acute phase of myocardial infarction. Findings from a meta-analysis of all randomized controlled studies of magnesium in acute myocardial infarction (68 684 patients) demonstrated that patients at low risk of mortality from acute myocardial infarction and who benefit from thrombolysis and aspirin probably gain little benefit from magnesium therapy (108). This was further supported by an Italian study, which demonstrated that intravenous magnesium, delivered before, during and after reperfusion did not decrease myocardial damage and did not improve short-term clinical outcomes in patients with acute myocardial infarction treated with direct angioplasty (109). In high-risk patients who may not be suitable for thrombolysis, magnesium appears to be useful (110). Overall there is no indication for the routine administration of intravenous magnesium in patients with acute myocardial infarction. However, magnesium is well tolerated and there is no apparent harm from its use. Hence magnesium can be continued to be administered for repletion of documented electrolyte deficits and for life-threatening arrhythmias.

### 7.2.2. Magnesium and arrhythmias

Hypomagnesaemia has been implicated as a cause for arrhythmias of both atrial and ventricular origin. However, establishing a direct association between hypomagnesaemia and arrhythmias is problematical, since there is only a poor correlation between serum and cardiac magnesium concentrations and because hypomagnesaemia is closely coupled with hypokalaemia, which itself is arrhythmogenic. In arrhythmias linked to hypomagnesaemia, concurrent hypokalaemia is almost always present and hypomagnesaemia exacerbates potassium-mediated arrhythmias (111). Despite extensive experimental data there is little clinical evidence that isolated hypomagnesaemia induces arrhythmias. Most studies have demonstrated a good therapeutic response to magnesium therapy, which is sustained when both potassium and magnesium concentrations are normalized. Consequently, it is recommended that both potassium and magnesium be administered for acute control of arrhythmias associated with hypokalaemia (55,112). Mechanisms whereby magnesium induces its anti-arrhythmogenic effects may involve changes in the activity of ionic membrane channels, particularly calcium and potassium channels (113). For example, magnesium blocks the inward calcium current, which reduces sinus node rate firing, prolongs AV conductance and increases AV node refractoriness.

#### 7.2.2.1. Ventricular arrhythmias

Magnesium has been successfully used in the treatment of ventricular arrhythmias associated with long QT syndromes (torsades de pointes, or polymorphic ventricular tachycardia) and with digoxin toxicity (114-116). *Torsades de pointes* consists of paroxysms of ventricular tachycardia, is accompanied by lengthening of the QT interval and is commonly precipitated by anti-arrhythmic drugs which extend the QT interval such as quinidine, amiodarone and procainamide (117). *Torsades de pointes* is the form of arrhythmia for which treatment with magnesium is most effective (114-117). The 1992 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care includes the infusion of magnesium sulfate in the treatment of *torsades de pointes*. The recommended dose is 2 g MgSO4 (8 mmol elemental magnesium) given over 10-15 minutes, repeated if necessary.

Although the use of magnesium is accepted in the treatment of *torsades de pointes*, its role in monomorphic
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ventricular tachycardia is less clear. Results from small studies have reported conflicting results (118) whereas data from the Magnesium in Cardiac Arrhythmias MAGICA trial showed a significant reduction in the incidence of ventricular tachyarrhythmias in patients with frequent ventricular arrhythmias after increasing magnesium and potassium intake by 50% (119). The American Heart Association “Advanced Cardiac Life Support” guidelines (1997-1999) recommend that treatment of ventricular fibrillation or of ventricular tachycardia without pulse should include magnesium sulfate if epinephrine, lidocaine and bretylium are ineffective.

7.2.2.2. Atrial fibrillation

Atrial fibrillation is linked to a high incidence of thromboembolic events and increased mortality. In many patients, treatment with electrical or pharmacological cardioversion is associated with relapse of atrial fibrillation. Numerous studies have investigated whether magnesium administration would prevent relapse of atrial fibrillation (120,121). However, the data are controversial. Some studies demonstrated beneficial effects of magnesium, while others failed to show any improvement when magnesium was added to standard treatment (121-123). To investigate the effectiveness of magnesium sulfate in the prophylaxis of atrial fibrillation after coronary bypass surgery, Kaplan et al. (124) recently conducted a prospective, randomized, placebo-controlled clinical study on 200 consecutive patients in whom elective coronary artery bypass grafting operations were performed. In the treatment group 100 patients received 3 g of MgSO\textsubscript{4} (12 mmol elemental magnesium) in 100 mL of saline solution that was administered over 2 hours (50 mL/h) preoperatively, whereas the control group was given saline solution. Although a significant relationship was found between low magnesium levels and increased incidence of atrial fibrillation, there was no significant difference in incidence of atrial fibrillation between magnesium- and saline-treated groups (124). Thus the therapeutic role of magnesium in the management of atrial fibrillation remains unclear and should be limited to those patients for whom other drugs are contraindicated or have been shown to be ineffective.

7.2.2.3. Arrhythmias induced by cardiac glycosides

Cardiac glycosides, such as digoxin, which inhibit membrane-bound Na\textsuperscript{+},K\textsuperscript{-}-ATPase, are used for the treatment of atrial arrhythmias. However, these agents themselves are arrhythmogenic at toxic doses (51,125). Hypermagnesemia facilitates digoxin-induced arrhythmias, which may be terminated by treatment with magnesium (126,127). In fact magnesium has been used since the 1930s for digitalis toxicity (128) and remains an effective therapeutic modality in this condition. The association between magnesium and many cardiac arrhythmias remains unresolved. However, there is good evidence that magnesium should be used for the treatment of long QT syndromes and digoxin toxicity and that it should be considered for all refractory arrhythmias.

7.3. Magnesium, pre-eclampsia and eclampsia

Pre-eclampsia, defined as hypertension after 20 weeks of gestation with proteinuria (129), has been treated with magnesium salts since the early 1900s. During pre-eclampsia, both cardiac output and plasma volume are reduced whereas systemic vascular resistance is increased (130-132). These changes result in reduced perfusion of the placenta, kidney, liver and brain, leading to maternal and foetal morbidity and mortality (131). Magnesium has been shown to improve endothelial function in preeclampsia (133). This may be due to the direct vasodilatory properties of magnesium and/or to the ability of magnesium to stimulate release of the endothelial vasodilator prostacyclin, which induces vasodilatation and inhibits platelet adherence and aggregation (133,134).

Acute magnesium sulfate administration elicits a rapid fall in systemic vascular resistance, a rise in the cardiac index and a transient decrease in blood pressure (135). Magnesium sulfate infusion also increases renal blood flow and stimulates production and release of prostacyclin in preeclampsia, but not in preterm labour (130-132,134). In healthy nonpregnant women these effects are inhibited by indomethacin, a cyclooxygenase inhibitor, suggesting that the fall in blood pressure is mediated by magnesium-induced prostacyclin release (132,134).

Data relating to magnesium concentrations in preeclampsia are conflicting. Some studies demonstrate no differences between preeclamptic versus uncomplicated pregnancies. Others report decreased serum and intracellular magnesium in preeclamptic women (136-140). Although the exact role of magnesium in the pathogenesis of preeclampsias is still unclear, it has been suggested that magnesium can be used as a predictive tool for preeclampsia. Standley et al. (137) found that magnesium decreases in both preeclamptic and uncomplicated pregnancies, but that the magnesium concentration was lowered earlier in women with preeclampsia. This difference has been proposed as a marker of severity of the condition. It has also been suggested that alterations in the Na\textsuperscript{+}/Mg\textsuperscript{2+} exchanger in trophoblast cells may be important (141).

Magnesium sulfate remains the most frequently used treatment in the management of preeclampsia and eclampsia in United States (142). The Collaborative Eclampsia Trial provides level I evidence (high level of evidence) of the superiority of magnesium sulfate for the treatment of eclampsia. Magnesium sulfate had a 52% lower risk of recurrent convulsions versus diazepam and a 67% lower risk of recurrent convulsions versus phenytoin (143). Use of magnesium sulfate for prophylactic treatment in women with preeclampsia is more controversial. A recent large trial among severe preeclamptic women compared magnesium sulfate with placebo. The trial was terminated prematurely after finding a significant reduction in the development of eclampsia with magnesium sulfate (0.3 vs 3.2%) (144). The largest clinical trial comparing magnesium sulfate with phenytoin in hypertensive pregnancies also reported that eclampsia was significantly reduced in women taking magnesium sulfate compared to those on phenytoin (142,145). The Magnie trial, which involved 10 141 women with pre-eclampsia in 175 hospitals in 33 countries recently showed that magnesium...
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### Table 4. Treatment of magnesium deficiency

<table>
<thead>
<tr>
<th><strong>Emergency conditions – intravenous</strong></th>
<th>8-16 mmol magnesium over 1-2 minutes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>40 mmol magnesium over the next 5 hours</td>
</tr>
<tr>
<td><strong>Severe illness – intravenous or intramuscular</strong></td>
<td>40-48 mmol magnesium on the first day</td>
</tr>
<tr>
<td></td>
<td>16-25 mmol magnesium on days 2-5</td>
</tr>
<tr>
<td><strong>Oral maintenance</strong></td>
<td>15-24 mmol magnesium per day</td>
</tr>
</tbody>
</table>

Conversion for magnesium units: 1 g of MgSO₄ = 4 mmol, 8 mEq or 98 mg of elemental magnesium, ′ Adapted from references 54 and 151.

Magnesium deficiency has also been associated with other pathological conditions associated with hypomagnesemia, Soliman et al, who demonstrated that development of hypomagnesemia during an ICU stay is associated with worse prognosis and higher mortality rates (163).

### 7.5. Other pathological conditions associated with hypomagnesemia

Magnesium plays an important role in conduction in the nervous system where it functions as a voltage-gated antagonist at the NMDA receptor. For this reason, magnesium has been considered in the management of cerebral ischemia, postoperative pain and seizures (164,165). The neuroprotective effect of magnesium was evidenced in a large prospective study among 43 738 men (Health Professional Follow-up Study), which demonstrated an inverse relationship between dietary magnesium intake and the risk of stroke (166). Results from a large multicenter trial assessing the role of intravenous magnesium sulfate treatment after acute stroke is currently in progress and should clarify whether or not magnesium should be included in the management of acute stroke (164,165).

Magnesium has bronchodilator effects and has therefore been implicated in the management of asthma (167). Mechanisms underlying magnesium-induced bronchodilation include inhibition of smooth muscle contraction, reduced histamine release from mast cells and decreased acetylcholine release from cholinergic nerve terminals (167,168). Studies as early as the 1940s reported reduced serum magnesium levels in asthmatics (169,170). Recent clinical trials demonstrated that magnesium administration improves the peak expiratory flow rate and pulmonary function and decreases hospitalization rate in asthmatics, particularly in patients with severe asthma (166,171-173). Magnesium should not be used routinely in the management of moderate asthma, however it may be useful, especially in the nebulized form, as adjuvant therapy for severe or refractory asthma (174).

Magnesium deficiency has also been associated with atherosclerosis, cardiac failure, diabetes mellitus, osteoporosis and migraines (150,175-181). However, the therapeutic role of magnesium in these conditions remains unclear.

### 7.6. Management of hypomagnesemia

Because of the lack of well-controlled clinical studies regarding the directional changes in time-matched serum total and ionized Mg²⁺ concentrations and the confounding effects of associated changes in ionized Ca²⁺, K⁺ and PO₄ levels, treatment guidelines for magnesium deficiency are not yet available. Nevertheless several generalizations are appropriate regarding the management of hypomagnesemia (182) (table 4). Since the kidney is the major route of magnesium excretion, it is essential to evaluate renal function prior to the commencement of magnesium therapy. In general the intravenous route is safe. However patients should be hemodynamically and electrocardiographically monitored as there may be prolongation of atrioventricular and intra-atrial nodal conduction times and hypotension (183). Oral magnesium salts can be used as maintenance therapy in conditions...
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associated with chronic magnesium wasting, such as diuretic use.

8. Hypermagnesemia- causes, clinical manifestations and management

Hypermagnesemia is less common than hypomagnesemia (182). Serum magnesium levels are increased above 1 mmol/L in 3-5% of hospitalized patients (183,184). Most patients with hypermagnesemia have impaired renal function. Crook et al reported that more than 70% of all patients with hypermagnesemia (serum levels above 1.0 mmol/L) had abnormal renal function tests (185). In chronic renal failure, patients usually maintain their serum magnesium at normal, or slightly above normal, levels in the early stages of the disease. With progressive renal failure, magnesium retention occurs with consequent hypermagnesemia. Severe hypermagnesemia is most often observed during the therapeutic administration of magnesium in patients with chronic renal failure, during treatment of eclampsia and in the elderly who overdose magnesium-containing laxatives and antacids (186-190).

Clinical manifestations of hypermagnesemia include neuromuscular and cardiovascular changes (182,190). However, clinical severity may not correlate with the degree of hypermagnesemia (191). Central neurological signs range from drowsiness to coma (192), due in large part to magnesium-induced blockade of neuromuscular junctions, suppression of acetylcholine release and diminishing postsynaptic membrane responsiveness (192). Deep tendon reflexes are depressed at serum magnesium levels above 2.5 mmol/L and are absent at levels above 5 mmol/L (192). Severe muscle weakness is seen at levels greater than 5 mmol/L with the potential for respiratory muscle paralysis (193). Autonomic sympathetic blockade is manifested clinically as cutaneous flushing, dry mouth, pupillary dilatation, urinary retention, and hypotension (193). Cardiovascular abnormalities include hypotension, conduction disorders and bradycardia (182,190,194). Electrocardiographic observations in humans and animals have shown an increase in the P-R interval at magnesium concentrations of 2.5-5 mmol/L. Very rarely severe hypermagnesemia (>7.5 mmol/L) may result in heart block and asystole (195).

Management of hypermagnesemia is based on stopping magnesium administration. In severe cases, infusion of calcium, as the gluconate salt, can be used as a physiological antagonist. For cardiac arrhythmias, 8 mmol MgSO4 given intravenously over 1-2 minutes, followed by an additional 40 mmol over the next 5 hours is considered safe. Simultaneous administration of calcium and potassium may be also be necessary because of the concomitant changes in Ca2+ and K+ with magnesium depletion (151). For patients with renal insufficiency, dialysis involving a magnesium-poor fluid is suggested (187).

9. CONCLUSIONS AND PERSPECTIVES

Magnesium plays a key role in regulating physiological processes whereas alterations in magnesium status contribute to numerous pathologies. Magnesium deficiency has been implicated in various disease states and many indications have been claimed for the use of this ion as a pharmacological agent. However, despite sound experimental and epidemiological data supporting a role for magnesium in these diseases, clinical observations and clinical trials have provided controversial and often conflicting results. This makes it very difficult for the clinician to know which magnesium effects are of clinical importance and which are not. An area where magnesium has an established and beneficial therapeutic role is in the treatment of pre-eclampsia/eclampsia, where clinical research has demonstrated unambiguously that magnesium is superior to either diltiazem or phenytoin for the prevention of recurrent convulsions. Magnesium is the also agent of choice in the treatment of torsades de pointes. There are exciting possibilities for the use of magnesium in several areas, particularly in the fields of neurology and cardiology. However, until such time as we have improved methods for accurate assessment of magnesium status in patients, a better understanding of how magnesium induces its physiological and pathological actions and results from controlled clinical trials, the role of magnesium in clinical medicine remains elusive. Although less common than hypomagnesemia, hypermagnesemia is also a condition with significant clinical relevance, especially in patients with chronic renal failure and in elderly patients taking magnesium-containing laxatives and antacids. In the past few years there has been an explosion of interest in both the physiological and pharmacological properties of magnesium. With the development of new technologies, increasing interest in magnesium research and the initiation of new clinical trials, the role of magnesium in clinical medicine will become clearer. This is of practical importance considering the ease, safe handling, low toxicity and low costs of magnesium.

10. ACKNOWLEDGEMENTS

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