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Magnesium for the prevention and treatment of cardiovascular disease

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INTRODUCTION

Magnesium is an essential mineral found in the body. It is naturally present in many foods and is also available as a dietary supplement.[1] It serves as a cofactor in more than 300 enzymatic reactions, such as those responsible for regulating blood pressure, glycaemic control and lipid peroxidation. It is therefore also critical to the cardiovascular system.[1] The adult body contains approximately 24 g of magnesium, with 50% to 60% present in bones with the rest being contained in soft tissues. Serum magnesium represents less than 1% of total body magnesium.[2] In industrialised western countries, a low intake of magnesium often predisposes to a high prevalence of magnesium deficiency increasing the risk of cardiovascular events and cardiovascular death.[3] This article aims to review of effect of magnesium deficiency on the cardiovascular system.

BIOCHEMICAL INTERACTIONS OF MAGNESIUM IN CARDIOVASCULAR DISEASES

In recent studies of hospitalised patients, 42% were shown to be hypomagnesaemic.[4] However, physicians request magnesium testing in only 7% of these patients.[4] In a study conducted among patients in the intensive cardiac care unit, 53% of patients had mononuclear cell magnesium content below the lowest normal control.[5]

Clinically, serum magnesium is usually measured despite the fact that less than 1% of magnesium exists extracellularly; hence, serum magnesium does not always accurately reflect total body magnesium stores. In fact, serum magnesium levels may be normal despite depletion of total body magnesium content.[5] In experimental settings, total body magnesium stores can be estimated by measuring retention of an oral or intravenous magnesium load; however, measurement is cumbersome and requires a 24-hour urine collection.[6 7] In many instances, intracellular levels of magnesium serve as a better indicator for total body magnesium content compared with serum magnesium levels with the most accurate test being blood mononuclear cell magnesium.[8] Intracellular mononuclear magnesium content also correlates better with cardiac magnesium status.[9–12]

Magnesium plays diverse roles in the pathogenesis of cardiovascular diseases on the biochemical and cellular levels. First, magnesium activates adenosine triphosphatase (ATPase), which is essential for cell membrane functioning and is also the energy source of the Na+–K+ pump.[13] In rat models, magnesium deficiency has been shown to decrease the activity of the Na+–K+ pump, leading to an increase in intracellular sodium, which alters the membrane potential.[14] In studying the sodium kinetic and membrane potential in the aorta of magnesium-deficient rats, Madden *et al* also showed that magnesium deficiency caused the membrane potential to be less polarised as a result of intracellular sodium accumulation, suggesting Na+–K+pump inhibition.[15] This change in membrane potential has been hypothesised as a potential mechanism for causing arrhythmias. Magnesium is also known to be a cofactor important for the functioning of the enzymes in cardiac mitochondria. Additionally, magnesium has been demonstrated to modulate the potassium-proton exchange. Cation selectivity in sodium and potassium exchange for protons is highly dependent on magnesium. Thus, magnesium also protects against potassium loss. Intracellular magnesium deficiency may also cause an increase in intracellular sodium and calcium, which predisposes to arterial vasospasm, increased catecholamine release, increased fatty acids and lipids, as well as intravascular hypercoagulability.[13 16]

Furthermore, magnesium deficiency has been shown to play a role in inflammation in the rat model. Weglicki *et al* showed that during progression of magnesium deficiency, there is an increase in the serum levels of

inflammatory cytokines interleukin-1, interluein-6 and tumour necrosis factor after 3 weeks of magnesium-deficiency diet.[17] Magnesium deficiency also leads to an exaggerated response to immune stress and oxidative stress through activation of neuroendocrinological pathways. This inflammatory response predisposes to proatherogenic changes in lipoprotein metabolism, endothelial dysfunction, thrombosis and hypertension, contributing to the pathogenesis of metabolic syndrome as well as cardiovascular diseases.[3]

EPIDEMIOLOGY

Despite the importance of magnesium for the proper functioning of the cardiovascular system, surveys and studies have shown that dietary magnesium intake is often inadequate in the USA, which is consistent with the pattern observed in North European countries. Several factors were thought to be contributory, including the loss of magnesium during food processing, low magnesium content of vegetarian diets, metabolic effects exerted by pregnancy, osteoporosis medication therapy, alcoholism, stress, as well as the differing magnesium content in water.[18] Human dietary requirement for essential minerals such as magnesium is not precisely known. Based on earlier balance studies, recommended dietary magnesium intakes were 300 to 354 mg/day for American women and 420 to 483 mg/day for American men.[19] However, other studies have indicated that around 180 mg of magnesium per day may be enough to maintain positive magnesium balance.[8] Actual intakes in American women and men are approximately 228 mg/day and 331 mg/day, respectively.[19]

Interestingly, there may be an association between cardiovascular disease and drinking water hardness due to its differing magnesium content. A study by Catling *et al* systematically reviewed observational epidemiological studies investigating the association between levels of drinking water hardness and cardiovascular disease. Of the seven studies included that examined drinking water magnesium and risk of death from cardiovascular disease, a pooled OR of 0.75 (95% CI 0.68 to 0.82) showed a statistically significant inverse correlation between magnesium and cardiovascular mortality.[20] Additionally, changes in water hardness and a change to soft water tended to predispose to increased death rates from cardiovascular diseases including heart attacks and strokes.[21] Autopsies of patients in soft-water areas who died from non-cardiac causes were found to have lower levels of magnesium in cardiac tissues, more coronary atheroma and evidence of myocardial ischaemia compared with residents living in hard water areas.[21 22] However, the results of these studies may be confounded by the presence of many other trace elements found in hard water, such as calcium, which have also been found to have beneficial effects in preventing cardiovascular diseases. The magnesium content also differed among the hard waters in the studies, representing another confounding factor. Other studies have found no difference in cardiovascular disease morbidity and mortality in hard-water versus soft-water regions.[23–27]

HYPERTENSION

Hypertension is a complex, multifactorial, heterogeneous disorder for which the exact aetiology has yet to be elucidated. Clinical and experimental trials have suggested that magnesium may play a role in the pathogenesis of hypertension by affecting arterial smooth muscle contraction. Magnesium is found mainly at the inner surface of cell membranes. Therefore, it plays a role in cell membrane permeability for sodium and calcium.[28] Magnesium activates the Na+–K+–ATPase pump, which plays a major role in regulating sodium and potassium transport by moving potassium into the cells and sodium out of the cells. Alterations in vascular membrane magnesium can also result in leaky arterial and arteriolar membranes, thus contributing to the intracellular reduction of potassium and the gain of calcium and sodium. Increased intracellular calcium can then lead to hypertension, vasospasm, as well as potentiation of vasoconstrictor agents.[29]

A number of observational and experimental studies have supported the role of magnesium depletion in the pathogenesis of hypertension. Hypertension has been shown to develop in magnesium-deficient rats.[30] In humans, a similar effect of magnesium deficiency was observed. A study by Shibutani *et al* studying a group of 380 Japanese junior high school students found that higher systolic blood pressure was associated with positive family history of hypertension as well as lower serum and erythrocyte magnesium levels, suggesting that magnesium deficiency may at least be partially responsible for a rise in blood pressure in the students with positive family history of hypertension, and that a genetic predisposition of hypertension maybe closely related to magnesium deficiency.[31]

Multiple studies have analysed the effect of magnesium supplementation on blood pressure. The effect of water with added magnesium and natural mineral water on blood pressure have been studied by dividing a group of 70 subjects with borderline hypertension into consuming water low in minerals, magnesium-enriched water and natural mineral water for 4 weeks. Among persons with initial low excretion of magnesium (suggesting magnesium deficiency), the subjects consuming the two waters containing magnesium after 4 weeks had a significant decrease in blood pressure.[32] In a meta-analysis conducted by Zhang *et al* including randomised double-blind placebo control trials, magnesium supplementation at a median dose of 368 mg/day for a median duration of 3 months was found to significantly reduce systolic blood pressure (SBP) by 2.00 mm Hg (95% CI 0.43 to 3.58) and diastolic BP (DBP) by 1.78 mm Hg (95% CI 0.73 to 2.82). Additionally, these reductions were accompanied by 0.05 mmol/L (95% CI 0.03 to 0.07) elevation of serum magnesium compared with placebo.[33] Similarly, Kass *et al* also found that magnesium supplementation leads to a

small but clinically significant reduction in both DBP and SBP (SBP of 3 to 4 mm Hg and DBP of 2 to 3 mm Hg).[34] These studies suggest that magnesium supplementation may be beneficial for lowering blood pressure in certain patient populations.

The effect of magnesium supplementation on patients taking diuretics has been studied in several trials. Hattori *et al* looked at 20 patients with essential hypertension receiving long-term thiazide diuretic treatment and 21 age-matched untreated patients. The diuretic group received magnesium supplementation for 4 weeks. There were significant decreases in intra-erythrocyte sodium content and mean blood pressure, as well as increases in red cell magnesium content in the diuretic group who received magnesium supplementation. The effect of magnesium on blood pressure reduction was more evident in the nine patients who were unresponsive to diuretic therapy.[35] In a meta-analysis involving 135 hypertensive subjects on antihypertensive medications, Rosanoff and Plesset found that oral magnesium supplementation decreases both systolic (mean change of −18.7 mm Hg (95% CI −14.95 to −22.45)) and diastolic blood pressures (−10.9 mm Hg (95% CI −8.73 to −13.1)).[36]

CARDIOMYOPATHY

Magnesium deficiency has been implicated in the cause of cardiomyopathy in both animal models and studies involving humans. In animal models, hamsters fed a magnesium-deficient diet developed a cardiomyopathy with foci of myocardial necrosis, calcification and modest mononuclear and giant cell infiltration. Additionally, hamsters given nifedipine had a dose-dependent reduction in lesion abundance and diameter, while hamsters given digoxin produced a dose-dependent increase in lesion abundance and diameter. These results support the hypothesis that the lesions are secondary to calcium overload following an increase in myocardial sodium due to inhibition of the Na+–K+–ATPase and secondary sodium, calcium exchange in a magnesium-deficient state.[37] In a different study involving Syrian male hamsters fed either a magnesium-deficient diet or identical diet supplemented with 100 mmol/kg of MgCl, animals were found more vulnerable to ischaemia-induced damage to the heart when magnesium deficient at the time the animals were sacrificed.[38] The release and effects of catecholamines have been shown to intensify during cellular magnesium depletion. The detrimental effect of catecholamine excess and magnesium deficiency has been found to be synergistic in the myocardium. In rabbits, magnesium supplementation has been found to reduce the ultrastructural features of myocardial damage induced by epinephrine injection without an effect on changes in intracellular distribution of calcium induced by epinephrine.[39]

In humans, studies also support the role of magnesium in cardiomyopathy. Patients with hypoparathyroidism can manifest cardiomyopathy, which responds to magnesium supplementation.[40] Cardiomyopathy and magnesium deficiency are commonly observed in patients with heavy alcohol consumption.[41] Additionally, people who live in low magnesium equatorial areas, and those consuming a magnesium-deficient diet, have developed spontaneous endomyocardial fibrosis of undetermined aetiology.[41–43]

CONGESTIVE HEART FAILURE

Magnesium deficiency is commonly found in patients with congestive heart failure due to various mechanisms. Patients with congestive heart failure may have an increased urinary excretion of magnesium, secondary to decreased tubular absorption of magnesium as a result of increased extracellular volume and the effects of secondary hyperaldosteronism found in heart failure. Medications, such as diuretics and digoxin, can also worsen the problem and decrease tubular reabsorption of magnesium. Hyperactive renin–angiotensin system may further elevate aldosterone levels in the body, further exacerbating a state of magnesium deficiency. Additionally, norepinephrine in a state of heart failure has been shown to reduce magnesium through increased fatty acids.[44–52] Adding to the vicious cycle, magnesium deficiency may worsen hyperaldosteronism, which may lead to fluid retention.

In patients with heart failure, hypomagnesaemia also predisposes to hypokalaemia, therefore increasing the chance of developing ventricular arrhythmias and haemodynamic derangements. Finally, magnesium depletion may worsen cardiac contractility, increase vasoconstriction and deplete cardiac energy stores.[53] Magnesium deficiency has even been shown to worsen clinical outcomes in patients with congestive heart failure. Micronutrient deficiency is found to be independently predictive of poor health-related quality of life (HRQoL) and shorten cardiac event-free survival in patients with heart failure.[54] Storm and Zimmerman reported a case of cardiogenic shock developing after cardiopulmonary bypass that was initially unresponsive to therapeutic intervention, which resolved promptly after magnesium administration.[55] Gottlieb *et al* found that patients with normal versus low magnesium levels had 2-year survival rates of 61% and 42%, respectively. It was hypothesised that hypomagnesaemia lead to deaths due to ventricular arrhythmias.[56]

Because electrolyte abnormalities are a frequent and potentially hazardous complication in patients with heart failure, magnesium likely improves outcomes in patients with congestive heart failure by preventing ventricular arrhythmias. Bashir *et al* investigated the effect of oral magnesium supplementation in a randomised, double-blind, cross-over trial involving 21 patients with stable congestive heart failure secondary to coronary artery disease and who were receiving long-term loop diuretics. Oral magnesium supplementation was found to lower mean arterial pressure, systolic vascular resistance and the frequency of isolated ventricular premature complexes, couplets and non-sustained ventricular

tachyarrhythmia.[57] However, more studies are needed to establish whether routine supplementation of magnesium in patients with heart failure is warranted. In fact, Ralston *et al* showed that the prevalence of hypomagnesaemia in ambulatory patients with dilated cardiomyopathy is relatively low (9%); however, magnesium is 99% intracellular and hence there is a poor correlation between serum, mononuclear cells, skeletal muscles cells and cardiac muscle cell magnesium levels.[58]

CARDIAC ARRHYTHMIA

The importance of magnesium supplementation in preventing arrhythmias in patients with congestive heart failure has long been established. Magnesium deficiency can lead to QT interval prolongation, ST-segment depression and low amplitude T waves.[59–61] Magnesium also influences the movement of other ions such as potassium, sodium and calcium across the cell membranes. The association between magnesium and potassium is probably best demonstrated in that magnesium deficiency is often accompanied by potassium deficiency. In patients with congestive heart failure, both magnesium and potassium are depleted with thiazide diuretics, particularly in patients requiring high doses of thiazide diuretics.[62–65] It has been shown that the level of potassium in muscle will not normalise unless magnesium is replaced, even though serum potassium rises with repletion.[62 66 67] The ominous role of magnesium depletion in predisposing to arrhythmias in patients with congestive heart failure is perhaps best demonstrated in a recent prospective study showing that among the 66% of patients with cardiac arrest who had magnesium abnormalities, none were successfully resuscitated.[68]

SUPRAVENTRICULAR TACHYCARDIA

A large percentage of patients with supraventricular arrhythmias have an intracellular magnesium deficiency despite having normal serum magnesium concentrations, and this may explain the rationale for magnesium's benefits as an atrial antiarrhythmic agent.[69] Magnesium enhances atrial antiarrhythmic efficacy when used as monotherapy.[69] Maurat *et al* found that in vitro, changes in atrial action potential can be induced experimentally by a fall in extracellular potassium or by digoxin overdose. Increasing magnesium concentration in the medium can correct these changes in atrial action potential. Magnesium does not seem to act on the Na+–K+–ATPase activity but rather exert its effect through moderating the calcium inflow into the cell, which is favoured by hypomagnesaemia.[70] In the Framingham Heart Study, individuals in the lowest quartile of serum magnesium were 50% more likely to develop atrial fibrillation compared with those in the upper quartiles. Results were similar after the exclusion of individuals on diuretics. As a result, low serum magnesium is moderately associated with development of atrial fibrillation in individuals without cardiovascular disease.[71] To make matters worse, hypomagnesaemia is common among patients with symptomatic atrial fibrillation,[72] and replacement of magnesium deficiency may be beneficial in patients with symptomatic atrial fibrillation who are receiving digoxin therapy. Similarly, a study by Lewis *et al* suggested that treatment with magnesium may be associated with a decreased prevalence of ventricular ectopy in some patients receiving digoxin with chronic atrial fibrillation and mild–moderate hypomagnesaemia.[73]

However, not all studies find a clinically significant association between hypomagnesaemia and improved outcomes in atrial fibrillation. Eray *et al* assessed the effect of magnesium supplementation on lowering the rate in patients with atrial fibrillation with rapid ventricular response and evaluated the effect of this therapy in magnesium-deficient and non-deficient patients. The decrease in the ventricular rate was statistically significant at 15, 30 and 60 min after magnesium therapy; however, there was no difference in the response to magnesium between magnesium-deficient and non-deficient patients. The authors concluded that magnesium supplementation had a statistically significant but clinically limited effect on ventricular rate and its effect did not differ between patients with and without magnesium deficiency.[74]

In addition to atrial fibrillation, the effect of hypomagnesaemia has also been studied in other forms of supraventricular dysrhythmias. Cohen *et al* studied two groups of patients with multifocal atrial tachycardia treated with intramuscular and continuous intravenous magnesium and found that both routes of administration were successful in reverting patients back to sinus rhythm. However, the intramuscular regimen attains higher and more sustained serum concentrations.[75] In a separate study, seven patients with congestive heart failure receiving long-term diuretics as well as digoxin experienced idional tachycardia. Intravenous administration of magnesium followed by intramuscular magnesium repletion was noted to abolish the arrhythmias. Interestingly, decreased lymphocyte magnesium and potassium content but normal serum magnesium levels were found in five patients, again suggesting that normal serum magnesium does not preclude total body magnesium deficiency, and a decreased cellular magnesium level predisposes to digitalis-induced arrhythmias.[76]

VENTRICULAR ARRHYTHMIA

Magnesium therapy has also been shown to be effective in patients with ventricular tachycardia. Magnesium supplementation may be a viable therapeutic option when other antiarrhythmic agents fail to suppress ventricular tachycardia and ventricular fibrillation.[77] In animal models, magnesium-deficient dogs showed increased pressor sensitivity to epinephrine as determined by the dose of epinephrine required to cause a maximum pressor response. Magnesium-deficient dogs also had a significantly lower threshold for triggering

ventricular premature beats. Administration of magnesium in these dogs restored the pressor sensitivity level and abolished premature ventricular beats.[78] In humans, a significant increase in cellular potassium content and likewise a significant decrease in frequency of ventricular ectopic beats were noted after magnesium infusions.[63] Magnesium may be exerting its antiarrhythmic effects by preventing prolonged QTc. Krasner *et al* studied 24 patients scheduled electively for mitral valve replacement and found that all patients who developed arrhythmias postoperatively had not been pretreated with oral magnesium and had abnormal QTc intervals both before and after operation.[79]

The role of intravenous magnesium supplementation has also been studied in patients with acute myocardial infarction who received thrombolytic therapy. Ventricular arrhythmias were less in the experimental group supplemented with magnesium, suggesting that magnesium supplementation may be a safe and effective adjuvant to thrombolytic therapy in reducing the short-term mortality and ventricular arrhythmias after acute myocardial infarction.[80] Magnesium depletion has long been associated with severe ventricular arrhythmias such as torsades de pointes. Papaceit *et al* reported a case of a patient with chronic magnesium depletion who developed torsades de pointes and had good response to magnesium supplementation.[81] However, magnesium supplementation has not been shown to reduce implantable cardioverter-defibrillator (ICD) firing rates. The trial, however, was underpowered. More prospective, large, randomised controlled trials are needed to further elucidate the effect of magnesium supplementation on ventricular arrhythmias in ICD patients.

SUDDEN CARDIAC DEATH

A link between magnesium deficiency and sudden cardiac death has been suggested by a number of studies published over the past few decades. Data from epidemiological, autopsy, clinical and animal studies suggest that sudden cardiac death is more common in areas where community water supplies are low in magnesium content. Additionally, myocardial magnesium content is found to be low in patients who died of sudden cardiac death. Sudden cardiac death secondary to magnesium deficiency may be secondary to cardiac arrhythmias and coronary artery vasospasm. Finally, repletion of magnesium has been found to reduce the risk of arrhythmias and death after an acute myocardial infarction.[82]

Magnesium likely predisposes to sudden cardiac death through several mechanisms. First, magnesium deficiency sensitises the myocardium to toxic effects of various drugs as well as to hypoxia. Therefore, magnesium supplementation may have significant cardioprotective effects. Second, magnesium activates the Na–K–ATPase, which may be inhibited by non-glucose fuels such as lactate and free fatty acid in the setting of ischaemia. Third, deficiency in magnesium may also lead to chronic electrical instability of the myocardium by affecting the sodium and calcium flow into the cells.[83] A fourth potential mechanism is via the effect of hypomagnesaemia on vascular tone. In in vitro experiments, extracellular magnesium ions have been found to exert a profound beneficial influence on the contractility and reactivities of the arteries, arterioles and veins from a number of regional vasculatures and in several mammalian species, including humans. Hypomagnesaemia has also been observed to increase the contractile activity of a variety of neurohumoral substances and to potentiate vasospasm, likely by controlling the entry and distribution of calcium ions into the cells. Coronary vasospasm has thus been suggested as a possible mechanism of sudden cardiac death.[84] Other experiments have taken isolated coronary arteries from dogs and exposed them to different concentrations of magnesium in the medium. High concentrations of magnesium were found to decrease the basal tension of the coronary arteries, whereas sudden withdrawal of magnesium increased the contractile function of both small and large coronary arteries.[85] Similarly, Altura also found that lowering the magnesium contents around perfused arterioles can lead to spontaneous vasoconstriction as well as increased arteriolar resistance, tissue ischaemia and reduced venous outflow. Lastly, the concentration of circulating vasoconstrictor hormones, such as angiotensin, serotonin and acetylcholine, are increased when extracellular magnesium is lower than normal.[86] It is possible that hypomagnesaemia produces progressive vasoconstriction and vasospasm, which then leads to ischaemia, giving rise to sudden cardiac death overtime.

Ways to supplement magnesium as a possible method to reduce sudden cardiac death include changing dietary habits to include magnesium-rich foods, adding magnesium to community water supplies, fortifying foods with magnesium as well as oral supplementation.[82] More prospective, large-scale studies are needed to study the effect of magnesium supplementation as a means of primary prevention for sudden cardiac death.

ATHEROSCLEROSIS

Magnesium deficiency has been shown to play a role in lipoprotein metabolism and may be contributing to atherosclerosis as a cardiovascular risk factor. Endothelial cells cultured in low magnesium have been found to activate nuclear factor-kappa beta, which may in turn trigger the downstream cytokine network. Low magnesium levels in culture also increases the endothelial cell secretion of RANTES (regulated on activation, normal T cell expressed and secreted), interleukin 8 and platelet-derived growth factor-BB. All play an important role in atherogenesis. Additionally, endothelial cells when exposed to low magnesium increase the secretion of matrix metalloprotease-2 and matrix metalloprotease-9 and their inhibitor, tissue inhibitor of metalloproteinases (TIMP-2). All of these pathways lead to endothelial dysfunction by promoting the expression

of inflammatory cytokines in a state of magnesium deficiency.[87]

In rats fed a short-term magnesium-deficient diet, there is a reduction in the serum magnesium level, sphingomyelin level, phosphatidylcholine, high-density lipoprotein (HDL) cholesterol and the phosphatidylcholine:cholesterol ratio, concomitant with decreases in tissue levels of glutathione, leakage of cardiac creatine kinase (CK) and lactic dehydrogenase (LDH), as well as activation of nitric oxide synthetase (e-NOS and n-NOS) in all chambers of the heart. In addition, the changes in these parameters are dose dependent on the degree of magnesium deficiency, and they can lead to oxidative stress. Reductions in glutathione content as well as activation of e-NOS and n-NOS in various chambers of the heart have been hypothesised to produce early cardiac damage characterised by leakage of CK and LDH. Additionally, rats exposed to low dietary magnesium had de novo synthesis of ceramide, which was attenuated by inhibition of sphingomyelinase and serine palmitoyl CoA transferase. Hence, the activation of the sphingomyelin–ceramide pathway in a state of magnesium deficiency may also play a role in the pathogenesis of atherosclerosis.[88] Low magnesium concentrations may also reversibly inhibit endothelial proliferation and alter endothelial migration via significant downregulation of CDC25B and an upregulation of interleukin-1 (IL-1), vascular cell adhesion molecule-1 and plasminogen activator inhibitor-1 after magnesium deficiency leading to a pro-atherosclerotic state.[89]

In one study, the effects of thiamine, magnesium and sulfate salts on the growth, thiamine levels and serum lipid level were tested in rats. Deficiency of both magnesium and sulfate salts in thiamine-supplemented groups decreased body weight gain and liver thiamine content, but elevated serum triglycerides.[90] Animals given cyclophosphamide or methotrexate also had greater cardiac damage while on a low magnesium diet via its effect on blood lipid levels and atherogenesis.[91] In humans, long-term magnesium deficiency has been found to lower serum magnesium levels and increase levels of lipids as well as serum glucose. In young, apparently healthy athletes, persistent magnesium deficiency as a result of strenuous physical activity was found to correlate with long-term increases in cholesterol, triglycerides and blood sugar.[92] These studies suggest that magnesium supplementation may be beneficial as treatment for the primary prevention of atherosclerosis.

CORONARY VASOSPASM

Multiple studies have suggested a link between magnesium deficiency and coronary artery spasm. Magnesium controls the movement of calcium into smooth muscle cells, leading to smooth muscle contraction. In dogs, coronary arteries incubated in low magnesium solutions are predisposed to vasospasm.[85] Additionally, low magnesium solution can significantly increase the potential for contractile responses of both small and large arteries to norepinephrine.[85] Experiments of intact dogs[93] and isolated coronary arteries of pigs also showed similar results.[94] Low magnesium levels have been associated with variant angina in humans, and measurement of erythrocyte magnesium content is useful to determine how easily vasospasm may occur.[95] Guo *et al* also evaluated the intracellular and extracellular magnesium status in 12 women with variant angina and found that the 24-hour magnesium retention rate and intracellular concentrations of magnesium in erythrocytes correlated well with the activity of variant angina.[96] Teragawa *et al* demonstrated that magnesium infusion can produce non-site-specific basal coronary dilatation and suppresses acetylcholine-induced coronary spasm in patients with vasospastic angina. Magnesium infusion was also effective in reducing the severity of chest pain and ST-segment deviations during coronary spasm. After the magnesium infusion, the per cent change in the diameter of the spastic segments improved from −62.8±2.6% to −43.7±4.7% during coronary spasm.[97] These studies suggest that magnesium may be beneficial for symptom control in patients with variant angina.

OXIDATIVE STRESS AND MYOCARDIAL INJURY

Evidence suggests that magnesium deficiency plays a role in myocardial infarction via increased oxidative stress. Magnesium deficiency has been associated with the production of reactive oxygen species, cytokines, as well as vascular compromise in vivo.[98] Magnesium deficiency has also been shown to produce myocardial lesions in different animal models. In rats fed a diet deficient in magnesium, there is a significant lowering of superoxide dismutase and catalase in the rat heart, leading to depressed antioxidant defence in the heart and increased myocardial susceptibility to oxidative injury.[99] Hans *et al* also demonstrated that magnesium deficiency is associated with increased oxidative stress through reductions in plasma antioxidants and increased lipid peroxidation, suggesting that the increased oxidative stress may be due to increased susceptibility of body organs to free radical injury.[100] In Syrian hamsters placed on a magnesium-deficient diet, oxidation (isoprenaline)-induced injury was dramatically increased in magnesium-deficient rats.[101] This finding suggests that magnesium deficiency increases the susceptibility of the cardiovascular system to oxidative damage. In humans, similar findings were reported. Kharb and Singh estimated serum malonaldehyde (MDA), magnesium, vitamin E and total glutathione levels (GSH) in 22 patients with acute myocardial infarction and 15 healthy controls. Low levels of magnesium, GSH, vitamin E and elevated levels of MDA were observed in patients with acute myocardial infarction. The findings suggest that magnesium deficiency can potentiate oxidative injury in post-ischaemic myocardium.[102]

Patients with acute myocardial infarction also tend to have lower magnesium content, particularly in the early hours after infarction. Urdal *et al* studied mononuclear

cell magnesium and retention of magnesium after intravenous loading in patients with acute myocardial infarction compared with healthy volunteers. The study found that mononuclear cell magnesium concentrations before magnesium retention test were slightly higher in patients with acute myocardial infarction compared with healthy volunteers indicting no magnesium depletion in the acute myocardial infarction group. However, when magnesium retention test was performed 4–11 days after admission in the subjects with acute myocardial infarction, the retention of magnesium was 45±23% of the 30 mmol given intravenously (retention of more than 20% generally represents magnesium deficiency). It is unclear what caused the increased retention of magnesium during the acute phase of myocardial infarction, but it may be due to increased concentrations of circulating catecholamines during the early hours of myocardial infarction.[103] Rasmussen *et al* also found that patients with ischaemic heart disease both with and without acute myocardial infarction retained significantly more magnesium than did the control group of healthy volunteers. The increase in magnesium retention points to a state of magnesium deficiency in patients with ischaemic heart disease. Unsurprisingly, when the patients with ischaemic heart disease were subgrouped according to long-term diuretic treatment, the patients receiving long-term diuretic treatment had a 39% retention of magnesium (11.6 mmol/L (28.2 mg/dL)) compared with a 29% retention (8.7 mmol/L (21.1 mg/dL)). This study indicates that patients with ischaemic heart disease may be severely magnesium deficient and that long-term diuretic treatment may contribute to this deficiency.[104] The beneficial effect of intravenous magnesium treatment in acute myocardial infarction has also been demonstrated in regards to reducing both mortality and early cardiac insufficiency. Besides antiarrhythmic and vasodilatator effects, magnesium also seems to protect cardiac cells against the harmful effects of ischaemia.[70]

THROMBOSIS

In both animals and human models, magnesium deficiency has been linked to a prothrombotic state. In an uncontrolled study in 1954, Parsons *et al* found that patients with angina or myocardial infarction had a reduced death rate, from 30% to 1%, if they were treated with magnesium sulfate intramuscularly. The improvement was thought to be secondary to favourable effects in reducing the inhibition of plasmin, an enzyme that plays an essential role in fibrinolysis and responsible for the degradation of fibrin clots.[105] A more recent study in 1986 demonstrated that bleeding time increased with magnesium infusion in patients with acute myocardial infarction.[106] Magnesium has been shown to inhibit ADP-induced platelet aggregation.[107] In patients with pre-eclampsia, treatment with magnesium infusion has been shown to reduce certain clotting factors.[108] In a 1989 paper, Paolisso *et al* found that magnesium administration can reduce platelet hypercoagulability in patients with non-insulin-dependent diabetes.[109] Shecter also found that low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease by exposing porcine aortic media to their flowing un-anticoagulated venous blood for 5 min by using an ex vivo perfusion chamber.[110] These studies suggest that magnesium may play a role in thrombosis and supplementation with magnesium may be beneficial in certain population of patients.

MAGNESIUM AND MITRAL VALVE PROLAPSE

The mechanism of mitral valve prolapse has not been fully elucidated. However, magnesium deficiency has been proposed to be related to mitral valve prolapse syndrome. In a study comparing 49 subjects with mitral valve prolapse to age-matched and gender-matched subjects without mitral valve prolapse, both groups were found to have similar serum magnesium levels. However, subjects with mitral valve prolapse had lower magnesium levels in the lysate of their lymphocytes. The results suggest that lymphocyte magnesium deficiency may play a role in mitral valve prolapse.[111] In a separate study by Licholdzie-jewska *et al*, serum magnesium levels in 141 subjects with heavily symptomatic mitral valve prolapse and 40 healthy subjects were compared. The group found that many patients with heavily symptomatic mitral valve prolapse have low serum magnesium, and magnesium supplementation leads to improvement in most symptoms such as chest pain, dyspnoea, weakness, palpitations and anxiety along with a decrease in catecholamine excretion.[112] Further studies are needed to further elucidate the relationship between magnesium deficiency and mitral valve prolapse syndrome.

DIABETES AND GLYCAEMIC CONTROL

Magnesium deficiency has also been implicated in the pathogenesis of diabetes and poor glycaemic control. In animal models, magnesium deficiency as well as excess sucrose intake has been shown to be associated with the generation of reactive oxygen species. When male Wistar rats were divided into groups fed control, low-magnesium, high-sucrose and low-magnesium high-sucrose diet for a period of 3 months, the rats fed high sucrose and low magnesium diet were found to have significantly higher levels of lipid peroxidation in the plasma and liver tissue; however, the same effect was not observed in the other groups. These findings suggest that a diet low in magnesium and high in sucrose causes oxidative stress in rats, as reflected by increased lipid peroxidation and reduced antioxidant potential.[113] In humans, randomised double-blind placebo-controlled trials have been done to study the effect of magnesium deficiency in diabetic patients. In a study conducted by Simental-Media *et al*, 62 men and non-pregnant women with a diagnosis of pre-diabetes and hypomagnesaemia were enrolled in the double-blind, placebo-controlled trial to receive either

magnesium supplementation or placebo. At the end of the trial, subjects receiving magnesium supplementation were found to have higher levels of serum magnesium, as well as lower levels of high-sensitivity C reactive protein.[114] In a separate randomised controlled trial, Guerrero-Romero *et al* showed that supplementation of oral magnesium in subjects with pre-diabetes and hypomagnesaemia improved glycaemic control. At the end of the follow-up period, subjects in the treatment group had significantly lower fasting and post-load glucose, homeostatic model assessment for insulin resistance indices and triglycerides, whereas HDL cholesterol and serum magnesium levels were significantly increased in those receiving magnesium supplementation. Remarkably, a total of 50.8% of those in the magnesium treatment group improved their glycaemic level compared with only 7% in the placebo group.[115]

STROKE

Hypomagnesaemia has also been found to be a risk factor for cerebrovascular events and complications. Szabo *et al* found that a slight decrease in extracellular magnesium from 1.2 to 0.8 mM resulted in sustained relaxation when the endothelium was intact; however, when the endothelium was interrupted, the slight reduction in magnesium resulted in elevation of vascular tone. These results suggested that magnesium modules human cerebra-arterial tone through an endothelium-derived relaxing factor rather than by altering smooth muscle tone directly, and magnesium deficiency appears to drive endothelial dysfunction and hence atherosclerosis.[116] Amighi *et al* investigated the prognostic impact of magnesium serum levels with respect to the occurrence of neurological events in patients with advanced atherosclerosis in 323 patients with symptomatic peripheral artery disease and intermittent claudication. Compared with patients in the highest tertile of magnesium serum levels (>0.84 mmol/L), patients with magnesium serum values <0.76 mmol/L (lowest tertile) exhibited a 3.29-fold increased adjusted risk (95% CI 1.34 to 7.90; p=0.009) for neurological events. However, patients with magnesium serum values of 0.76 mmol/L to 0.84 mmol/L (middle tertile) had no increased risk (adjusted HR 1.10; 95% CI 0.35 to 3.33; p=0.88). Hence, low serum magnesium levels appear to correlate with an increased risk for neurological events, defined as ischaemic stroke and/or carotid revascularisation.[117] In a different study involving 40 patients with acute ischaemic strokes, low serum magnesium concentration was found to correlate with the intensity of neurological deficit at 48 hours after the onset of ischaemic stroke, as measured by the National Institute of Health Stroke Scale. Severity of paresis was also higher in patients with low serum magnesium levels.[118] In summary, these studies seem to suggest that magnesium plays an important role in the pathogenesis of acute ischaemic stroke. However, more studies are necessary to further elucidate the mechanism by which magnesium exerts these effects in the cerebral–vascular system.

CONCLUSION

Magnesium plays an important role in cardiovascular health. It is instrumental for the proper maintenance of cellular membrane potential, functioning of the mitochondria and plays a key role in the body's antioxidative pathways. As a result, magnesium deficiency can lead to serious morbidity and mortality, and has been implicated in multiple cardiovascular diseases such as hypertension, cardiomyopathy, cardiac arrhythmia, atherosclerosis, dyslipidaemia and diabetes. Unfortunately, the western diet is often low in magnesium due to the refining and processing of foods, and hypomagnesaemia is often underdiagnosed in hospitalised patients. Studies have suggested that prompt diagnosis and timely supplementation of magnesium may be beneficial in patients with certain cardiac conditions. However, more prospective, randomised controlled trials are needed to be able to further elucidate the value of magnesium as a therapy to prevent or reverse some of the aforementioned cardiovascular conditions.

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