Magnesium and Cardiovascular Disease

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Magnesium is the most abundant intracellular divalent cation and essential for maintaining normal cellular physiology and metabolism, acting as a cofactor of numerous enzymes, regulating ion channels and energy generation. In the heart, magnesium plays a key role in modulating neuronal excitation, intracardiac conduction, and myocardial contraction by regulating a number of ion transporters, including potassium and calcium channels. Magnesium also has a role in regulating vascular tone, atherogenesis and thrombosis, vascular calcification, and proliferation and migration of endothelial and vascular smooth muscle cells. As such, magnesium potentially has a major influence on the pathogenesis of cardiovascular disease. As the kidney is a major regulator of magnesium homeostasis, kidney disorders can potentially lead to both magnesium depletion and overload, and as such increase the risk of cardiovascular disease. Observational data have shown an association between low serum magnesium concentrations or magnesium intake and increased atherosclerosis, coronary artery disease, arrhythmias, and heart failure. However, major trials of supplementation with magnesium have reported inconsistent benefits and also raised potential adverse effects of magnesium overload. As such, there is currently no firm recommendation for routine magnesium supplementation except when hypomagnesemia has been proven or suspected as a cause for cardiac arrhythmias.

Key Words: Magnesium, Cardiovascular, Arrhythmia, Coronary artery disease, Heart failure

INTRODUCTION

Cardiovascular disease (CVD) has been the leading cause of death globally over past 15 years and the greatest cause of premature, noncommunicable disease deaths. According to the World Health Organization report, ischemic heart disease and stroke accounted for 15 million deaths worldwide in 2015. Despite a declining trend in CVD mortality in high-income countries, there is a growing prevalence of CVD in low- and middle-income nations.[1] As such, it is important to determine potentially modifiable risk factors and establishing health promotion programs which are simple and affordable with applicable strategies.

Magnesium is an essential mineral for human health. The majority of magnesium is intracellular and although serum magnesium concentrations may not reflect intracellular magnesium, derangement of serum concentrations can lead to pathology, especially CVD. Growing evidence supports an increased CVD risk with low dietary magnesium intake and a benefit for higher magnesium on the prevention and treatment of CVD.[2-4] Mild-to-moderate magnesium deficiency might increase risk for abnormal cardiac excitation, atherosclerosis, ischemic heart disease, and congestive heart failure (HF), whereas severe magnesium deficiency can cause ventricular dysrhythmias and increase risk of sudden cardiac death. Because magnesium is a key cofactor of many enzymes, changes in intracellular and extracellular concentrations potentially involve in numerous metabolic pathways, especially as magnesium is required for energy (adenosine triphosphate [ATP])-dependent reactions. Magnesium also plays a major role in maintaining electrochemical gradients across cytoplasmic membranes, and as such, changes in magnesium concentrations alter membrane potentials and ion transport.

Patients with kidney disease are at risk of magnesium imbalances, as on one hand, a reduction in glomerular filtration rate results in magnesium retention, whereas on the other hand, a variety of disorders of kidney tubular handling of magnesium can lead to chronic hypomagnesemia. Increasingly, hypomagnesemia can be secondary to drugs including chemotherapeutic agents and diuretics, and gastrointestinal losses with proton pump inhibitors may all exacerbate magnesium imbalances and increase risk of cardiovascular complications.

ROLE OF MAGNESIUM IN THE CARDIOVASCULAR SYSTEM

Intracellular magnesium concentrations vary between 5 and 20 mmol/L, depending on the tissue type, with the highest concentrations in skeletal and cardiac muscle.[5] Within the cell, almost all magnesium is distributed between the nucleus, mitochondria, and sarcoplasmic reticulum. Approximately 4-5 mmol/L are in the cytosol, complexed with ATP (Mg^{2+}-ATP) and other phosphometabolites, with only around 0.5-1.2 mmol/L freely available.[6] Magnesium is important for cellular energy generation, as magnesium-dependent oxidative phosphorylation generates ATP, and all ATP-dependent reactions require magnesium to hydrolyze and transfer phosphate groups. As such, magnesium plays a key role in several metabolic pathways, including glycolysis, DNA synthesis and transcription, protein synthesis, intracellular signaling, regulation of ion channels generating intracellular ion currents, and determining membrane voltage.[5]

The Heart

Magnesium exerts effects on cardiac conduction and contraction predominantly by regulating ion channels. Cardiac excitation and automaticity are affected by magnesium modulating potassium and calcium channels and

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the sodium-potassium ATPase pumps (Na/K ATPase pumps) of cardiac myocytes and pacemaker cells. As such, magnesium regulates membrane potential phases 2, 3, and 4 of cardiac myocytes and phases 0 and 3 of pacemaker cells[6] as shown in Figures 1 and 2. In phase 0 of the pacemaker cells and phase 2 of cardiac myocytes, both intracellular and extracellular magnesium concentrations control calcium influx into the cells by inhibiting the L-type calcium channels (L-I_{Ca}),[7] preventing intracellular calcium overload and cell toxicity.[8] This L-I_{Ca} modulation depends on magnesium ion concentration and phosphorylation state, as binding of magnesium inhibits the phosphorylated channel from undergoing conformational changes which result in more frequent opening of this channel.[9] Acute myocardial infarction (AMI) and digitalis intoxication are examples of increased cytosol calcium, which then leads to an increased risk for arrhythmia by delayed afterdepolarization (DADs) (Fig. 3A). In phase 3, intracellular magnesium concentration controls the outward movement of potassium through inward and delayed rectifier potassium channels.[10,11] This regulation is critical for cardiac repolarization and results in prolongation of refractoriness, denoted by long QT intervals on the electrocardiogram (ECG). Prolonged QT intervals, common ECG findings in hypomagnesemia and hypermagnesemia (Table 1), can trigger arrhythmias through early afterdepolarization (EADs) (Fig. 3B). The constant resting membrane potential in phase 4 is maintained by Na/K ATPase pump activity and activity of sodium-calcium exchangers (NCX). These active transporters require energy from ATP hydrolysis to translocate sodium and potassium ions countercurrently across the cytoplasmic membrane against their respective concentration gradients to maintain both membrane potential and low cytoplasmic sodium concentrations. Magnesium play a role in not only ATP formation and hydrolysis but also directly driving the opening and closure of the cytoplasmic domains of Na^+/K^+ pump.[12] Moreover, in this phase, the inward rectification of potassium is modulated by blocking the potassium channel by intracellular magnesium.[11]

The effect of magnesium on myocardial contractility is primarily exerted by affecting calcium mobilization. Intracellular calcium is recognized to play a central role in cardiac excitation-contraction coupling by binding to troponin, thus activating myofilaments. In this setting, magnesium acts as a natural antagonist to calcium by competing with calcium for the binding of troponin C and calmodulin.[13] Moreover, magnesium may directly or indirectly modulate the function of several calcium transporters; calcium ATPase (Ca^{2+}-ATPase), NCX, L-I_{Ca}, and sarcoplasmic/endoplasmic reticulum calcium ATPase and therefore alters intracellular calcium mobilization from both extracellular fluid and also intracellularly from the sarcoplasmic reticulum.

CLINICAL SUMMARY

- Magnesium plays a key role in modulating intra-cardiac conduction and myocardial contraction.
- Magnesium regulates a number of ion transporters, including potassium and calcium channels.
- Observational data have shown an association between low serum magnesium and increased atherosclerosis, coronary artery disease, arrhythmias. and heart failure.
- Apart from treating torsade de pointe, and replenishing magnesium in hypomagnesemia patients with arrhythmias, trials of magnesium supplementation have failed to consistently demonstrate any clinical cardiac benefits.

Blood Vessels

Both extracellular and intracellular magnesium modulate vascular smooth muscle tone by altering cytosolic calcium, which mediates excitation-contraction coupling and actin-myosin crossbridges. Extracellular magnesium blocks calcium influx by inhibiting the calcium current in excitable cells. Neutralizing the negative surface charge of cell membranes by electrostatically binding results in raising the threshold for voltage-gated calcium channels.[14] Also, extracellular magnesium may directly bind to calcium channels, which results in either a mechanical block or allosteric modulation of channel gating, leading to an effective closure of channels.[15] Intracellular magnesium modulates vascular smooth muscle tone by altering the amplitude, activation/inactivation kinetic, and phosphorylation of voltage-dependent L-I_{Ca}, thereby decreasing intracellular calcium entry.[16] Magnesium also stimulates inositol-1,4,5-triphosphate breakdown and as such inhibits inositol-1,4,5-triphosphate-induced calcium release from the sarcoplasmic reticulum[17] and increases calcium sequestration in the sarcoplasmic reticulum by activating sarcoplasmic/endoplasmic reticulum calcium ATPase.[18]

Endothelial cells are known to regulate vascular tone and development of local thrombosis and atherogenesis. The endothelium regulates vasomotor tone by synthesizing natural vasodilators; prostacyclin (PGI_2) and nitric oxide. Extracellular magnesium can increase both PGI_2 production and release from endothelial cells.[19] Moreover, magnesium also enhances nitric oxide synthesis by upregulating endothelial nitric oxide synthase.[20] Other reports showed increasing extracellular magnesium concentration blunts vasoconstrictor actions such as the response to endothelin-1[21] and norepinephrine.[22] The effects of hypomagnesemia-induced vasoconstriction are more pronounced when the endothelium is damaged, as contraction is sustained without the transient vasorelaxation phase, in contrast to when the endothelium is intact.[23] As such, magnesium could potentially have different effects in the regulation of vascular reactivity, depending on the integrity or damage to the endothelium.

Apart from increasing vascular tone, low magnesium concentrations may inhibit endothelial proliferation and migration[24] and promote endothelial upregulation of the expression of interleukin 1β, interleukin-6, vascular cell