

# Magnesium and cardiovascular system

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**Abstract.** Hypomagnesemia is common in hospitalized patients, especially in the elderly with coronary artery disease (CAD) and/or those with chronic heart failure. Hypomagnesemia is associated with an increased incidence of diabetes mellitus, metabolic syndrome, mortality rate from CAD and all causes. Magnesium supplementation improves myocardial metabolism, inhibits calcium accumulation and myocardial cell death; it improves vascular tone, peripheral vascular resistance, afterload and cardiac output, reduces cardiac arrhythmias and improves lipid metabolism. Magnesium also reduces vulnerability to oxygen-derived free radicals, improves human endothelial function and inhibits platelet function, including platelet aggregation and adhesion, which potentially gives magnesium physiologic and natural effects similar to adenosine-diphosphate inhibitors such as clopidogrel. The data regarding its use in patients with acute myocardial infarction (AMI) is conflicting. Although some previous, relatively small randomized clinical trials demonstrated a remarkable reduction in mortality when administered to relatively high risk AMI patients, two recently published large-scale randomized clinical trials (the Fourth International Study of Infarct Survival and Magnesium in Coronaries) failed to show any advantage of intravenous magnesium over placebo. Nevertheless, there are theoretical potential benefits of magnesium supplementation as a cardioprotective agent in CAD patients, as well as promising results from previous work in animal and humans. These studies are cost effective, easy to handle and are relatively free of adverse effects, which gives magnesium a role in treating CAD patients, especially high-risk groups such as CAD patients with heart failure, the elderly and hospitalized patients with hypomagnesemia. Furthermore, magnesium therapy is indicated in life-threatening ventricular arrhythmias such as Torsades de Pointes and intractable ventricular tachycardia.

**Key words:** magnesium, diabetes, nutrition, endothelium, myocardial infarction, heart disease, hypertension, platelets

## The body magnesium distribution

In a 70 kg human being there are 20-24 g of magnesium, 60% in bones [1, 2] a 1/3 of which is interchangeable and is part of the body magnesium reservoir for high magnesium requirements. Almost 35% of

magnesium is located in high metabolic tissues such as muscles, brain, heart, kidneys and liver and only 1% of the total body magnesium is in the blood.

There is usually an equilibrium between intestine magnesium absorption and renal elimination. About 35-40% of daily magnesium intake occurs in the small intestine. Magnesium is eliminated mainly through the kidneys and accounts for 3-5% of the daily filtrated volume. More than 65% of the renal magnesium reabsorption occurs through the thick

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ascending loop of Henle. 35% of serum magnesium is non-specifically bound to albumin, while the rest is in a ionic form [3].

## **Magnesium measurements**

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### **Serum magnesium measurement**

As only 1% of total body magnesium is in the serum, its measurement does not reflect its intracellular level. While hypomagnesemia reflects low total body content, a normomagnesemia does not necessarily indicate normal or high total body magnesium [4, 5].

### **Intracellular magnesium**

The most accurate intracellular magnesium measurements, which also reflect the intramyocardial muscle cell content, are lymphocytic (more accurate) and erythrocyte (less accurate and cell age dependent) magnesium levels [6, 7]. Recently the EXA™ test, which measures intra epithelial cell magnesium content from buccal tissue, has been highly correlated to intramyocardial magnesium content [8]. This method is disadvantageous as there is only one laboratory in the US which carries out the test (IntraCellular Diagnostics Inc., CA). Additionally, electrodes for the measurement of free magnesium content are available, however, until now there has been no consensus regarding the normal and abnormal values in various populations and no standardization exists.

### **Magnesium retention after oral magnesium or intravenous load test**

This test for measuring magnesium retention is accurate but involves a 24 h urine collection [1, 9].

## **The magnesium in human nutrition**

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The main dietary magnesium sources are green vegetables, cereals, nuts, soy beans, and shell fish, as well as over the counter (OTC) food supplements and vitamins.

An accurate magnesium food content (or even high-magnesium food content) will keep people healthy and reduce the incidence of extreme or continuous stress-induced sudden death, or hyperthermia-induced death, heart disease, atherosclerosis and vascular atherogenesis, vascular complications in diabetics, early labor and congenital anomalies.

The magnesium content of food in the Western world is consistently decreasing. Data show that

the average daily intake of magnesium at the beginning of the 20<sup>th</sup> century was 410 mg while today it is only 200-300 mg. The reason for the reduced mineral consumption, including magnesium, in the modern menu, is mainly due to industrial food processing and over-utilization of fields dedicated for cultivating agricultural products [1].

Recommendations for magnesium are provided in the Dietary Reference Intakes (DRIs) developed by the Institute of Medicine of the National Academy of Sciences. "*Dietary Reference Intakes*" is the general term for a set of reference values used for planning and assessing nutrient intake for healthy people. Three important types of reference values included in the DRIs are *Recommended Dietary Allowances* (RDA), *Adequate Intakes* (AI), and *Tolerable Upper Intake Levels* (UL). The RDA recommends the average daily intake that is sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people. An AI is set when there is insufficient scientific data available to establish a RDA for specific age/gender groups. AIs meet or exceed the amount needed to maintain a nutritional state of adequacy in nearly all members of a specific age and gender group. The UL, on the other hand, is the *maximum* daily intake unlikely to result in adverse health effects. The current RDA for magnesium is 420 mg daily for males and 320 mg daily for females above 31 years, and in stressful situations such as in pregnancy or physical growth, an addition of 300 mg daily is recommended. Data from the 1999-2000 National Health and Nutrition Examination Survey suggest that substantial numbers of adults in the United States (US) fail to get recommended amounts of magnesium in their diets. Among adult men and women, the diets of Caucasians have significantly more magnesium than do those of African-Americans. Magnesium intake is lower among older adults in every racial and ethnic group. Among African-American men and Caucasian men and women who take dietary supplements, the intake of magnesium is significantly higher than in those who do not. In a population-based study of young Israelis of 30 years old, about 60% had magnesium deficiency [1, 10-14].

## **The role of magnesium in coronary artery disease**

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Prior epidemiological trials from various countries, such as the US, South Africa, Finland, France, England, Canada, Germany and the Netherlands [1, 2, 15-17] demonstrated that water magnesium con-

tent is associated with the incidence and mortality from CAD. Autopsies demonstrated high cardiac muscle magnesium concentration in high-(also called "hard water areas") compared to low-magnesium water areas (also called "soft water areas") and vice versa [1, 12, 15-17].

The Atherosclerosis Risk in Communities (ARIC) Study [18] with 13,922 healthy subjects without CAD on admission, after a 4-7 year follow-up, found that the highest risk for CAD occurred in subjects with the lowest serum magnesium and vice versa, even after controlling for the traditional CAD risk factors. The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study [19] demonstrated an inverse association of serum magnesium and mortality from CAD and all causes.

The Honolulu Heart Program [20] studied 7,172 men 45 to 68 years old during the years 1965-1968. In a 30-year follow-up low-magnesium in the food was found to increase the incidence of CAD by 2.1 compared to high magnesium concentration, even after controlling for traditional CAD risk factors and other food nutrients.

Amighi *et al.* [21] followed 323 patients with peripheral artery disease and intermittent claudication for 2 years. A low serum magnesium concentration was associated with a 3 fold increase of cerebrovascular accident compared to those with high serum magnesium levels.

Ka He *et al.* [22] followed 4,637 young Americans aged 18-30 without diabetes mellitus or metabolic syndrome. In a 16-year follow-up 608 (11%) subjects developed metabolic syndrome. Multivariate analysis demonstrated a significant inverse association between food magnesium content and the incidence of metabolic syndrome.

While the magnesium content in food products in the USA has fallen over the last 2 decades, it is currently below the RDA, and the incidence of CAD is increasing.

### **The rationale for magnesium in CAD**

There is a strong biological plausibility that the effect of magnesium in cardiovascular disease prevention may be partly related to a decreased inflammatory response. In animal models, experimental magnesium deficiency induces a clinical inflammatory syndrome characterized by leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins in addition to excessive production of free radicals [23-25]. An increase in extracellular magnesium decreases the

inflammatory response while a reduction in the extracellular magnesium results in phagocyte and endothelial cell activation. Inflammation occurring in experimental magnesium deficiency is the mechanism that induces hypertriglyceridemia and pro-atherogenic changes in the lipoprotein profile. Endothelial cells actively contribute to inflammation in magnesium deficiency states. Magnesium intake is inversely associated with markers of systemic inflammation and endothelial dysfunction in healthy [26] and postmenopausal women [27].

The available data suggest that a combination of mechanisms may act additively or even synergistically to protect myocytes and constitute the rationale of magnesium supplementation in patients with heart disease [1, 3, 28-30] (*table 1*). Exogenous administration of magnesium prevents intracellular depletion of magnesium, potassium and high-energy phosphates, improves myocardial metabolism, prevents intramitochondrial calcium accumulation and reduces vulnerability to oxygen-derived free radicals. Magnesium can impact on:

- vascular tone;
- platelet aggregation and coagulation system;
- endothelial function;
- infarct (scar) size;
- lipid metabolism;
- cardiac arrhythmias;
- myocardial infarction.

### **Impact of magnesium on vascular tone**

Magnesium is considered to be nature's physiologic calcium blocker [31]. It reduces the release of

**Table 1.** Beneficial effects of magnesium in coronary artery disease.

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Antiplatelet effects
Coronary vasodilation
Systemic vascular resistance reduction
Inhibition of calcium influx
Inhibition of vulnerability to oxygen free radicals
Inhibition of reperfusion injury
Improvement of endothelial function
Inhibition of catecholamines
Improvement of lipid profile
Enhanced angiogenesis
Reduced cardiac arrhythmias
Mild reduction of blood pressure
Improvement of exercise duration time and cardiac performance
Improvement of quality of life

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calcium from and into the sarcoplasmic reticulum and protects the cells against calcium overload under conditions of ischemia [31-44]. Magnesium reduces systemic and pulmonary vascular resistance, with a concomitant decrease in blood pressure and a slight increase in cardiac index [31-33]. Elevation of extracellular magnesium levels reduces the arteriolar tone and tension in a wide variety of arteries [34-36] and potentiates the dilatory action of some endogenous (adenosine, potassium and some prostaglandins) and exogenous (isoproterenol and nitroprusside) vasodilators [34, 35, 37, 38]. As a result, magnesium has a mild reducible effect on systolic and diastolic blood pressure [45], may act as afterload reduction and thus unload the ischemic ventricle. Kugiyama *et al.* [44] demonstrated that exercise-induced angina is suppressed by intravenous magnesium in patients with variant angina, most probably as a result of an improvement in regional myocardial blood flow by suppression of coronary artery spasms. Altura and Altura [42] found in an experimental vascular smooth muscle model, that magnesium deficiency, through potentiation of increased cellular calcium activity, may be responsible for the arterial hypertension that accompanies toxemia of pregnancy. The proven effectiveness of parenteral magnesium therapy in toxemia of pregnancy [35, 46] is most likely the result of its calcium antagonist action.

Shechter *et al.* [47] found that the intra lymphocytic magnesium levels in CAD patients after myocardial infarctions and/or coronary artery bypass operations were highly correlated to exercise duration time and cardiac performance and inversely correlated to the peak exercise double-product (heart rate x systolic blood pressure). Thereafter, Shechter *et al.* [48] demonstrated in Austria, Israel and the US, that a 6-month oral magnesium supplementation significantly improved exercise tolerance, exercise duration time, ischemic threshold and quality of life in stable CAD patients. Pokan *et al.* [49] reinforced Shechter's findings. They demonstrated that a 6-month oral magnesium supplementation significantly improved the intracellular magnesium levels,  $VO_{2max}$ , left ventricular ejection fraction and reduced the exercised-induced heart rate.

#### **Anticoagulant/antiplatelet properties of magnesium**

In 1943, Greville and Lehmann [50] found that a small amount of magnesium added to fresh unclotted human plasma prolonged the clotting time. In Germany, during and shortly after the 2<sup>nd</sup> World War,

magnesium sulfate was widely used as a muscle relaxant, and it was seen that the blood of patients examined post mortem after such treatment was unclotted [51]. In 1959 Anstall *et al.* [52] demonstrated that magnesium inhibits human blood coagulation.

Adams and Mitchel [53] found that magnesium both topically and parenterally, suppressed thrombus formation and increased the concentration of ADP, which was required to initiate thrombus production at human minor injury sites. Some experimental studies have demonstrated the antiplatelet effects of magnesium, which may prevent the propagation of coronary artery thrombi or re-occlusion of the infarct-related coronary artery after spontaneous or fibrinolysis-induced recanalization [63-66]. Recently some studies have demonstrated that magnesium reduces platelet aggregation in healthy volunteers [64]. High magnesium levels inhibit blood coagulation [62] and thrombus formation *in vivo* [63], diminish platelet aggregation [65-67], reduce the synthesis of platelet agonist thromboxane  $A_2$  [55], and inhibit the thrombin-stimulated calcium influx [65].

Platelet activation is a key element in acute vascular thrombosis, which is important in the pathogenesis of acute myocardial infarction and complications of coronary balloon angioplasty and stenting. Studies have demonstrated that magnesium can suppress platelet activation by either inhibiting platelet-stimulating factors, such as thromboxane  $A_2$ , or by stimulating synthesis of platelet-inhibitory factors, such as prostacyclin ( $PGI_2$ ) [54-60, 64, 67, 68]. Intravenous administration of magnesium to healthy volunteers inhibited both ADP-induced platelet aggregation by 40% and the binding of fibrinogen or surface expression of glycoprotein IIb-IIIa complex GMP-140 by 30% [67]. Thus, pharmacological concentrations of magnesium effectively inhibit platelet function *in vitro* and *ex vivo*.

Using an *ex vivo* perfusion (Badimon) chamber [70], Shechter *et al.* [61] recently demonstrated that platelet-dependent thrombosis was significantly increased in stable CAD patients with low mononuclear intracellular levels of magnesium, despite antiplatelet treatment with aspirin. Furthermore, Shechter *et al.* [62] found in a randomized, prospective, double-blind, cross-over, placebo-controlled trial that 3-months of magnesium oxide tablets (800-1,200 mg/day) significantly reduced the median platelet-dependent thrombosis by 35% compared to placebo in stable CAD patients who were on aspirin therapy. The antithrombotic effect of magnesium treatment was observed despite the 100% utilization of aspirin therapy.

Gawaz *et al.* [57, 59] demonstrated that platelet aggregation, fibrinogen binding, and expression of P-selectin on the platelet surface, are all effectively inhibited by intravenous magnesium supplementation. Since glycoprotein IIb-IIIa is the only glycoprotein on the platelet surface that binds fibrinogen, Gawaz *et al.* speculated that magnesium supplementation directly impairs fibrinogen interaction with the glycoprotein IIb-IIIa complex. Since fibrinogen binding to the platelet membrane and surface expression of P-selectin requires previous cellular activation, the inhibitory effect of magnesium might be a consequence of direct interference of the cation with the agonist-receptor interaction or with the intracellular signal transduction event. Fibrinogen-glycoprotein IIb-IIIa interaction is regulated by divalent cations, and at pharmacological levels magnesium may inhibit the binding of fibrinogen to glycoprotein IIb-IIIa by altering the receptor conformation. This might be caused by the competition of magnesium with calcium ions for calcium-binding sites in the glycoprotein IIb subunit.

Rukshin *et al.* [63] recently demonstrated that treatment with intravenous magnesium sulfate produced a time-dependent inhibition of acute stent thrombosis under high-shear flow conditions without any hemostatic or significant hemodynamic complications in an *ex vivo* porcine arteriovenous shunt model of high-shear blood flow, suggesting that magnesium inhibits acute stent thrombosis in animal model. Thereafter the same group [64] demonstrated that intravenous magnesium sulfate is a safe agent in acute coronary syndrome patients undergoing non-acute percutaneous coronary intervention with stent implantation, while magnesium therapy significantly inhibited platelet activation.

### Impact of magnesium on endothelial function

The vascular endothelium is an active paracrine, endocrine and autocrine organ, which plays a critical role in vascular homeostasis by secreting several mediators regulating vessel tone and diameter, coagulation factors, vascular inflammation, cell proliferation and migration, platelet and leukocyte interaction and activity and thrombus formation [66-73]. Endothelial dysfunction is therefore recognized as a major factor in the development of atherosclerosis, hypertension, and heart failure. Vascular endothelial dysfunction is an independent risk factor for cardiovascular events, and provides important prognostic data in addition to the classic cardiovascular risk factors and may be a "crystal ball prediction for enhanced cardiovascular risk" [74].

Shechter *et al.* [75] recently demonstrated that endothelial function is significantly correlated to intracellular magnesium levels, measured in sublingual epithelial cells, in CAD patients and oral magnesium 30 mmol/day (total magnesium 730 mg/day) for 6 months significantly increased intracellular magnesium compared to placebo. In addition the magnesium therapy resulted in a significant improvement in endothelial function, associated with improvement in exercise duration, exercise-induced chest pain and exercised-induced cardiac arrhythmias. Pearson *et al.* [76] demonstrated that hypomagnesemia selectively impaired the release of nitric oxide (NO) from coronary endothelium in a canine model. Paravicini *et al.* [77] demonstrated in a model of hypomagnesemia that blood pressure significantly increased in low intracellular magnesium levels compared with normal-high intracellular magnesium levels. The low intracellular magnesium levels were associated with impaired endothelial function together with decreased plasma nitrate levels and endothelial NO synthase expression when compared with normal-high intracellular magnesium levels. Because NO is a potent endogenous nitrovasodilator and inhibitor of platelet aggregation and adhesion, hypomagnesemia may promote vasoconstriction and coronary thrombosis in hypomagnesemic states.

Endothelial cells actively contribute to inflammation in magnesium deficiency states. Magnesium intake is inversely associated with markers of systemic inflammation and endothelial dysfunction in healthy [26] and postmenopausal women [27].

### Impact of magnesium on infarct size

Hypomagnesemia may increase coronary and systemic vasoconstriction and afterload, leading to increased myocardial oxygen depth [3, 28, 29]. Low concentrations of magnesium in laboratory animals seem to potentiate catecholamine-induced myocardial necrosis and cardiomyopathy [78]. Magnesium deficiency may adversely influence the healing and re-endothelialization of vascular injuries, the healing of myocardial infarction, and may also result in delayed or inadequate angiogenesis [79, 80]. Such effects could potentially lead to inadequate collateral development and infarct expansion. Magnesium reduces vulnerability to oxygen-derived free radicals [81], reperfusion injury and stunning of the myocardium.

### Impact of magnesium on lipids

Magnesium plays an interesting role in lipid regulation, although it is not yet fully understood [82-87].

Magnesium is an important cofactor of two enzymes that are essential in lipid metabolism: lecithin-cholesterol acyltransferase (LCAT) and lipoprotein lipase. In a rabbit animal model fed a normal diet or a high cholesterol diet supplemented with varying amounts of magnesium, the addition of supplemental magnesium achieved a dose dependent reduction in both the area of the aortic lesions and the cholesterol content of the aortas [85]. The 1% cholesterol diet significantly increased plasma cholesterol and triglyceride concentrations and decreased high density lipoprotein (HDL) cholesterol concentration. Additional magnesium had no further effect on cholesterol and HDL cholesterol concentrations, but it slightly decreased the rise in triglyceride concentration [85]. Rats, on the other hand, placed on diets severely deficient in magnesium, developed adverse lipid changes [86]. In a rat model, magnesium-deficient diets demonstrated an elevated plasma cholesterol level, low density lipoprotein (LDL) and triglycerides with a proportionate reduction in high-density lipoprotein (HDL) [87]. Rasmussen *et al.* [82] gave a daily dose of 15 mmol magnesium hydroxide to humans and found a 27% reduction in triglycerides and very low-density lipoprotein (VLDL) after 3 months of therapy and reduction in apoprotein B and elevation of HDL. Davis *et al.* [87] demonstrated a significant improvement in the ratio of HDL to LDL plus VLDL, by giving 18 mmol magnesium per day in a 4-month clinical trial.

Niemela *et al.* [84] showed that in men, but not in women, platelet intracellular magnesium levels significantly inversely correlated with serum total cholesterol ( $r = -0.52$ ,  $p < 0.02$ ), LDL ( $r = -0.54$ ,  $p < 0.009$ ) and apolipoprotein B ( $r = -0.42$ ,  $p < 0.04$ ). These investigators also speculated that decreased platelet intracellular magnesium level is a possible marker for platelet membrane alterations that may affect platelet involvement in thrombosis and atherogenesis [84].

### Impact of magnesium on cardiac arrhythmias

Magnesium deficiency is associated with intracellular hypopotassemia, hypernatremia and augmentation of cell excitability [88]. Magnesium has modest electrophysiologic effects: It prolongs the actual and corrected sinus node recovery time, prolongs the atrioventricular nodal function, relative and effective refractory periods, slightly increases the QRS duration during ventricular pacing at cycle lengths of 250 and 500 milliseconds, and increases the atrial-His interval and atrial paced-cycle length causing atrioventricular nodal Wenckebach con-

duction [89]. Zwillinger [90] in 1935 was the first to recognize the arrhythmic effect of magnesium, when used to convert paroxysmal tachycardia to normal sinus rhythm. Later on it was successfully used in resistant ventricular tachycardias [91], ventricular arrhythmias induced by digitalis toxicity [92] and episodes of torsade de pointes, a life threatening ventricular arrhythmia [92, 93].

Magnesium was also found to be effective in the termination of episodes of supraventricular arrhythmia, such as multifocal atrial tachycardia (MAT) [94] and increased the susceptibility of atrial tachycardia to pharmacological conversion with digoxin [82].

Magnesium has recently been recommended by the American Heart Association as the third drug of choice (after Amiodarone and Lidocaine) in the resuscitation of patients with pulseless ventricular tachycardias or ventricular fibrillation [53].

Magnesium therapy may correct resistant hypokalemia, since it is a cofactor of ATP molecule [95].

### Clinical trials of magnesium in acute myocardial infarction

In the last 2 decades, some relatively small prospective, randomized, double-blind and controlled trials have been reported, comparing intravenous magnesium to placebo in acute myocardial infarction (AMI) patients [96-105]. Morton *et al.* [96] published their study in 1984 and were the pioneers to show that magnesium reduced the infarct size by 20% in patients in Killip class I and in-hospital mortality in AMI patients.

The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) [106], was the first large clinical trial where 30% of the 2,316 patients received thrombolytic therapy. Intravenous magnesium reduced congestive heart failure (CHF) by 25% and all-cause mortality by 24% at 28 days [106] and 20% reduction in ischemic heart disease-related mortality over a mean follow-up of 4.5 years [107].

In mid 1990 Shechter *et al.* [108] demonstrated that 22 g (92 mmol) of intravenous magnesium sulfate for 48 hours in 215 AMI patients who were considered unsuitable for reperfusion, reduced the in-hospital mortality by almost 50% and the incidence of arrhythmias and CHF by 33% in elderly patients above the age of 70 years.

In the same era the Fourth International Study of Infarct Survival and Magnesium in Coronaries (ISIS-4) [109] study was conducted with approximately 58,000 AMI patients, of whom almost 70% received thrombolytic therapy, and showed no survival-benefit from intravenous magnesium

sulfate over placebo at 35-day and 1-year. The magnesium dose was almost identical to that of the LIMIT-2 study, but with an open control. However, the time from onset of symptoms to randomization was substantially longer (median of 8 hours rather than 3). The 30% patients not given thrombolytic therapy were randomized at a median of 12 hours after symptoms onset. The low mortality rate in the ISIS-4 control group, the late enrollment of patients, particularly those who did not receive thrombolytic treatment, plus the fact that magnesium infusions were delayed by 1-2 hours after thrombolytic therapy, suggest the possibility that the majority of patients in ISIS-4 were at low mortality risk and that an elevated magnesium blood level was not reached until well beyond the narrow time window for salvage of myocardium or prevention of reperfusion injury suggested by experimental data [79, 80].

Shortly thereafter Shechter *et al.* [110] showed a significant long-term (mean follow-up of 4.5 years) mortality reduction of 40% in 194 AMI patients, considered unsuitable candidates for reperfusion therapy at the time of enrollment, who received intravenous magnesium compared to placebo for 48 hours. The rest left ventricular ejection fraction, measured in all patients who survived the last year of follow-up, was significantly higher in patients who received magnesium versus placebo. Thus, the favorable effects of intravenous magnesium therapy can last several years after acute treatment, probably due to preserved left ventricular ejection fraction.

In 2002, the Magnesium in Coronaries (MAGIC) trial [111] was published. The MAGIC trial randomized 6,213 patients  $\geq 65$  years, of whom an unexpectedly high percentage (45%) were female with acute ST elevation AMI  $< 6$  hours who were eligible for reperfusion therapy (median age 73 years) (stratum 1); or patients of any age who were not eligible for reperfusion therapy (median age 67 years) (stratum 2), to a 2 g intravenous bolus of magnesium sulfate, administered over 15 minutes, followed by a 17 g infusion of magnesium sulfate over 24 hours ( $n = 3,113$ ) or matching placebo ( $n = 3,100$ ). The "magnesium community" was very disappointed by the results which demonstrated the null effects of magnesium on 30-day mortality or heart failure. In comparison to the MAGIC trial, the study of Shechter *et al.* [110] comprised thrombolysis-ineligible AMI patients, of whom one third were  $> 75$  years and therefore similar to the MAGIC stratum 2 patients but differing in 2 aspects: the Shechter *et al.* study patients (a) received a higher dose of intravenous magnesium sulfate (22 g *vs* 19 g); (b) for a longer period of time

(48 h *vs* 24 h). Furthermore, a significantly higher proportion of the MAGIC study population received aspirin,  $\beta$ -blockers and angiotensin-converting enzyme inhibitors than in the Shechter's study population, and as a result the postulated cardioprotective effects of magnesium could have been superseded by the effects of these medical regimens.

Recently published random-effect meta analyses have demonstrated a significant reduction in early mortality when comparing magnesium with placebo (OR: 0.66, 95% CI: 0.53-0.82), especially in patients not treated with thrombolysis (OR: 0.73, 95% CI: 0.56-0.94) and in those treated with  $< 75$  mmol of magnesium (OR: 0.59, 95% CI: 0.49-0.70) [112].

Following the data from the ISIS-4 and MAGIC studies, the current guideline recommendation is that magnesium should not be routinely administered to all AMI patients. However, it should be an adjunct therapy option in selected cases of high-risk AMI patients, such as elderly patients, those with left ventricular dysfunction and/or CHF, and/or patients not suitable for reperfusion therapy [30].

### Adverse effects

Magnesium supplementation is relatively safe [3, 28-30]. In all previous randomized controlled clinical trials only a few adverse effects were reported. In the ISIS-4 trial [109] with 58,000 patients with suspected AMI, no overall increase in the incidence of second or third degree heart block was observed, although there was a slight but not convincingly significant excess during or just after the magnesium infusion. These adverse effects were not confirmed in the LIMIT 2 trial [106] with 1,500 and in the MAGIC trial [111] with 6,200 AMI patients. Non-clinically significant sinus bradycardia, however, was observed in some but not all randomized clinical trials. As magnesium is a physiological calcium competitor, rapid intravenous (bolus) administration is prohibited as it can reduce blood pressure. Therefore an intravenous bolus dose of 1 g over 5 minutes is recommended [93].

A patient with normal kidney function excretes magnesium rapidly through the kidneys. Normally the kidneys filter approximately 2.5 g of magnesium and reclaim 95%, excreting some 100 mg/dL into the urine to maintain homeostasis. Approximately 25-30% is reclaimed in the proximal tube through a passive transport system that depends on sodium reabsorption and tubular fluid flow. Usually, as serum magnesium concentration increases, there is a linear increase in urinary magnesium excretion, paralleling

that of insulin. With normal kidney function, hypermagnesemia or magnesium intoxication does not usually develop, even during high intravenous magnesium infusion [3, 28-30].

Additionally, oral magnesium supplementation may cause diarrhea, soft stool, gastrointestinal irritation, weakness, nausea, vomiting and abdominal pain.

### **Reasons for magnesium deficiency**

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The prevalence of hypomagnesemia in hospitalized patients ranges from 8 to 30% [1, 3]. Elderly patients, particularly those with CAD and/or CHF, can have low body magnesium levels, the mechanisms of which are likely to be multi-factorial. Evidence suggests that the occidental "American-type diet" is relatively deficient in magnesium [1, 3, 10, 11], while the "oriental diet", characterized by a greater intake of fruit and vegetables, is richer in magnesium [4]. It has also been observed that CAD patients absorb more magnesium during magnesium loading tests than non CAD patients, suggesting that CAD is associated with excessive magnesium loss and a relative magnesium-deficient state [13].

Magnesium deficiency may usually be reflected in low-magnesium diet, blood loss, excessive sweating, drug and/or alcohol abuse or due to certain medication use (such as loop diuretics and thiazides, cytotoxic drugs, aminoglycosides, digoxin, steroids), or some physiological conditions of over utilization of magnesium such as pregnancy or infancy growth. Mental stress can also lead to magnesium deficiency due to high serum adrenalin [113, 114]. Diabetes mellitus is also associated with magnesium deficiency, mainly due to urinary magnesium loss [1]. Other diseases associated with magnesium deficiency: liver cirrhosis, diseases of the thyroid and parathyroid glands, renal diseases. Moreover, diets rich in animal foods and low in vegetables induce acidosis and increase magnesium urinary excretion.

Pure magnesium deficiency is characterized by a number of clinical features, including muscular tremor, vertigo, ataxia, tetany, convulsions and organic brain syndrome.

### **Magnesium and CHF**

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Patients with CHF are magnesium deficient. The activation of the renin-angiotensin-aldosterone system and the use of diuretics are associated with depletion of potassium and magnesium in CHF [1, 3, 28, 115]. Magnesium deficiency stimulates aldosterone pro-

duction and secretion, while magnesium infusion decreases aldosterone production by inhibiting cellular calcium influx [116]. Adamopoulos *et al.* [117] recently found that CHF in patients (mainly New York Heart Association [NYHA] II-II) with low serum magnesium  $\leq 2$  mEq/L was associated with increased cardiovascular mortality (but had no association with cardiovascular hospitalization) compared to those with serum magnesium  $> 2$  mEq/L in a long-term follow-up of 36 months, suggesting that most of these deaths were likely sudden (arrhythmic) in nature. Furthermore, Stepura and Martynow [118] demonstrated that oral magnesium orotate used as adjuvant therapy in severe NYHA IV CHF patients increased the 1-year survival rate and improved clinical symptoms and the patient's quality of life compared to placebo.

### **Conclusion**

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Magnesium plays a vital role in many cellular processes. Magnesium is essential for a number of metabolic activities since it is associated with a variety of enzymes which control carbohydrate, fat, protein and electrolyte metabolism. Several hundred enzymes, directly or indirectly, are dependent on magnesium. Most important among these enzymes are those which hydrolyze and transfer phosphate groups, including enzymes that are concerned with reactions involving energy production and ATP. Magnesium deficiency, or reduction in the dietary intake of magnesium, plays an important role in the etiology of diabetes and numerous cardiovascular diseases including thrombosis, atherosclerosis, ischemic heart disease, myocardial infarction, hypertension, cardiac arrhythmias and CHF in humans.

Magnesium deficiency may lead to reduced energetic metabolite production and the sense of fatigue and/or "chronic fatigue syndrome". Modern life styles and the Western industrial diet have enhanced the reduction of magnesium in our food, which contributes to marginal or absolute magnesium deficiency. The magnesium deficiency is mostly evidenced in the elderly population, those with myocardial infarction and/or CHF, diabetics, patients with chronic airway obstruction, pre- or toxemia of pregnancy, in post transplantation patients (especially in heart transplantation), patients with malignancies who receive cytotoxic chemical therapy, in competitive athletes and in metabolic syndrome patients.

It should be noted that magnesium deficiency can easily be treated by magnesium supplementation if we are aware of the situation. The best recommen-



dition is to increase consumption of magnesium-rich food. However, since magnesium deficiency is hard to treat only by increase consuming high-magnesium food products, it is recommended to take magnesium supplements which officially and safely increase the magnesium in the body and correct the deficit.

There are theoretical potential benefits of magnesium supplementation as a cardioprotective agent in CAD patients, as well as promising results from previous work in animal and humans. Magnesium is an essential element in treating CAD patients, especially high-risk groups such as CAD patients with heart failure, the elderly and hospitalized patients with hypomagnesemia. Furthermore, magnesium therapy is indicated in life-threatening ventricular arrhythmias such as Torsades de Pointes and intractable ventricular tachycardia

Serum magnesium levels are not to be routinely advocated for screening subjects with magnesium deficiency, rather it should be highly suspicious unless proved otherwise.

It should be remembered that magnesium is neither a "panacea" nor a "wonder drug" which is aggressively pushed by the pharmaceutical industry. After all, it is a relatively simple nutrient, relatively non-expensive and easy to administer, with relatively few adverse events but also a "nutrient which is the sparkle of life" and an important life gatekeeper.

## Disclosure

The author has no conflict of interest to disclose.

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