Magnesium: Novel Applications in Cardiovascular Disease – A Review of the Literature

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Abstract

Magnesium is an ubiquitous element and its formulation determines its efficacy and administration. It is used for gastrointestinal and obstetric disease and recently cardiovascular and neurological indications have also been explored. The role of serum/dietary magnesium intake on cardiovascular disease, carotid intima-media thickness (CIMT), hypertension (HTN) and cholesterol synthesis has been investigated. Despite differences in patient populations, some observational and interventional studies have suggested that low serum/dietary magnesium is associated with higher CIMT and more cardiovascular risk factors. A few clinical and basic science interventional studies have also shown the benefits of magnesium administration in cardiovascular disease prevention and as a neuroprotective agent. Low magnesium levels have been implicated in inflammation and endothelial dysfunction. Hypomagnesemia results in increased C-reactive protein and cytokine exaggeration, increased nuclear factor kappa B and platelet dysfunction, which can lead to thrombosis. Magnesium appears to play a vital function in cardiovascular stability and health, but an optimal dose and formulation has not been defined. Potentially promising avenues include the combination of magnesium with a statin to reduce cholesterol, C-reactive protein and CIMT, and its early use to reduce stroke morbidity and mortality. Understanding the role of magnesium in inflammation and mineralization and how it has the potential for playing a role in modulating cardiovascular and neurological disease can be a new frontier in medicine.

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Introduction

Magnesium is a common mineral found compounded and usually in crystalline form. First discovered for its wound-healing properties in Epsom, England, in the 17th century, it has multiple uses in the medical field, especially in cardiovascular disease [1]. It is the second most common intracellular cation in the body after potassium [1]. Because about 90% of the intracellular magnesium in the body is bound to organic matrices, levels of serum magnesium, which represent only 0.3% of the total, may not accurately reflect the total magnesium status [1], so current methods for magnesium measurement are often

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imprecise. Serum magnesium levels are further divided into ionized, protein-bound and anion-complexed (i.e. magnesium citrate and phosphate) [1]. Convention and practicality are applied to obtain the total magnesium value. Other modalities have been attempted, but are controversial. In the blood, erythrocytes contain more magnesium than serum [2] and studies have shown that intracellular (erythrocyte) magnesium could potentially be useful [3–5]. On the frontier of radiological advances, intracellular ionized magnesium in body tissues can be measured noninvasively with nuclear magnetic resonance, but the practicality of this modality for blood measurement may be questionable due to cost [2, 6].

This review will discuss the most common applications of magnesium, its efficacy in terms of bioavailability and the potential mechanisms of action in the cardiovascular system. Trial data will demonstrate how magnesium has been used to prevent atrial fibrillation, hypertension (HTN), inflammation, carotid intima-media thickness (CIMT) and atherosclerosis, stroke and coronary heart disease.

Magnesium Compounds and Efficacy

Generally, magnesium supplements are found in low quantities in multivitamins and over-the-counter laxative preparations, like magnesium hydroxide or Milk of Magnesia, or as prescriptions for various other indications. Magnesium oxide and magnesium gluconate, for example, are orally administered and are generally used to treat mild hypomagnesemia. Magnesium sulfate ($MgSO_4$) is given intravenously or intramuscularly and is usually used in obstetrics as a tocolytic or in the critically ill setting to treat severe hypomagnesaemia, while magnesium citrate is often used for acute constipation. Patients with renal impairment should be cautious when taking excessive magnesium supplements and baseline creatinine should be assessed. Serum magnesium can also increase, especially in cases of ingestion of doses >50 mEq/day (4.8–7.2 mg/dl), which is rare because of the kidney's ability to respond to maintain homeostasis [7]. For practical purposes and for those not critically ill, oral supplementation is recommended with magnesium oxide, magnesium lactate or magnesium hydroxide [8].

Magnesium L-lactate and L-aspartate are the oral magnesium compounds that have the greatest bioavailability, are the most water-soluble and have the greatest serum and plasma concentrations [8]. Magnesium can be made more water-soluble by chelating it with salicylate, as in magnesium salicylate, or with amino acids, such as magnesium malate, or magnesium diglycinate [8]. The latter two compounds may be beneficial for those patients with intestinal resection or complications since they have low gastrointestinal distress and diarrhea [8, 9]. A study to determine the bioavailability of magnesium in the rat revealed that citrate, lactate, aspartate and most organic salts were more bioavailable than inorganic salts. Gluconate, however, was the most bioavailable [10]. The authors of the study concluded that as pH increases, the solubility and intestinal bioavailability decrease [10]. The main sites for magnesium absorption in both humans and rats are the ileum and cecum, respectively. As they generally have a higher pH than the proximal intestine, organic magnesium-salt exposure may lower the pH, generating a higher solubility [10].

Magnesium and Cardiovascular Applications

Tables 1–3 summarize the animal and human trials with magnesium discussed in this review.

In the scope of using magnesium in cardiovascular medicine, the data are mostly based on basic science and preclinical rodent studies with occasional human observations and some controlled studies.

Mechanisms of Action

In vascular medicine, magnesium induces vascular smooth-muscle cell relaxation by acting as a mild physiological calcium blocker; increased extracellular magnesium decreases intracellular calcium [11, 12] and reduces angiotensin-induced aldosterone synthesis, which can lower blood pressure (BP) [12, 13]. It reduces triglycerides and increases high-density lipoprotein (HDL) through increased lipoprotein lipase activity, which catabolizes triglyceride lipoproteins and produces HDL [12]. Magnesium also inhibits HMGCoA reductase, the rate-limiting enzyme for cholesterol synthesis, like statin drugs, it is necessary for lecithin cholesterol acyl transferase activity [14] and thus lowers low-density lipoprotein (LDL) triglycerides and raises HDL levels [15].

A possible explanation for the beneficial effects of magnesium is based on observations in magnesium-deficient animals. The studies by Mazur et al. [11] demonstrated that in the hypomagnesemic state, the immune system of these animals was more likely to have proinflammatory, exaggerated responses marked by elevations in C-reactive protein, leukocyte and macrophage activation, nuclear factor kappa B, cytokines and platelet ag-

Table 1. Summary of magnesium basic science and clinical studies

Study type	Organism/patient characteristics	Design	Intervention or plan	Results
Basic science Mazur et al. [11]	Rats	interventional	blood and organs harvested and analyzed after 1 week on a severely magnesium-deficient diet	magnesium-deficient rats developed edema, hyperemia, increased inflammatory cells in the blood (eosinophilia, neutrophils, proinflammatory cytokine activation, substance P, IL-6, NF-κB, C-reactive protein) and accumulation of LDL and triglycerides
Basic science Marinov et al. [41]	male rats	interventional	30 or 90 mg/kg $MgSO_4$ or vehicle was injected into the carotid arteries of the rats. Middle cerebral artery was occluded, then reperfused after 1.5 or 2 h	rats given 90 mg/kg before 1.5 h of ischemia had a 59.8% reduction in infarct volume compared to controls ($p < 0.001$) and a 43.1% reduction compared to the 30 mg/kg group ($p < 0.001$). All groups showed significant effects of $MgSO_4$ doses on infarct volume across all groups (ANOVA; $p < 0.0001$)
Clinical Reinhart et al. [16]	patients with elective, isolated 1st time coronary artery bypass grafting	interventional, prospective, RCT	patients in the $MgSO_4$ group (n =100) received 6 mmol of $MgSO_4$ infusion in 100 ml 0.9% NaCl solution (25 ml/h) the day before surgery, just after cardiopulmonary bypass, and once daily for 4 days after surgery. The control group (n = 100) received only 100 ml 0.9% NaCl solution (25 ml/h) at the same time points	postoperative atrial fibrillation occurred in 2 (2%) patients in the $MgSO_4$ group and in 21 (21%) patients in the control group ($p = 0.001$)
Clinical Kawano et al. [17]	Japanese patients who were either untreated or already on antihypertensive medication	interventional RCT, crossover	treatment group (n = 30) given magnesium oxide 400 mg twice daily for 8 weeks then crossed over. Placebo group (n = 30) allowed to take their antihypertensive for 8 weeks then crossed over. Subjects could remain on antihypertensive throughout the entire study. BPs measured at the office, at home and over 24 h, day and night	significantly lower BPs in the magnesium oxide supplementation period vs. in the control period, although the differences were small (office 3.7 ± 1.3/1.7 ± 0.7 mm Hg, home 2.0 ± 0.8/1.4 ± 0.6 mm Hg and 24-hour period 2.5 ± 1.0/1.4 ± 0.6 mm Hg)
Clinical Rosanoff [19]	patients on antihypertensive therapy who had stage 1 uncomplicated HTN vs. those patients who had stage 1 HTN but who remained untreated or were off their antihypertensive therapy for at least 4 weeks vs. normotensive patients (systolic BP <120 mm Hg and diastolic BP <80 mm Hg)	comprehensive analytical review	reviewed 44 studies in 43 publications of magnesium supplementation for stage 1 HTN vs. normotensive BP, then stratified by dose of magnesium (high vs. low) and degree of BP reduction	significant BP-lowering effect was increased when dose was doubled from 230 mg/day to 460 mg/day

gregation [12]. This proinflammatory state is believed to disrupt the arterial endothelium and promote thrombosis, which leads to atheroma formation and atherosclerosis, HTN, arteriosclerosis and vascular mineralization. This, combined with the changes seen in metabolic syndrome (hypercholesterolemia, obesity, diabetes and HTN), is aggravated by hypomagnesemic states and by a subsequent exaggerated immune response, at least in the animal model [11].

Atrial Fibrillation

The therapeutic modality of $MgSO_4$ administration, as an anti-inflammatory and anti-arrhythmic after coronary artery bypass grafting to avoid postoperative atrial fibrillation, has recently come to light [16]. In one prospective randomized controlled trial (RCT), of 100 participants receiving $MgSO_4$ only 2% had postoperative atrial fibrillation compared to 21% of patients receiving a placebo [16]. While prophylaxis is not currently recom-

Table 2. Summary of magnesium clinical studies

Study type	Patient characteristics	Design	Intervention or plan	Results
Clinical Song et al. [20]	female US health professionals ≥45 years old in the Women's Health study, who initially reported normal BP	large prospective cohort	females participated in the study (n = 28,349). Magnesium intake was estimated via the semi-quantitative food-frequency questionnaire in 1993 and mean follow-up was for 9.8 years. Patients equally divided into quintiles of magnesium intake: 256 mg/day (low) to 400 mg/day (high)	after adjustment for confounders women in the highest quintile had a decreased HTN risk ($p < 0.0001$) vs. those in the lowest quintile
Clinical Ma et al. [21]	postmenopausal, 50- to 79-year-old women enrolled in the Women's Health Initiative observational study	cross-sectional	data from women enrolled (n = 1,958) examined high-sensitivity C-reactive protein , IL-6 and TNF-α receptor 2 and food-frequency questionnaire to estimate fiber intake for the past 3 months	decreased IL-6 and TNF-α receptor 2 were observed and were correlated with an increased intake of total fiber and soluble fiber, which are high in magnesium
Basic science Altura et al. [23]	normal rabbits	interventional	low- or high-magnesium diet with or without a 1 or 2% cholesterol chow	the lower the magnesium and the higher the cholesterol, the greater the atherosclerotic plaque thickness in the aorta
Basic science Li et al. [28] Kupetsky-Rincon et al. [29]	$Abcc6^{-/-}$ mice	interventional	5-fold magnesium oxide added to diet	CIMT decreased 26%. Prevented connective tissue mineralization in $Abcc6^{-/-}$ mice
Clinical Turgut et al. [32]	hemodialysis patients	interventional, RCT	treatment group (n = 32) was given 98.6 mg elemental magnesium every other day for 2 months and control group (n = 12) was given calcium acetate for 2 months	magnesium treatment arm showed a statistically significant drop in CIMT over 2 months to 0.70 mm ± 0.2 ($p = 0.001$)
Clinical Ma et al. [33]	ARIC: males/females, blacks/whites, 45–64 years olds	cross-sectional	blood was drawn from subjects (n = 14,982) and analyzed for serum magnesium, cholesterol, glucose and insulin. Dietary magnesium intake was queried by questionnaire. BMI and CIMT measurements calculated	low serum/dietary magnesium may be related to etiologies of cardiovascular disease, HTN, diabetes and atherosclerosis (elevated CIMT)

mended, it is prudent to treat presurgical hypomagnesemia in these patients who are predisposed to postoperative atrial fibrillation [16].

Hypertension

Significant reductions in systolic and diastolic BPs have been shown in studies where magnesium oxide was consumed in quantities of 400 mg twice daily [17]; however, a review of the literature suggests that BP may be reduced further when combined with a potassium and low-sodium intake [13]. Another comprehensive analytical review also showed that oral magnesium improved the BP-lowering effect of the antihypertensive medications of patients who were diagnosed with stage 1 HTN, which is defined by a systolic BP of 140–159 mm Hg or a diastolic BP of 90–99 mm Hg. This effect was increased when the dose was doubled from 230 to 460 mg daily, sug-

gesting that magnesium supplements above the recommended daily allowance [18] may be necessary to significantly lower high BP in these patients [19]. Finally, a large prospective Women's Health study, composed of female US health professionals aged ≥45 years without previous myocardial infarction, stroke, transient ischemic attack or cancer, who initially reported normal BP (systolic BP <140 mm Hg, diastolic BP <90 mm Hg and no history of HTN or antihypertensive medication) included a semi-quantitative food-frequency questionnaire for daily magnesium intake [20]. After a mean follow-up of 9.8 years and adjusting for confounders, the authors concluded that women in the highest quintile (an intake of 400 mg/day of magnesium) had a decreased HTN risk ($p < 0.0001$) versus those in the lowest quintile (approx. 200 mg/day of magnesium) [20].

Table 3. Summary of magnesium clinical studies

Study type	Patient characteristics	Design	Intervention or plan	Results
Clinical Liao et al. [39]	ARIC 2: males/females, blacks/whites, 45–64 years old	prospective	blood was drawn from subjects (n = 13,992) and analyzed for serum magnesium, cholesterol and glucose. Dietary magnesium intake was queried by questionnaire. BMI and BP calculated	in women, low serum magnesium was strongly related to coronary heart disease, dietary magnesium was weakly associated to coronary heart disease in men
Clinical Larsson et al. [40]	literature search on Pubmed and EMBASE for 'magnesium intake' and 'stroke'	meta-analysis of prospective studies	7 studies included; results (n = 241,348) divided by magnesium intake (highest = about 500 mg/day) compared with lowest = about 250 mg/day), and stroke risk factors, years of follow-up, and number of cases	after adjustments for confounders, an increase increment of 100 mg of magnesium/day was associated with an 8% decreased risk of total stroke and a 9% decreased risk of ischemic stroke
Clinical Muir et al. [46]	IMAGES: >18 years old, ischemic stroke symptoms ≥1 h, patients could have received tissue plasminogen activator and brain CT/MRI must have been done within 7 days of trial entry	multicenter, double-blinded, placebo-controlled, parallel-group RCT	patients (n = 2,386) randomized to receive $MgSO_4$ or normal saline with median treatment time of 7 h of clinically diagnosed stroke	no reduction in morbidity or mortality at 90 days. The OR for death, the primary outcome, was 1.22 indicating no protective effect of $MgSO_4$ for ischemic stroke, with CIs crossing the null value, indicating nonsignificance
Clinical Saver et al. [47]	FAST-MAG: 45–95 years old, ambulance transported, stroke within ≥15 min of symptoms, ≤12 h of treatment	open-label, phase-II, feasibility, nonrandomized clinical trial	all enrolled patients (n = 20) received 2.5 mg $MgSO_4$ in the field, over 10 min, followed by 1.5 mg, then 16 mg over 24 h. Stroke scale performed at hospital arrival, 24 h, 48 h, 4 days and 90 days. Other assessments done	42% of the patients with <2 h infarcts had early recovery and at 90 days, 69% of all patients and 75% of those patients with <2 h infarct achieved good overall global functional outcome
Clinical Abbott et al. [48]	Honolulu Heart Program: men, 45–68 years old, of Japanese ancestry living in Oahu, history from 1965–1968 followed for the development of cardiovascular disease	observational	patients (n = 7,172) divided by quintiles of magnesium intake (low = 50 mg/day, high = 1,138 mg/day) and by incidence of coronary heart disease (defined by fatal coronary event and nonfatal myocardial infarction). Coronary heart disease risk factors were also considered. Up to 30 years of follow-up data available on each patient	in the first 15 years of follow-up, there was a 1.8-fold excess incidence of coronary heart disease for men in the lowest dietary magnesium intake quintile vs. the highest quintile. Risk factors were also greatest at lower quintiles. After adjustments for risk factors, coronary heart disease decreased with increasing magnesium intake (p = 0.04)

Inflammation

Decreased plasma levels of inflammatory markers (interleukin-6 and tumor necrosis factor-α receptor 2) were also observed in the Women's Health Initiative Observational Study, a 5-year, multi-center, national study of postmenopausal women. These levels were correlated with an increased intake of total and soluble fiber [21], both high in magnesium [22]. The purpose of this study was to examine epidemiological data on the influence of inflammatory markers of chronic diseases (i.e. atherosclerosis, diabetes and cancer) [21]. These inflammatory markers may be highly sensitive to fiber and magnesium intake and perhaps influence C-reactive protein via an indirect mechanism in postmenopausal women and directly in younger individuals [21]. It has previously been reported in the literature that in younger men and women, C-reactive protein levels are significantly decreased with fiber supplementation [21].

Carotid Intima-Media Thickness and Atherosclerosis

Magnesium is known to affect calcium uptake into soft tissues, especially vascular smooth-muscle cells, an important factor in atherosclerosis [23]. In vitro experiments with human cultured endothelial cells exposed to low magnesium create a state of chronic inflammation, upregulate nuclear factor kappa B and increase the endothelial permeability which allows LDLs to migrate into the media and become oxidized and later combine with cholesterol and macrophages as foam cells promoting atherogenesis [24]. When aortic rat segments were ex-

posed to high phosphate to promote vascular calcification and then incubated in either the presence or absence of magnesium chloride, the presence of magnesium decreased vascular calcification [25]. While calcium, phosphate and cytokines can promote mineralization or calcification, magnesium is considered an inhibitor of vascular calcification [26, 27].

A study in 1990 in normal rabbits fed either a low- or high-magnesium diet with or without a 1 or 2% cholesterol chow revealed that the lower the magnesium and the higher the cholesterol, the greater the atherosclerotic plaque thickness in the aorta [23]. The aortas were only minimally thickened in the cohort treated with high magnesium and high cholesterol [23]. These results suggest that the high dietary magnesium prevented the atherosclerotic plaque formation [1].

The influence of magnesium on mineralization was recently tested in a mouse model with an autosomal recessive ectopic mineralizing disorder, pseudoxanthoma elasticum (PXE), a condition marked with vascular deposits of calcium phosphate [28, 29]. This disease manifests clinically with HTN, intermittent claudication, myocardial infarction, stroke, loss of visual acuity, blindness and elevated CIMT (a biomarker for atherosclerosis) [30]. This disease has features similar to atherosclerosis and Monckeberg-type arteriosclerosis, or medial stiffening of the arteries [31]. In humans, there is no effective treatment and no validated biomarker for PXE. When a knock-out mouse model for this disease *(Abcc6$^{-/-}$)*, which also shows elevated CIMT, was administered with a 5-fold excess of magnesium oxide in its standard rodent chow for 2 months, the CIMT was significantly reduced by 26% (p = 0.02) [29]. Magnesium, calcium, vitamin D and parathyroid hormone levels in the blood were normal. There was, however, a 10-fold increase in calcium and a 77% decrease of phosphorus in the urine of a similar cohort of mice [28]. Histological examination revealed prevention of calcium phosphate deposition in the vascular connective tissues in these mice.

Because of the success in mouse studies, pharmaceutical interventions with dietary magnesium are already being contemplated for the treatment of PXE patients. In addition, magnesium is already in vitamin supplements, but the dose that may be safe and cardioprotective and produce antimineralizing effects is unknown because RCTs are lacking. Results from these studies on PXE, an inheritable disorder, may have widespread application in cardiovascular medicine and disease prevention as well as in other mineralizing disorders and nutrition in general.

Turgut et al. [32] demonstrated that magnesium citrate reduces CIMT in hemodialysis patients (n = 47). The dose was 98.6 mg elemental magnesium (8.275 mEq) every other day for 2 months. Both the treated and the control groups of HD patients received calcium acetate as a phosphate binder and a magnesium washout period of 3 months prior to the start of the RCT. Both groups of hemodialysis patients had a similar baseline CIMT (0.96 mm), but only the magnesium treatment arm showed a statistically significant drop in CIMT over 2 months to 0.70 mm ± 0.2, (p value = 0.001) [32]. Further translational and clinical work is needed to define the potential of magnesium and the mechanism of its action in reducing CIMT, not only in atherosclerosis but also in other mineralizing disorders, such as PXE.

The Atherosclerosis Risk in Communities (ARIC) study, which looked at magnesium dietary intake in men and women aged 45–64 years, concluded that low dietary magnesium intake and low serum magnesium levels contributed to atherosclerosis development and a mean CIMT increase [33]; for each 0.1 mmol/l decrease in serum magnesium, the CIMT increased 0.0059 mm in women who were not on diuretics. This result was significant (p = 0.003) [33] and remained so, despite the use of diuretics which can confound results by increasing the urinary excretion of magnesium (0.0124 mm, p = 0.004) [33]. This result was not significant in men. According to the Cardiovascular Health Study and NOMAS, normal CIMT ranges vary from 0.7 to 0.9 mm in 45- to 75-year-olds [34] and the progression of CIMT – depending on risk factors – can range from 0.01 ± 0.05 mm/year [35]. If low-serum magnesium can potentially cause a significant increase in CIMT in women in this age range (similar to the pathological progression of CIMT), the risk of stroke incidence increases as the CIMT rate of change increases [35], resulting in increased cardiovascular morbidity and mortality [36–38].

Gender differences with magnesium have also been found in a second ARIC study in 1998, which revealed that after adjusting for cardiovascular confounders, low-serum magnesium is an independent predictor of the incidence of coronary heart disease in women (adjusted relative risk: 1.32 vs. 0.69 in men) [39]. Low dietary magnesium, however, was weakly associated with incident coronary heart disease in men in this study [39]. More RCT investigations are needed to determine the impact of serum magnesium levels and dietary magnesium on atherosclerosis, CIMT and coronary heart disease, especially in women.

Stroke

A recent prospective meta-analysis, in which the authors conducted a Pubmed and EMBASE literature review for 'magnesium intake' and 'stroke', identified 7 studies published from 1998 to 2011 (241,348 participants in total) and found that these stroke patients were on a median dose of 250 (low)–500 mg (high) of magnesium per day [40]. After adjustment for stroke risk factors, the consumption of magnesium at an increment of 100 mg/day, as determined by food questionnaires in these studies, was inversely associated with ischemic stroke [40]. Similar positive results have also been seen in basic science studies. Intracarotid administration of 3 different doses of $MgSO_4$ in rats followed by middle cerebral-artery occlusion, a model for cerebral ischemia and then reperfusion, demonstrated neuronal protection or less infarct with the higher $MgSO_4$ dose (p < 0.001) [41]. Intra-arterial or intravenous $MgSO_4$ may have mechanisms of action in the brain that involve inhibition of the presynaptic release of excitatory neurotransmitters, noncompetitive block of the N-methyl-D-aspartate receptors, presynaptically potentiate adenosine, block calcium channels, relax vascular smooth muscle (causing vasodilation that increases cerebral blood flow) or antagonize endothelin-1 (a vasoconstrictor) [42].

Although there have been other successful animal stroke or brain injury models with $MgSO_4$ [43–45], its use for neuroprotection in human trials has yielded less clear results. In the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial, a placebo-controlled, double-blinded, parallel-group, multi-center RCT, where $MgSO_4$ was administered to patients with a median time of 7 h to treat clinically diagnosed ischemic stroke, there was no reduction in morbidity or mortality at 90 days [46]. It was postulated that perhaps the reason why translating the treatment to humans was not successful was because the drug had to be delivered in a shorter time span from the onset of stroke symptoms because 'time lost is brain lost', or that delay of treatment results in neuronal death. Design challenges faced by investigators – to deliver timely care to stroke patients in a shorter time-window, rapidly identify potential subjects, provide informed consent, enroll them and assess the degree of stroke severity – led to the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) being initiated [42]. The first FAST-MAG, which was a safety and feasibility nonrandomized trial, enrolled 20 patients (80% ischemic and 20% hemorrhagic strokes) and initiated the infusion of $MgSO_4$ at 100–120 min after diagnosis [47]. At 90 days, 42% of the patients with <2 h infarcts had early recovery, and 69% of all patients and 75% of those patients with <2 h infarct achieved good overall global functional outcome [47]. There were no serious adverse events [47]. FAST-MAG RCT phase III, which is still ongoing, allows the subject to be rapidly assessed, screened, provide consent, enrolled and receive the study drug (a blind study kit) in under 2 h (while still in the ambulance) [42]. Thus far, it has enrolled 73% of patients with ischemic stroke and 24% with hemorrhagic stroke. The trial is impressive in that a neuroprotective agent is being delivered in the field in the shortest time possible (aka 'the golden hour') prior to patients arriving at the hospital and receiving tissue plasminogen activator (if they are a candidate); this early intervention has the potential to save as much brain tissue as possible [42].

Coronary Heart Disease

The 2003 study in Honolulu [48], which analyzed the future risk of coronary heart disease and magnesium intake based on dietary recall, concluded that a higher daily intake of magnesium was associated with a lower incidence of coronary heart disease. Although observational studies are helpful at establishing associations, large-scale interventional trials or RCTs are required to evaluate the safety, efficacy and dose ranges of magnesium in order to verify a cause and effect hypothesis (e.g. that magnesium treats stage 1 HTN). In addition, comparative studies are needed to determine how this supplement equates with other drugs currently in use for cardiovascular indications.

Magnesium – Future Applications

Because of magnesium's anti-inflammatory, statin-like and anti-mineralizing effects, a role for it is emerging in cardiovascular and neurological medicine. As indicated above, patients with the mineralizing disorder, PXE, are being treated with magnesium due to its success in animal studies. The actual efficacy of magnesium supplements in offsetting the complications of coronary heart disease, CIMT, HTN, stroke or cardiovascular disease is currently unknown, and the optimal dose has not been established. As a consequence, larger RCTs are needed.

Because statin drugs have already been approved for lowering cholesterol in humans and there are data to support the notion that magnesium reduces C-reactive protein levels and also inhibits HMG-CoA reductase, indirectly (like the statins) [12], the potential for combining

magnesium with a statin for a more potent cholesterol-lowering effect may be worth investigating. Magnesium-ATP complex is required for the deactivation or phosphorylation of HMG-CoA reductase, and in states of hypomagnesemia, the balance between active and inactive forms of HMG-CoA reductase shifts, favoring a hypercholesterolemic state [15]. Since magnesium is required for lecithin cholesterol transferase, which lowers LDL and triglycerides and raises HDL, its function to possibly enhance or to a lesser degree mimic the effect of a statin drug is still to be elucidated [15]. Moreover, the use of statins has been proven to reduce CIMT in humans [49–51]; thus, a magnesium-statin combination for reduced CIMT might be more efficacious and may reduce morbidity and mortality to a larger extent than a statin only. The future application of magnesium supplementation for neuroprotective and cardiovascular health for potentially reducing cholesterol, BP, atherosclerosis and CIMT is a much-needed area of study.

Conclusions

The potential impact of magnesium in cardiovascular and neurological health, the abundance and low cost of the supplement, the relatively low side effect profile and the paucity of information in the literature about this common mineral suggest that more studies should be conducted to determine its safety and efficacy. The majority of human trials with magnesium thus far have not been interventional, but based on food questionnaires which may not be accurate and are subject to a recall bias. Further work is also needed to determine the mechanism of action by which magnesium modulates the mineralization and inflammation of the cardiovascular and nervous systems.

Acknowledgments

References

1 Fawcett WJ, Haxby EJ, Male DA: Magnesium: physiology and pharmacology. Br J Anaesth 1999;83:302–320.

2 Arnaud MJ: Update on the assessment of magnesium status. Br J Nutr 2008;99(suppl 3):S24–S36.

3 Simsek E, Karabay M, Kocabay K: Assessment of magnesium status in newly diagnosed diabetic children: measurement of erythrocyte magnesium level and magnesium tolerance testing. Turk J Pediatr 2005;47:132–137.

4 Malon A, Brockmann C, Fijalkowska-Morawska J, Rob P, Maj-Zurawska M: Ionized magnesium in erythrocytes – the best magnesium parameter to observe hypo- or hypermagnesemia. Clin Chim Acta 2004;349:67–73.

5 Emelyanov A, Fedoseev G, Barnes PJ: Reduced intracellular magnesium concentrations in asthmatic patients. Eur Respir J 1999;13:38–40.

6 Andrade CS, Otaduy MC, Valente KD, Maia DF, Park EJ, Valerio RM, Tsunemi MH, Leite CC: Phosphorus magnetic resonance spectroscopy in malformations of cortical development. Epilepsia 2011;52:2276–2284.

7 Moe SM: Disorders involving calcium, phosphorus, and magnesium. Prim Care 2008;35:215–237.

8 Ranade VV, Somberg JC: Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. Am J Ther 2001;8:345–357.

9 Schuette SA, Lashner BA, Janghorbani M: Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. J Parenter Enteral Nutr 1994;18:430–435.

10 Coudray C, Rambeau M, Feillet-Coudray C, Gueux E, Tressol JC, Mazur A, Rayssiguier Y: Study of magnesium bioavailability from ten organic and inorganic Mg salts in Mg-depleted rats using a stable isotope approach. Magnes Res 2005;18:215–223.

11 Mazur A, Maier JA, Rock E, Gueux E, Nowacki W, Rayssiguier Y: Magnesium and the inflammatory response: potential physiopathological implications. Arch Biochem Biophys 2007;458:48–56.

12 Bo S, Pisu E: Role of dietary magnesium in cardiovascular disease prevention, insulin sensitivity and diabetes. Curr Opin Lipidol 2008;19:50–56.

13 Houston M: The role of magnesium in hypertension and cardiovascular disease. J Clin Hypertens (Greenwich) 2011;13:843–847.

14 Rayssiguier Y: Magnesium, lipids and vascular diseases. Experimental evidence in animal models. Magnesium 1986;5:182–190.

15 Rosanoff A, Seelig MS: Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. J Am Coll Nutr 2004;23:501S–505S.

16 Reinhart K, Baker WL, Siv ML: Beyond the guidelines: new and novel agents for the prevention of atrial fibrillation after cardiothoracic surgery. J Cardiovasc Pharmacol Ther 2011;16:5–13.

17 Kawano Y, Matsuoka H, Takishita S, Omae T: Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. Hypertension 1998;32:260–265.

18 Standing Committee on the Scientific Evaluation of Dietary Reference Intakes FaNB, Institute of Medicine Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington, National Academy Press, 1997.

19 Rosanoff A: Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects. Magnes Res 2010;23:27–40.

20 Song Y, Sesso HD, Manson JE, Cook NR, Buring JE, Liu S: Dietary magnesium intake and risk of incident hypertension among middle-aged and older US women in a 10-year follow-up study. Am J Cardiol 2006;98:1616–1621.

21 Ma Y, Hebert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, Tinker L, Rosal MC, Ockene IS, Ockene JK, Griffith JA, Liu S: Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative observational study. Nutrition 2008;24:941–949.

22 Galland L: Diet and inflammation. Nutr Clin Pract 2010;25:634–640.

23 Altura BT, Brust M, Bloom S, Barbour RL, Stempak JG, Altura BM: Magnesium dietary intake modulates blood lipid levels and atherogenesis. Proc Natl Acad Sci USA 1990;87:1840–1844.

24 Maier JA: Endothelial cells and magnesium: implications in atherosclerosis. Clin Sci (Lond) 2012;122:397–407.

25 Salem S, Bruck H, Bahlmann FH, Peter M, Passlick-Deetjen J, Kretschmer A, Steppan S, Volsek M, Kribben A, Nierhaus M, Jankowski V, Zidek W, Jankowski J: Relationship between magnesium and clinical biomarkers on inhibition of vascular calcification. Am J Nephrol 2012;35:31–39.

26 Sage A, Tintut Y, Garfinkel A, Demer L: Systems biology of vascular calcification. Trends Cardiovasc Med 2009;19:118–123.

27 Luft FC: Vascular calcification and magnesium. J Mol Med (Berl) 2010;88:437–439.

28 Li Q, Larusso J, Grand-Pierre AE, Uitto J: Magnesium carbonate-containing phosphate binder prevents connective tissue mineralization in *Abcc6(–/–)* mice-potential for treatment of pseudoxanthoma elasticum. Clin Transl Sci 2009;2:398–404.

29 Kupetsky-Rincon EA, Li Q, Uitto J: Magnesium reduces carotid intima-media thickness in a mouse model of pseudoxanthoma elasticum: a novel treatment biomarker. Clin Transl Sci 2012;5:259–264.

30 Kobolos G AH, Prohaszka Z, Tordai A, Varadi A, Aranyl T: The R1141X loss-of-function mutation of the ABCC6 gene is a strong genetic risk factor for coronary artery disease. Genet Test Mol Biomarkers 2010;14:75–78.

31 Germain DP, Boutouyrie P, Laloux B, Laurent S: Arterial remodeling and stiffness in patients with pseudoxanthoma elasticum. Arterioscler Thromb Vasc Biol 2003;23:836–841.

32 Turgut F, Kanbay M, Metin MR, Uz E, Akcay A, Covic A: Magnesium supplementation helps to improve carotid intima-media thickness in patients on hemodialysis. Int Urol Nephrol 2008;40:1075–1082.

33 Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA: Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. J Clin Epidemiol 1995;48:927–940.

34 Walker MD, Fleischer J, Rundek T, McMahon DJ, Homma S, Sacco R, Silverberg SJ: Carotid vascular abnormalities in primary hyperparathyroidism. J Clin Endocrinol Metab 2009;94:3849–3856.

35 Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB: Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. Stroke 2011;42:3017–3021.

36 Simon A, Megnien JL, Chironi G: The value of carotid intima-media thickness for predicting cardiovascular risk. Arterioscler Thromb Vasc Biol 2010;30:182–185.

37 O'Leary DH, Bots ML: Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J 2010;31:1682–1689.

38 Yamagishi T, Kato M, Koiwa Y, Omata K, Hasegawa H, Kanai H: Evaluation of plaque stabilization by fluvastatin with carotid intima-medial elasticity measured by a transcutaneous ultrasonic-based tissue characterization system. J Atheroscler Thromb 2009;16:662–673.

39 Liao F, Folsom AR, Brancati FL: Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 1998;136:480–490.

40 Larsson SC, Orsini N, Wolk A: Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. Am J Clin Nutr 2012;95:362–366.

41 Marinov MB, Harbaugh KS, Hoopes PJ, Pikus HJ, Harbaugh RE: Neuroprotective effects of preischemia intra-arterial magnesium sulfate in reversible focal cerebral ischemia. J Neurosurg 1996;85:117–124.

42 Saver JL: Targeting the brain: Neuroprotection and neurorestoration in ischemic stroke. Pharmacotherapy 2010;30:62S–69S.

43 Izumi Y, Roussel S, Pinard E, Seylaz J: Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. J Cereb Blood Flow Metab 1991;11:1025–1030.

44 Kass IS, Cottrell JE, Chambers G: Magnesium and cobalt, not nimodipine, protect neurons against anoxic damage in the rat hippocampal slice. Anesthesiology 1988;69:710–715.

45 McIntosh TK, Vink R, Yamakami I, Faden AI: Magnesium protects against neurological deficit after brain injury. Brain Res 1989;482:252–260.

46 Muir KW, Lees KR, Ford I, Davis S: Magnesium for acute stroke (intravenous magnesium efficacy in stroke trial): randomised controlled trial. Lancet 2004;363:439–445.

47 Saver JL, Kidwell C, Eckstein M, Starkman S: Prehospital neuroprotective therapy for acute stroke: results of the field administration of stroke therapy-magnesium (FAST-MAG) pilot trial. Stroke 2004;35:e106–108.

48 Abbott RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H, Yano K, Curb JD: Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). Am J Cardiol 2003;92:665–669.

49 Peters SA, den Ruijter HM, Bots ML: Attenuation of rate of change in carotid intima-media thickness by lipid-modifying drugs: impact on clinical outcomes. Am J Cardiovasc Drugs 2011;11:253–263.

50 Sivapalaratnam S, van Loendersloot LL, Hutten BA, Kastelein JJ, Trip MD, de Groot E: Long-term LDL-C lowering in heterozygous familial hypercholesterolemia normalizes carotid intima-media thickness. Atherosclerosis 2010;212:571–574.

51 Riccioni G, Vitulano N, Mancini B, Zanasi A, D'Orazio N: One-year treatment with rosuvastatin reduces intima-media thickness in 45 hypercholesterolemic subjects with asymptomatic carotid artery disease. Pharmacology 2010;85:63–67.