Int J Clin Exp Physiol. 2022;9(2):63-74
www.ijcep.org

Review Article

Molecular Physiology of Magnesium in Cardiovascular System and Pathobiology of Hypomagnesaemia in Cardiovascular Diseases

Leta Shiferaw Melaku

ABSTRACT
Magnesium, the fourth most abundant cation in the human body, is involved in several essential physiological, biochemical, and cellular processes regulating cardiovascular function. Mammalian cells regulate Mg^{2+} concentration through specialized influx and efflux transport systems that have only recently been characterized. Mg^{2+} influx is controlled by recently cloned transporters including Mrs2p, SLC41A1, SLC41A1, ACDP2, MagT1, TRPM6 and TRPM7. Magnesium efflux occurs via Na^{2+}-dependent and Na^{2+}-independent pathways. It plays a critical role in modulating vascular smooth muscle tone, endothelial cell function, and myocardial excitability and is thus central to the pathogenesis of several cardiovascular disorders such as hypertension, atherosclerosis, coronary artery disease, congestive heart failure, and cardiac arrhythmias. Much research is still needed to clarify the exact mechanisms of Mg^{2+} regulation in the cardiovascular system and the implications of aberrant transcellular Mg^{2+} transport in the pathogenesis of cardiovascular disease. This review discusses the vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties of magnesium and its current role in the prevention and treatment of cardiovascular disorders.
Key words: Magnesium, Endothelium, Heart, Blood vessel, Hypomagnesaemia, Cardiovascular disease.

INTRODUCTION

Magnesium is the eight most common element in the Earth crust.[1] The most plentiful source of biologically available magnesium is the hydrosphere (*i.e.*, oceans and rivers).[2-4] In the sea, the concentration of magnesium is about 55 mmol/L and in the dead sea as an extreme example, the concentration is reported to be 198 mmol/L magnesium and has steadily increased over time.[5] Magnesium is an essential electrolyte for living organisms and it is the second most abundant intracellular cation and the fourth most abundant cation in the human body (Ca^{2+} > K^{+} > Na^{+} > Mg^{2+}).[1,6] The normal adult human body contains approximately 1,000 mmols of magnesium (22 – 26 g).[7] About 60% of the magnesium is present in bone, 20% is in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid,[6] which is primarily found in serum and red blood cells. Normal serum magnesium concentration is about 0.76 – 1.15 mmol/L.[8] In normal adults, total serum magnesium ranges are between 0.70 – 1.10 mmol/L and both intra and extracellular Mg^{2+} exist in 3 functional states:- (1) free or ionized (the physiologically active form), (2) protein bound, and (3) complexed to anions.[9] With regard to extracellular Mg^{2+}, 20% – 30% is protein bound, 55% – 70% is ionized (the physiologically active form) and the rest is complexed with various anions.[7] Of the protein bound fraction, 60 – 70% is associated with albumin and the rest is bound to globulins.[10] Within cells, Mg^{2+} is compartmentalized in the nuclei, mitochondria, and endo/sarcoplasmic reticulum.[11] Within these compartments, Mg^{2+} binds to chromatin and nucleic acid, matrix adenine phospho-nucleotides and inter-membrane proteins, and ribonuclear proteins and phospholipids, respectively.[11,12] As a result of this binding, only a small fraction of intracellular Mg^{2+} exists in the free form. The total intracellular Mg^{2+} concentration ranges between 14 and 20 nM, whereas the intracellular free Mg^{2+} concentration is estimated to be about 0.5 – 0.7 nM.[13] The distribution of magnesium within the cell is heterogenous, with lower concentrations in the peripheral regions of the cytoplasm than in the perinuclear region.[14] The rate of magnesium transport across cell membranes also varies in different cell types, being higher in heart, liver and kidney and lower in skeletal muscle, red cells and brain.[6] Additionally, intracellular magnesium is higher in rapidly proliferating cells indicating that cellular magnesium transport is linked to metabolic activity of the cell.[15] The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/Kg/day or 12 mmol/day.[6,7]

Leta Shiferaw Melaku

Department of Biomedical Sciences, College of Health Sciences, Arsi University, Asella, Oromia, ETHIOPIA.

***Correspondence**

Leta Shiferaw Melaku
Department of Biomedical Sciences,
College of Health Sciences,
Arsi University, Asella, Oromia,
ETHIOPIA.

Email: letamelaku@gmail.com

History
- Submission Date: 04-04-2022;
- Review completed: 01-06-2022;
- Accepted Date: 29-06-2022.

DOI : 10.5530/ijcep.2022.9.2.15

Article Available online
http://www.ijcep.org

Copyright
© 2022 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.

Cite this article: Melaku LS. Molecular Physiology of Magnesium in Cardiovascular System and Pathobiology of Hypomagnesaemia in Cardiovascular Diseases. Int J Clin Exp Physiol. 2022;9(2):63-74.

www.ijcep.org

The daily requirement is higher in pregnancy, lactation and following debilitating illness.[7] Magnesium homeostasis is maintained by the intestine, the bone and the kidneys. Of the total dietary magnesium consumed, only about 24% – 76% is absorbed in the gut and the rest is eliminated in the faeces.[7] Intestinal absorption of magnesium proceeds in both a passive paracellular manner and an active transcellular manner.[16] The majority of magnesium is absorbed in the small intestine by a passive paracellular mechanism, which is driven by an electrochemical gradient and solvent drag.[17] Paracellular magnesium absorption is responsible for 80% – 90% of intestinal magnesium uptake, which is presumably mediated by claudin-16/paracellin-1.[18] The driving force behind this passive magnesium transport is supplied by the high luminal magnesium concentration, which ranges between 1.0 and 5.0 mmol/L, and the lumen-positive transepithelial voltage of ~15 Mv.[19] On the contrary, active transcellular absorption of magnesium occurs almost exclusively in the colon and may involve Na^+/Mg^{2+} antiport systems and the transcellular transporter, Transient Receptor Potential Melastatin 6 (TRPM6).[20] The exact mechanism facilitating paracellular magnesium absorption still remains unknown. Studies suggest a role for parathyroid hormone (PTH) in regulating magnesium absorption, but the role of vitamin D and its active metabolite 1, 25 dihydroxyvitamin D is more controversial. Phytates in the diet bind to magnesium and impair its absorption. However the quantities present in normal diet do not affect magnesium absorption. Other dietary factors that are thought to affect magnesium absorption are oxalate, phosphate, proteins, potassium and zinc.[21] It is worth noting that intestinal absorption is not directly proportional to magnesium intake but is dependent mainly on magnesium status. The lower the magnesium level, the more of the mineral is absorbed in the gut, thus relative magnesium absorption is high when intake is low and vice versa.[22] There is usually equilibrium between intestine magnesium absorption and renal elimination. The kidneys are crucial in magnesium homeostasis as serum magnesium concentration is primarily controlled by its excretion in urine. Under physiological conditions, ~2400 mg of magnesium in plasma is filtered by the glomeruli. Of the filtered load, ~2300 mg is immediately reabsorbed and only 3% – 5% is excreted in the urine, *i.e.*, ~100 mg.[7] Approximately 15 – 20% of filtered magnesium is reabsorbed in the proximal tubular segments, 65 – 75% in thick ascending loop of henle (TALH) and the rest in the distal segments.[23]

Magnesium transport in the proximal tubule appears to be primarily a unidirectional passive process depending on sodium/water reabsorption and the luminal magnesium concentration. Magnesium transport in TALH is directly related to sodium chloride reabsorption and the positive luminal voltage in the segment.[14] In TALH, approximately 25% of the filtered sodium chloride is reabsorbed through the active transcellular transport, (sodium-chloride-potassium transport) and passive paracellular diffusion, which is mediated by claudin-16 and -19.[24] This creates a favourable luminal positive potential at TALH where most of the magnesium is reabsorbed. Magnesium reabsorption is also inversely related to the rate of fluid flow in the tubular lumen. Reabsorption in the distal convoluted tubule is active via TRPM6.[25] Mg^{2+} is a dynamic ion, the transcellular transport of which involves several efflux and influx systems.[20] Mg^{2+} efflux involves Na^+-dependent (Na^+/Mg^{2+} exchanger) and Na^+-independent (Ca^{2+}/Mg^{2+} exchanger, Mn^{2+}/Mg^{2+} antiporter and Cl^-/Mg^{2+} exchanger) systems.[26] The Na^+/Mg^{2+} exchanger is expressed in cardiac, renal, and VSMCs and is regulated by several neurohormones implicated in the pathophysiology of hypertension.[27] Angiotensin II, vasopressin, aldosterone, epinephrine, and norepinephrine have all been shown to enhance Mg^{2+} efflux and decrease intracellular Mg^{2+}.[28] Pharmacological and functional studies have shown that Mg^{2+} influx occurs via Mg^{2+}/anion cotransport, counter-transport pathways using the electrochemical gradient of Na^+, and via cation channels. At least 7 transcellular Mg^{2+} channels have been cloned, including the mitochondrial RNA splicing 2 protein, the human solute carrier family 41, members 1 and 2 (SLC41A1, SLC41A2) channels, magnesium transporter 1, ancient conserved domain protein 2, and transient receptor potential melastatin cation channels 6 and 7 (TRPM6, TRPM7). A paracellular Mg^{2+} transporter, paracellin-1, has also been identified.[29] The above transport processes are intricately involved in the intestinal absorption of Mg^{2+} and renal regulation of Mg^{2+} excretion and no single hormone has been shown to be specifically related to magnesium homeostasis.[20] Several hormones including PTH, antidiuretic hormone (ADH), calcitonin, glucagon and insulin have been shown to affect magnesium reabsorption. Of these, PTH is the most important. PTH increases reabsorption in the distal tubules by a cyclic AMP mediated process.[30] Phosphate depletion is associated with a significant increase in urinary magnesium excretion and may cause hypomagnesaemia.[31] Hypercalcaemia is associated with an increased urinary excretion of both calcium and magnesium.

In addition, the high peritubular concentration of calcium directly inhibits the transport of both ions in this segment. Osmotic diuretics such as mannitol and glucose cause a marked increase in magnesium excretion. Loop diuretics induce hypermagnesuria, and the increase in magnesium excretion is greater than that of sodium or calcium suggesting that loop diuretics may directly inhibit magnesium transport.[32] Magnesium plays an essential physiological role in many functions of the body.[33] This role is achieved through two important properties of magnesium; the ability to form chelates with important intracellular anionic-ligands, especially ATP, and its ability to compete with calcium for binding sites on proteins and membranes.[6] Magnesium (Mg^{2+}) is, therefore, involved in several essential physiological, biochemical, and cellular processes regulating cardiovascular function. It plays a critical role in modulating vascular smooth muscle tone, endothelial cell function, and myocardial excitability by influencing the intracellular calcium concentration and the electrical activity of myocardial cells and the specialized conducting system of the heart by its ability to influence movement of ions such as sodium, potassium and calcium across the sarcolemmal membrane and is thus central to the etiopathology of several cardiovascular disorders, including hypertension, atherosclerosis, coronary artery disease (CAD), congestive heart failure (CHF), and cardiac arrhythmias.[34] Magnesium has also a key role in many other important biological processes such as cellular energy metabolism, cell replication, and protein synthesis.[25]

MOLECULAR IDENTITIES OF THE TRANSPORTERS INVOLVED IN MAGNESIUM HOMEOSTASIS

Over the last 20 years, it has been the main focus of research. Although the exact role of many of these proteins needs further investigation, researchers have identified several proteins critical to cellular Mg^{2+} homeostasis.

Transient Receptor Potential Melastatin Type 7 (TRPM7)

TRPM7 is a ubiquitously expressed divalent cation channel that is responsible for much of the Mg^{2+} flux in the cell.[35] TRPM7 activity is generally regarded as a prerequisite for cell viability.[36] However, recent reports with tissue-specific TRPM7 KO mice suggest that TRPM7-deficient T cells are still viable and have normal intracellular Mg^{2+} concentrations.[37]

TRPM7 constitutes a tetrameric channel, where each subunit consists of six transmembrane regions with a pore region between the fifth and sixth transmembrane domain.[38] The intracellular COOH terminus contains a kinase domain that regulates autophosphorylation of the channel, although its mechanism is poorly understood, as TRPM7 channel

function is not dependent on its kinase activity.[39] Initially, the kinase was reported to exist as separate entity,[40] and indeed, recently it was shown that the kinase is cleaved from TRPM7 by caspase-8, although the exact function of the cleaved kinase remains unknown.[41]

Mg^{2+} Transporter 1 (MagT1)

Originally identified in MDCT cells, Mg^{2+} transporter 1 (MagT1) has been described as a ubiquitously expressed Mg^{2+} channel.[42] Survival and growth of TRPM7-deficient cells can be partially rescued by MagT1 overexpression.[43] Although identification of MagT1 dates back almost 10 years, the functional characteristics of MagT1 are still undetermined.[35] MagT1 mediates highly specific Mg^{2+} currents in Xenopus laevis oocytes, but these results could not be reproduced in mammalian cells.[42] Recent studies in T cells suggest that MagT1 mediates a rapid Mg^{2+} influx upon receptor activation.[44] Since T cells do not require TRPM7 for maintaining normal intracellular Mg^{2+} concentrations,[37] this suggests that MagT1 has a similar function as TRPM7 in certain cell types.

Extrusion

In 1984, Theodor Gunther *et al.*[45] proposed that the main route of Mg^{2+} efflux from the cell is Na^+ dependent. A large body of evidence obtained in a wide range of cell types supports this notion.[12] Over the last decades, the mechanism has been further characterized in a variety of cell types, demonstrating inhibition by Na^+ channel blockers such as amiloride, imipramine, and quinidine.[35] The stoichiometry of this exchange mechanism is still not fully elucidated; Na^+-dependent Mg^{2+} extrusion is activated by cAMP in several cell models and conditions,[12] but Na^+-independent Mg^{2+} extrusion has also been proposed. Ebel *et al.*[46] reported the presence of a choline-dependent Mg^{2+} transporter in erythrocytes. However, the molecular identity of this proposed Mg^{2+} efflux mechanism remains controversial.

Solute Carrier Family 41 Member 1

Recent reports by Kolisek and co-workers[47] suggested that solute carrier family 41 member 1 (SLC41A1) functions as a Na^+/Mg^{2+} exchanger with a 2:1 stoichiometry. SLC41A1 contains 11 transmembrane domains and was originally described as a Mg^{2+} transporter mediating Mg^{2+} currents in Xenopus laevis oocytes.[48] Although electrophysiological analysis could not confirm these measurements in mammalian cells, Mg^{2+} efflux studies using mag-fura 2 show Na^+-dependent Mg^{2+} extrusion.[47] Gain-of-function SNPs have been associated with Parkinson's disease, and one mutation inSLC41A1was identified in a patient with a nephronophthisis-like phenotype.[49] SLC41A1 is part of a larger protein family including two additional members, SLC41A2 and SLC41A3, which are studied less extensive.[35] Although SLC41A2 was initially described as a plasma membrane protein, it has a topology opposite to SLC41A1. This finding suggests that SLC41A2 might be expressed on the membranes of organelles and may be involved in subcellular Mg^{2+} transport.

Cyclin M

Members of the Cyclin M (CNNM) family have been proposed to function as Mg^{2+} transporters.[50] CNNM1 is mainly expressed in brain, CNNM2 expression is high in kidney, and CNNM4 is primarily expressed in intestine.[51] In contrast, CNNM3 has a ubiquitous expression pattern and may play a role in the maintenance of cellular Mg^{2+} homeostasis. A recent study shows that CNNM3 transports Mg^{2+}, and its activity is regulated by oncogene PRL2.[52] The interaction between PRL2 and CNNM3 is essential for Mg^{2+} influx that drives tumor growth.[35] Therefore, CNNM3 should be considered in future studies on cellular Mg^{2+} handling in non-pathological conditions.

Mitochondrial RNA Splicing 2

Although most studied in yeast, mitochondrial RNA splicing 2 (MRS2) is considered to be the primary Mg^{2+} channel on the mitochondrial membrane.[53] Knockdown of MRS2 results in reduced Mg^{2+} uptake in mitochondria and cell death.[54] Using the newly developed mitochondrial Mg^{2+} fluorescent probe KMG-301, Shindo *et al.*[55] revealed that MRS2 regulates intramitochondrial Mg^{2+} concentrations. This finding is interesting, since it indicates that mitochondria may store intracellular Mg^{2+}.

Given that Mg^{2+} is of major importance for ATP binding, intramitochondrial Mg^{2+} concentrations may indirectly influence the progression of the citric acid cycle.[35] Recently, it was shown that MRS2 mutations cause demyelination. The relevance of this observation to Mg^{2+} homeostasis still remains to be determined.[56]

Others

In addition to the aforementioned Mg^{2+} transporters, several other proteins have been proposed to transport Mg^{2+}. However, these claims are based mainly on overexpression in the Xenopus oocytes model, and functional evidence for these proteins is scarce. For example, the nonimprinted in Prader-Willi/Angelman syndrome (NIPA) family of proteins has been proposed to transport Mg^{2+}, based on Mg^{2+} currents in Xenopus laevis oocytes,[57] but recent studies indicate that NIPA proteins have a role in bone morphogenetic protein (BMP) signalling.[58] Likewise, Huntingtin interacting protein 14 (HIP14) was thought to mediate Mg^{2+} fluxes at the Golgi membrane.[59] Now it has become apparent that its main function consists of palmitoyl acyltransferase activity, specifically involved in the palmitoylation of Huntington.[60] Therefore, the role of NIPA proteins and HIP14 in Mg^{2+} transport should be questioned. Additionally, members of the membrane Mg^{2+} transporter (MMgT) family have been shown to transport divalent cations in Xenopus oocytes.[61] However, as they have only one transmembrane domain after signal peptide cleavage, it is unlikely that they form functional Mg^{2+} transporters themselves.[35] It is possible that MMgT proteins may form subunits of other Mg^{2+} channels, and as a consequence, future studies should be directed to the identification of its protein partners.

MAGNESIUM AND CARDIOVASCULAR SYSTEM

Role of Magnesium in Heart

Mg^{2+} plays an important role in heart function by influencing myocardial metabolism, Ca^{2+} homeostasis, vascular tone, peripheral vascular resistance, and cardiac output. Mg^{2+} exerts its effects by regulates the activity of ion channels in the cardiac cells, thereby affecting the electrical properties of the myocardium.[62]

The cardiac action potential consists of five phases:[35] phase 0 is the rapid depolarization by the influx of Na^+. Phase 1 consists of rapid repolarization by efflux of K^+. Phase 2, named the plateau phase, is the longest phase and marks Ca^{2+} entry. Phase 3 allows final repolarization of the cell by restoration of the membrane potential. Phase 4 is the stable phase with a resting potential of +90 mV.[63] Mg^{2+} is mainly important in phases 2 and 3 of the myocardial action potential, exerting its effect on K^+ and Ca^{2+} channels. In phase 2, Mg^{2+} inhibits L-type Ca^{2+} channels ($Ca_v1.2$) to prevent Ca^{2+} overload and cell toxicity.[64] Mg^{2+} can bind a COOH-terminal EF hand motif of the channel and thereby influences the Ca^{2+} current.[65] The effects of Mg^{2+} on the current through the L-type Ca^{2+} channels (I_{CaL}) may depend on the channel's phosphorylation state, since phosphatase treatment decreases the inhibitory effects of Mg^{2+}.[66] In phase 3, delayed rectifier K^+ channels repolarize the cell by rapid-activating (I_{Kr}) and slow-activating (I_{Ks}) currents. High $[Mg^{2+}]_i$ inhibits I_K currents in frog and guinea pig cardiomyocytes.[67]

This effect probably depends on the slow-activating component of the current, since rapid-activating currents seem insensitive to Mg^{2+} inhibition.[68] The intracellular block of inward rectifier K^+ channels Kir2.1 and Kir2.2 by Mg^{2+} substantially influences phase 3 and phase 4 of the action potential.[69] This block of the I_{K1} current is relieved by high extracellular K^+ concentrations.[70] In recent years an increasing amount of attention has been directed to the role of $[Mg^{2+}]_i$ in cardiac excitation-contraction coupling.[71] Mg^{2+} has often been considered as a natural Ca^{2+} antagonist, since it can compete with Ca^{2+} for binding sites in proteins and Ca^{2+} transporters.[72] The effect of Mg^{2+} on cardiomyocytes is mainly explained by its role of Ca^{2+} mobilization.[35] Mg^{2+} binds calmodulin, troponin C, and parvalbumin, and therefore a reduced $[Mg^{2+}]_i$ may result in alterations in the unbound Ca^{2+} fraction.[73] Mg^{2+} may also affect the main Ca^{2+}-transporting proteins in the cardiomyocytes. Mg^{2+} acts as substrate in a complex with ATP for cardiac Ca^{2+}-ATPases and alters the affinity of Na^+-Ca^{2+} exchanger type 1 for Ca^{2+} (NCX1).[71,74-75] There is a dearth of physiological studies on the effect of Mg^{2+}on NCX1 and SERCA activity, and available studies mainly rely on modeling and *in vitro* experiments.[35] Nevertheless, tight regulation of $[Mg^{2+}]_i$ in cardiac cells is necessary for optimal cardiac function. This is substantiated by the fact that high $[Mg^{2+}]_i$ can cause cardiac arrest, and by the impressive capacity of cardiomyocytes to maintain constant $[Mg^{2+}]_i$. Magnesium may play a role in reducing coronary vascular resistance, increasing coronary artery blood flow parameters, and prevention of arrhythmia.[76]

Probably the most widely accepted and practiced use of magnesium in cardiovascular medicine is for the prevention and/or treatment of cardiac arrhythmias.[77] Another meta-analyses have shown that intravenous magnesium is indeed an effective and safe strategy for prophylaxis against post-cardiac surgery atrial fibrillation and for acute management of rapid atrial fibrillation.[78] Cagli *et al.* recently showed that combined prophylactic therapy with intravenous low-dose amiodarone and $MgSO_4$ in the early postoperative period is an effective, simple, well-tolerated, and cost-effective regimen for the prevention of post-cardiac surgery atrial fibrillation in high-risk, normomagnesemic patients.[79] Similarly, concurrent use of intravenous Mg^{2+} enhances the ability of intravenous ibutilide and dofetilide to successfully convert atrial fibrillation or atrial flutter to sinus rhythm.[80] Thus, intravenous Mg^{2+} is an effective adjuvant therapy for atrial fibrillation or atrial flutter for both rate and rhythm control and can act synergistically with the class III antiarrhythmic agents to prevent their proarrhythmogenic effects and reduce the need for potentially harmful antiarrhythmic drugs such as amiodarone. The use of magnesium for the treatment of ventricular arrhythmias associated with long QT syndrome (polymorphic ventricular tachycardia/torsades de pointes) is well established.[81] Torsades de pointes is a form of ventricular tachycardia associated with a long QT or QTc and is electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line.[82] Long QT syndrome can be congenital (eg, Jervell and Lange-Nielsen syndrome) or acquired, caused by drugs such as class Ia and III antiarrhythmic agents and electrolyte abnormalities, including hypokalemia and hypomagnesemia. Magnesium is therefore the drug of choice for suppressing early after depolarizations and terminating the arrhythmia and is effective even in patients with normal Mg^{2+} levels.[83] Supplementation with intravenous Mg^{2+} has been shown to cause a significant decrease in the number of ventricular ectopic beats, couplets, and episodes of non-sustained ventricular tachycardia in patients with New York Heart Association class II–IV heart failure.[84] Ventricular arrhythmias are common following coronary artery bypass grafting, and their occurrence coincides with the postoperative decline in serum Mg^{2+} levels.[20] Parikka et al showed that correction of the postoperative decline in serum Mg^{2+} concentration decreases the occurrence of early ventricular premature complexes and complex ventricular arrhythmias in coronary artery bypass surgery patients, and the benefit appears to be the greatest in patients with extensive underlying CAD and prior diuretic therapy.[85]

Lastly, data from the Magnesium in Cardiac Arrhythmias (MAGICA) trial showed a significant reduction in ventricular premature beats in patients with frequent ventricular arrhythmias (>720 beats/24h) following a 50% increase in the minimum daily dietary intake of Mg^{2+} and K^+ for 3 weeks, further emphasizing the beneficial effects of Mg^{2+} in the management of ventricular arrhythmias.[86] Magnesium exerts its antiarrhythmic effect via modulation of myocardial excitability.[20] The role of voltage-dependent Na^+, Ca^{2+}, and K^+ channels in the generation of cardiac action potential and the pathogenesis of cardiac arrhythmias is well-established; however, very few studies have evaluated the effect of magnesium on cardiac voltage-dependent Na^+ channels. Using inside-out patches from guinea pig ventricular myocytes to measure currents through single cardiac Na^+ channels, Mubagwa *et al.*[62] showed that $[Mg^{2+}]_i$ had no effect on inward currents but decreased the outward current amplitude in a concentration and voltage-dependent manner. This suggests that $[Mg^{2+}]_i$ primarily exerts only an open channel blocking effect, with little or no direct allosteric modulatory action on the voltage-dependent Na^+ channels. The cardiac membrane stabilizing action of magnesium is primarily due to its modulation of the voltage-dependent L-type calcium channels (LCa). As mentioned earlier, changes in $[Mg^{2+}]_i$ are known to influence LCa by affecting its amplitude, its activation/inactivation kinetics, and its modulation by factors such as phosphorylation, ultimately leading to decreased Ca^{2+} entry via these channels.[87] LCa amplitude is decreased by high $[Mg^{2+}]_i$ and increased by low $(Mg^{2+})_i$.[64,66] An $[Mg^{2+}]_i$ -induced decrease in current amplitude involves change in channel gating in the form of shift in voltage-dependent inactivation and/or decreased channel availability. Raising $[Mg^{2+}]_i$ has been shown to increase the rate and extent of the decay of Ca^{2+} current, an effect attributed to allosterically induced inactivation.[88] High $[Mg^{2+}]_i$ also causes a leftward shift in the steady state voltage-dependent inactivation, probably as a result of screening of internal charges by $[Mg^{2+}]_i$.[66] The effects of magnesium on LCa amplitude are modulated by the state of phosphorylation of the LCa. Phosphorylation via the protein kinase A-dependent pathway enhances the LCa current amplitude and also enhances the inhibitory action of magnesium.[20] Conversely, dephosphorylation of the channels by either protein kinase inhibitors or phosphatases decreases the magnesium effect.[66]

The effect of magnesium is not due to changes in cyclic adenosine monophosphate concentration or channel phosphorylation but appears to be a direct effect of magnesium on the phosphorylated channel or on channel dephosphorylation.[64] Binding of magnesium inhibits phosphorylated channels from undergoing the conformational changes that result in more frequent opening. Nonetheless, the ATP-bound form of magnesium (Mg^{2+}-ATP) is required for protein kinase A– or PKC-mediated LCa phosphorylation.[89] $[Mg^{2+}]_i$ and guanosine triphosphate (GTP) act synergistically to inhibit LCa. GTP and other guanine di or trinucleotides have been shown to inhibit LCa channels in a G-protein–independent manner.[90] Both magnesium and GTP can directly bind to LCa, but because of different charges, magnesium and GTP^{2-} have independent binding sites, with the binding of one allosterically preventing the binding of the other.[20] Most LCa bind Mg^{2+} and/or GTP and remain in a non-available state under basal conditions. Depletion of $[Mg^{2+}]_i$ relieves the magnesium block because the blocking device in the C-terminal region of α-subunit of LCa can no longer block the channel when free of Mg^{2+}.[91] However, in the presence of GTP, depletion of $[Mg^{2+}]_i$ allows GTP to bind to LCa, thereby allowing it to exert its inhibitory effect, thus maintaining the channels in a non-available state. Besides voltage-dependent Na^+ and LCa channels, magnesium can also

influence the inward and delayed rectifier K^+ channels expressed in cardiac cell membrane. The inward rectifier K^+ channels (I_{K1}) are highly expressed in atrial and ventricular contractile cells, and in ventricular conduction cells, but less expressed in nodal cells.[62] I_{K1} current is the primary determinant of resting membrane potential of cardiac cells. It is well-established that the strong inward rectification results from voltage-dependent block by intracellular organic cations called polyamines.[92] Although the polyamines spermine and spermidine are the most potent inducers of inward rectification, $[Mg^{2+}]_i$ also plays an important role.[93] Furthermore, this strong voltage-dependent rectification is influenced by extracellular K^+ such that elevated extracellular K^+ levels relieve the polyamine- or Mg^{2+}-induced rectification.[94] The delayed rectifier K^+ (I_K) current, composed of rapidly activating (I_{Kr}) and slowly activating (I_{Ks}) components mediated by 2 different channel proteins, HERG and K_vLQT1, respectively, is critical for the repolarization phase of cardiac action potential.[95] Elevated $[Mg^{2+}]_i$ in mammalian cardiac myocytes decreases I_K current, whereas decreased $[Mg^{2+}]_i$ produces the opposite effect.[67] A small increase in $[Mg^{2+}]_i$ in the physiological range from 0.3 to 1.0 mM suppresses the current by 50 – 60%.

Because this effect is observed in both non-stimulated cells and cyclic adenosine monophosphate–treated cells, it has been speculated that these modulatory effects of $[Mg^{2+}]_i$ on I_K are independent of channel phosphorylation.[96] Lastly, because voltage-independent modulation of both outward and inward current through I_K occurs, the $[Mg^{2+}]_i$ modulation of these channels does not appear to result from the open channel blocking effect observed on the I_{K1} channels. Rather, it has been suggested that the I_K channels express a binding site for $[Mg^{2+}]_i$, which may modulate the availability or opening of these channels.[91] Based on the physiological effects of magnesium on cardiac ion channels, it is obvious that Mg^{2+} influences cardiac impulse formation and conduction and thereby plays a critical role in the pathogenesis and treatment of cardiac arrhythmias.

Role of Magnesium in Blood Vessel

Both extracellular and intracellular free magnesium can modulate vascular smooth muscle (VSM) tone. Extracellular magnesium inhibits calcium current in excitable cells via several mechanisms.[20] First, extracellular divalent cations such as magnesium effectively neutralize the fixed negative charges on the external surface of the cell membrane either by binding or by electrostatic screening. This stabilizes the excitable membranes and raises the excitation threshold for voltage-gated channels. This shift in the current-voltage relationship is responsible for diminished current via the voltage-gated calcium channels in response to normal stimuli.[97] The screening of surface charges is more marked extracellularly than intracellularly probably due to an asymmetrical distribution of negatively charged sialic acid residues in the cell membrane.[98] Second, some evidence suggests that extracellular magnesium can decrease calcium current by directly binding to the calcium channels.[99] Binding of magnesium may either mechanically block the channel pore or may cause an allosteric modulation of the channel gating, eventually resulting in its closure. Bara and Guiet-Bara have shown that $MgCl_2$ and $MgSO_4$ act at an extracellular site on L-type calcium channels to regulate the influx of calcium through voltage-gated calcium channels in VSMCs and endothelial cells.[100] Serrano et al have shown a similar inhibitory effect of extracellular magnesium on T-type calcium channels.[101] Besides inhibiting calcium entry through voltage-gated calcium channels, extracellular magnesium has also been shown to inhibit capacitative calcium entry in VSMCs.[102]

Intracellular magnesium [$(Mg^{2+})_i$] modulates VSM tone via its effects on ion channels and signal transduction pathways, especially those involving calcium.[20] Calcium plays an important role in excitation-contraction coupling in smooth muscle cells. Angiotensin II, vasopressin, endothelin, and epinephrine/norepinephrine exert their vasoconstrictor effect via stimulation of AT_1, V_{1a}, ET_A, and α_1 receptors, respectively, on VSMCs. Activation of these Gq-protein–coupled receptors initiates the phospholipase C, inositol-1, 4, 5-trisphosphate (IP_3), diacylglycerol, calcium, protein kinase C (PKC) signal transduction pathway.[20] Evidence suggests that following receptor-ligand interaction $(Mg^{2+})_i$ is also altered and that it too functions as a second messenger to modulate signal transduction.[103] $(Mg^{2+})_i$ regulates G-protein activity, phospholipase C translocation, and PKC activation. Elevated $(Mg^{2+})_i$ stimulates IP_3 breakdown, inhibits IP_3-induced calcium release from the sarcoplasmic reticulum, and competes with $(Ca^{2+})_i$ for cytoplasmic and reticular binding sites.[104] Lastly, $(Mg^{2+})_i$ activates sarcoplasmic/endoplasmic reticular Ca^{2+} ATPase pump that sequesters $(Ca^{2+})_i$ into the sarcoplasmic reticulum. Magnesium is, therefore, considered to be nature's physiologic calcium blocker.[72] Clinical and experimental evidence suggests that magnesium promotes vasodilation, reduces vascular resistance, and improves blood flow in systemic, coronary, cerebral, and renal circulations.[105] Kugiyama *et al.* demonstrated that exercise-induced angina is suppressed by intravenous magnesium in patients with variant angina, most probably as a result of an improvement in regional myocardial blood flow by suppression of coronary artery spasms.[106] Shechter *et al.* found that the intra lymphocytic magnesium levels in CAD patients after myocardial infarctions and/or coronary artery bypass operations were highly correlated to exercise duration time and cardiac performance and inversely correlated to the peak exercise double-product (heart rate x systolic blood pressure).[107] Thereafter, Shechter *et al.* demonstrated in Austria, Israel and the US, that a 6-month oral magnesium supplementation significantly improved exercise tolerance, exercise duration time, ischemic threshold and quality of life in stable CAD patients.[108] Pokan *et al.*[109] reinforced Shechter's findings. They demonstrated that a 6-month oral magnesium supplementation significantly improved the intracellular magnesium levels, VO_2 max, left ventricular ejection fraction and reduced the exercised-induced heart rate.

Besides the direct effects of magnesium on VSMCs, magnesium also modulates endothelial function, which in turn contributes to its vasodilatory actions. Normal endothelium plays a fundamental role in regulating vasomotor tone by synthesizing vasodilatory prostacyclin (PGI_2) and nitric oxide (NO). Magnesium has been shown to increase endothelial release of PGI_2 in cultured human endothelial cells and in healthy human volunteers.[110] However, because extracellular magnesium has also been shown to inhibit both calcium influx and intracellular calcium release in endothelial cells, it has been speculated that the magnesium-induced PGI_2 release could be via a calcium-independent mechanism.[111] Unlike VSMCs, calcium entry in endothelial cells is receptor-mediated and/or capacitative (activated in response to decreased $(Ca^{2+})_i$ rather than voltage-dependent.[112] Extracellular calcium is essential for endothelium-dependent VSM relaxation because elevated $(Ca^{2+})_i$ levels stimulate the synthesis and release of NO via endothelial NO synthase (eNOS) in response to various stimuli. The effects of elevated extracellular magnesium level on endothelial calcium entry and NO synthesis are controversial.[20] Although an elevated level of extracellular magnesium has been shown to inhibit both receptor-mediated and capacitative calcium entry in cultured endothelial cells, it has been shown to enhance NO synthesis, in part, via the up-regulation of eNOS.[113] In addition, Yang *et al.* have shown that magnesium stimulates NO release from intact rat aortic rings in a concentration-dependent manner and that the release of NO requires Ca^{2+} and formation of cyclic guanosine monophosphate.[114] Last, Pearson *et al.* have demonstrated that hypomagnesemia selectively impairs the release of NO from canine epicardial coronary artery endothelium, suggesting

that magnesium supplementation can promote vasodilation.[115] Studies have demonstrated that magnesium can also suppress platelet activation by either inhibiting platelet-stimulating factors, such as thromboxane A_2, or by stimulating synthesis of platelet-inhibitory factors, such as prostacyclin (PGI_2).[116-118] Intravenous administration of magnesium to healthy volunteers inhibited both ADP-induced platelet aggregation by 40% and the binding of fibrinogen or surface expression of glycoprotein IIb-IIIa complex GMP-140 by 30%.[118] Thus, pharmacological concentrations of magnesium effectively inhibit platelet function *in vitro* and *ex vivo*.[119] Gawaz *et al*. demonstrated that platelet aggregation, fibrinogen binding, and expression of P-selectin on the platelet surface, are all effectively inhibited by intravenous magnesium supplementation.[116]

Since glycoprotein IIb-IIIa is the only glycoprotein on the platelet surface that binds fibrinogen, Gawaz *et al*. speculated that magnesium supplementation directly impairs fibrinogen interaction with the glycoprotein IIb-IIIa complex.[117] Since fibrinogen binding to the platelet membrane and surface expression of P-selectin requires previous cellular activation, the inhibitory effect of magnesium might be a consequence of direct interference of the cation with the agonist-receptor interaction or with the intracellular signal transduction event. Fibrinogen-glycoprotein IIb-IIIa interaction is regulated by divalent cations, and at pharmacological levels magnesium may inhibit the binding of fibrinogen to glycoprotein IIb-IIIa by altering the receptor conformation. This might be caused by the competition of magnesium with calcium ions for calcium binding sites in the glycoprotein IIb subunit. Rukshin *et al.* recently demonstrated that treatment with intravenous magnesium sulphate produced a time-dependent inhibition of acute stent thrombosis under high-shear flow conditions without any hemostatic or significant hemodynamic complications in an *ex vivo* porcine arterio-venous shunt model of high-shear blood flow, suggesting that magnesium inhibits acute stent thrombosis in animal model.[120] Thereafter the same group demonstrated that intravenous magnesium sulfate is a safe agent in acute coronary syndrome patients undergoing non-acute percutaneous coronary intervention with stent implantation, while magnesium therapy significantly inhibited platelet activation.

Hypomagnesaemia

Hypomagnesaemia is defined as serum magnesium concentration < 0.75 mmol/L.[121] Early signs of magnesium deficiency are non-specific and include loss of appetite, lethargy, nausea, vomiting, fatigue, and weakness. More pronounced magnesium deficiency presents with symptoms of increased neuromuscular excitability such as tremor, carpopedal spasm, muscle cramps, tetany and generalized seizures. Hypomagnesemia can cause cardiac arrhythmias including atrial and ventricular tachycardia, prolonged QT interval and torsades de pointes.[7] Hypomagnesaemia is frequently associated with other electrolyte abnormalities such as hypokalemia and hypocalcaemia. Conditions that may lead to hypomagnesemia include alcoholism, poorly-controlled diabetes, malabsorption (e.g., Crohn's disease, ulcerative colitis, coeliac disease, short bowel syndrome, and Whipple's disease), endocrine causes (e.g., aldosteronism, hyperparathyroidism, and hyperthyroidism), renal disease (e.g., chronic renal failure, dialysis, Gitelman's syndrome) and medication use.

A variety of drugs including antibiotics, chemotherapeutic agents, diuretics and proton pump inhibitors can cause magnesium loss and hypomagnesemia. In addition, magnesium deficiency exacerbates potassium mediated arrhythmia, in particular in the presence of digoxin intoxication.[122]

Hypomagnesaemia and Cardiovascular Diseases

The vascular endothelium is an active paracrine, endocrine and autocrine organ, which plays a critical role in vascular homeostasis by secreting several mediators regulating vessel tone and diameter, coagulation factors, vascular inflammation, cell proliferation and migration, platelet and leukocyte interaction and activity and thrombus formation.[118,123] It is well accepted that endothelial dysfunction is central to the pathogenesis of atherosclerosis, thrombosis, hypertension, and diabetes.[124] Experimental evidence exists, suggesting that magnesium deficiency potentiates free radical production and oxidative stress in endothelial cells through reduction in plasma antioxidants and increased lipid peroxidation.[125] The role of reactive oxygen species and oxidized low density lipoprotein (OxLDL) in the pathogenesis of atherosclerosis is well-established.[126] Low magnesium levels have been shown to inhibit endothelial proliferation and migration and up-regulate the expression of interleukin-1, -6, vascular cell adhesion molecule, and plasminogen activator inhibitor-1, thereby producing a proinflammatory, prothrombotic, and proatherogenic environment.[127] Moreover, in conditions of low Mg^{2+}-induced oxidative stress, the endothelium develops a state of permanent inflammation, which is marked by increased NFκB activity.[128] NF κB is the master regulator of transcription of cytokines and pro-inflammatory genes, including IL-1α.[129] As a result of this local inflammation, the vessel wall will recruit monocytes and trigger the proliferation and migration of vascular smooth muscle cells. These processes are facilitated by the increased expression of matrix metalloproteases 2 and 9 in low Mg^{2+} conditions.[128] Eventually low Mg^{2+} concentrations may, therefore, result in atherosclerosis, vascular calcifications, or thrombosis. Several animal and human experiments support the role of magnesium in the pathogenesis and treatment of atherosclerosis and its complications.

Recently it was demonstrated that rabbits with inadequate dietary intake of magnesium developed more plaques and had higher total and non-high-density lipoprotein cholesterol and triglyceride levels than controls, suggesting that inadequate intake of magnesium is an independent risk factor for atherosclerosis.[130] An important role of Mg^{2+} in vasculature function is a substantial vasodilatory effect that has been reported in animal and human studies.[131-132] Based on the vascular effects of magnesium, it is not surprising that low magnesium levels have been implicated in the pathogenesis of hypertension.[20] Altura and Altura found in an experimental vascular smooth muscle model, that magnesium deficiency, through potentiation of increased cellular calcium activity, may be responsible for the arterial hypertension.[133] Pearson *et al.* demonstrated that hypomagnesemia selectively impaired the release of nitric oxide (NO) from coronary endothelium in a canine model.[115] The low intracellular magnesium levels were associated with impaired endothelial function together with decreased plasma nitrate levels and endothelial NO synthase expression when compared with normal high intracellular magnesium levels. Because NO is a potent endogenous nitro-vasodilator and inhibitor of platelet aggregation and adhesion, hypomagnesemia may also promote vasoconstriction and coronary thrombosis in hypomagnesemic states.[17] In a line with the above researches, there are several epidemiological studies have revealed an inverse association between magnesium consumption and blood pressure. Analysis of 61 dietary variables in 615 elderly participants of the Honolulu Heart Study showed that magnesium was the variable that had the strongest association with blood pressure.[134] Ascherio *et al*. examined the relationship of various nutritional factors with blood pressure levels in 2 prospective studies and found that when adjusted for age, weight, and alcohol consumption, Mg^{2+}, K^+, and fiber were significantly associated with lower risk of hypertension among men but not women who reported a diagnosis of hypertension.[135] However,

among both men and women who did not report hypertension during the follow-up period, Mg^{2+}, K^+, and fiber were each inversely associated with systolic and diastolic pressures.[20] Similarly, a prospective study conducted on 28,349 female health professionals participating in the Women's Health Study revealed that magnesium intake was inversely associated with the risk of developing hypertension, suggesting that magnesium intake might be beneficial in the primary prevention of hypertension.[136]

These data are in support of those from the Dietary Approaches to Stop Hypertension (DASH) clinical trial, which demonstrated that in hypertensive patients, a Mg^{2+}- and K^+-rich diet of fruits, vegetables, and low-fat dairy products lowered blood pressure by 11.4/5.5 mmHg.[137] These epidemiological studies, together with experimental evidence, suggest a strong relationship between magnesium and blood pressure levels and support a role for hypomagnesemia and/or decreased magnesium intake in the pathogenesis of hypertension.[20] Mg^{2+}-ATP is essential for the normal functioning of Na^+/K^+ ATPase, which is responsible for the active transport of K^+ intracellularly during cardiac action potential.[138] Therefore, because Mg^{2+} can act as an indirect antagonist of digoxin at the Na^+/K^+ ATPase pump, intravenous Mg^{2+} is an effective treatment for suppression of cardiac arrhythmias caused by digoxin toxicity. Hypomagnesemia therefore leads to depressed activity of Na^+/K^+ ATPase, cellular K^+ depletion, less negative resting membrane potential, prolongation of the QT interval, and enhanced vulnerability to ventricular arrhythmias and digoxin toxicity.[138-139] A recent study of 3530 participants from the Framingham Offspring Study showed that low serum Mg^2 is moderately associated with the development of atrial fibrillation in individuals without CVD.[140] Magnesium abnormalities are common in patients with CHF. CHF patients with hypomagnesemia have more frequent ventricular premature complexes and episodes of ventricular tachycardia than patients with normal serum Mg^{2+} levels.[141]

Hypomagnesaemia and Coronary Artery Disease

Over the last 20 years, an increasing number of studies have demonstrated that low serum Mg^{2+} levels and low Mg^{2+} intake are associated with an increased risk of coronary artery disease (CAD), artherosclerosis, and metabolic syndrome.[142] Low serum Mg^{2+} levels have been associated with a higher mortality risk in CAD patients.[143] There may be several ways in which Mg^{2+} supplementation benefits patients with CAD. Since Mg^{2+} has a strong anti-inflammatory role, Mg^{2+} results in an improved lipid profile, reduced free oxygen radicals, and improved endothelial function.[144] Mg^{2+} prevents blood clotting by reducing platelet aggregation,[145] and it has a strong vasodilator effect.[132] These properties make Mg^{2+} an important factor in the development and management of CAD. Mg^{2+} improves several aspects of vascular function in CAD.[35] Reduced serum Mg^{2+} concentrations are associated with an increase in carotid intimamedia thickness and risk for sudden cardiac death.[146]

In a randomized, double-blind, placebo-controlled study of 50 CAD patients, oral Mg^{2+} supplementation ameliorated endothelial function.[147] Moreover, Mg^{2+} reduced platelet-induced thrombosis in a randomized prospective, double-blind, crossover, and placebo-controlled study in 42 CAD patients.[148] Six months of Mg^{2+} supplementation increased maximal oxygen uptake ($V^{\cdot}O2$ max) and left ventricular ejection fraction (LVEF) in 53 CAD patients.[109] Taken together, these studies suggest that Mg^{2+} levels should be closely monitored in CAD patients and propose Mg^{2+} as potential drug to improve quality of life in CAD patients.

Hypomagnesaemia and Myocardial Infarction

In the 1970s, a pioneering paper by Abraham *et al.*[149] associated myocardial infarction with a significant drop in serum Mg^{2+}. Indeed, low serum Mg^{2+} levels have been associated with an increased risk of acute myocardial infarction (AMI).[150] The role of Mg^{2+} in preventing myocardial infarction may be caused by relaxing endothelial and smooth muscle cells in the heart and vasculature.[131] Moreover, heart rate variability is a risk factor for AMI and Mg^{2+} may prevent arrhythmia.[150-151] Several studies have addressed the effect of Mg^{2+} on myocardial infarction. In the 1980s, studies reported a 20% reduction of infarct size in Mg^{2+}-treated patients, and decreased mortality after Mg^{2+} infusion.[152] Several follow-up studies suggested that decreased rates of arrhythmias after infarction explain the lower mortality.[153] After these initial promising results, several clinical trials have addressed this subject. The Leicester Intravenous Magnesium Intervention Trial 2 (LIMIT-2) included 2,316 AMI patients and found 24% reduced mortality after 28 days in the Mg^{2+} group (95% CI: 1– 43%).[154] Moreover, two smaller studies by Shechter and colleagues reported reduced mortality rates of 50 and 40%.[155] Contrary to these findings, in the fourth Infarct Survival and Magnesium in Coronies (ISIS-4) study, a randomized factorial trial in 58,050 patients showed no beneficial effects of intravenous Mg^{2+} administration on survival.[156] The results from the ISIS-4 study were called into question because the statistical analysis did not reflect the heterogeneous studies used in the analysis, the low mortality in the placebo-group was indicative of a low-risk comparison group, and the late time-point of Mg^{2+} administration, namely, after and not during reperfusion, was at odds with animal data demonstrating the effectiveness of Mg^{2+}.[157]

However, also a second large-scale randomized double-blind study with 6, 213 patients and an earlier time point of Mg^{2+} infusion (3.8 h compared with 8 hr in ISIS-4) also failed to show a decrease on 30-day mortality rates.[158] Indeed, a recent meta-analysis within the Cochrane collaboration concludes that there is no beneficial effect of Mg^{2+} on mortality in AMI patients (OR 0.99, 95% CI: 0.94 to 1.04).[159] However, it should be noted that the ISIS-4 study provides 72% of the power in this analysis and that the Mg^{2+} doses used within the analyzed studies differ significantly. Nevertheless, current guidelines do not recommend Mg^{2+} administration in AMI patients.[35]

Hypomagnesaemia and Arrhythmia

In 1935, Dr. Zwillinger was the first to report an antiarrhythmic effect of Mg^{2+}, and since then sporadic reports of patients treated with Mg^{2+} have appeared in the literature.[160] However, the field suffers from a lack of large scale randomized controlled trials, and therefore the exact clinical benefit of Mg^{2+} in treatment of arrhythmia remains to be determined. Mg^{2+} is known to have a function in regulating cardiac K^+ and Ca^{2+} channels, so it affects the cardiac action potential.[35] As a result, hypomagnesemia in itself has been proposed as a cause of arrhythmia, specifically in combination with stress or alcoholism.[161] Clinical studies have demonstrated that treatment success strongly depends on the type of arrhythmia.[162] Atrial fibrillation is one of the most common and dangerous complications after cardiac surgery. In the last few decades, several small-scale studies have examined the effect of Mg^{2+} in preventing these fibrillations.[163] Meta-analysis of these studies concluded that Mg^{2+} infusion may prevent atrial fibrillations.[151] Therefore, the European Association for Cardiothoracic Surgery and the Canadian Cardiovascular Society recommend prophylaxis with intravenous $MgSO_4$. However, recent reports point to problems associated with many studies at the level of double-blinding, primary outcome, and intention-to-treat analysis.[35] When only high quality studies are included, Mg^{2+} does not have a preventive effect on atrial fibrillations (OR: 0.94, 95% CI: 0.61 – 1.44).[163] A similar discrepancy between low- and high-quality studies has been noted for studies addressing the effects of Mg^{2+} on supraventricular arrhythmias.[164] Interestingly, for treatment of torsades des pointes, Mg^{2+} has been implemented as a first line of treatment after several studies in the 1980s showed beneficial effects.

However, due to the absence of large-scale clinical trials, optimal doses for treatment are still under debate.[165] Other arrhythmias, including refractory ventricular fibrillation and monomorphic ventricular tachycardia, are insensitive to Mg^{2+} treatment.[166]

Hypomagnesaemia and Hypertension

Low serum Mg^{2+} levels are frequently linked to high blood pressure.[134-135] Intracellular Mg^{2+} may reduce the intracellular Ca^{2+} concentration within vascular smooth muscle cells. This Mg^{2+}-induced vasodilation is thought to be the mechanism by which Mg^{2+} alters the blood pressure.[35] Moreover, high extracellular Mg^{2+} reduces the endothelin-1 expression and causes an increase in prostacyclin (PGI_2) levels, contributing to vasodilation.[111] Additionally, Mg^{2+} inhibits the production of NO.[115] Mg^{2+} was first used to lower blood pressure in 1925, when Mg^{2+} infusion was found to lower blood pressure by reducing the peripheral vascular resistance.[167] Several studies have shown that oral Mg^{2+} intake reduces both systolic and diastolic blood pressure;[168] however, other studies fail to see such an effect.[169] A systematic review of the Cochrane Hypertension Group reported a small reduction of diastolic blood pressure (DBP: -2.2 mmHg, 95% CI: -3.4 to -0.9), but not of the systolic blood pressure (SBP: -1.3 mmHg, 95% CI: -4.0 to 1.5).[170] Another meta-analysis detected a small but dose dependent effect of Mg^{2+} on blood pressure, for each 10 mmol/day -4.3 mmHg SBP (95% CI: -6.3 to -2.2) and -2.3 mmHg DBP (95% CI: -4.9 to 0.0).[171] However, the outcomes may be biased by the inclusion of poor quality studies that tend to overestimate the effects.[35] In contrast, a meta-analysis of a subset of studies, including patients on antihypertensive drugs with high blood pressure (SBP >155 mmHg) reports much stronger effects of oral Mg^{2+} treatment on SBP (-18.7 mmHg, 95% CI: -14.95 to -22.45) and DBP (-10.9 mmHg, 95% CI: -8.73 to -13.1).[172] These results suggest that Mg^{2+} may be beneficial for certain subgroups of hypertensive patients and that comparing the highly heterogeneous studies may underestimate the effects of Mg^{2+} in these groups. Since the 1950s, intravenous $MgSO_4$ administration has gradually become the standard treatment for preeclampsia and eclampsia, and nowadays the treatment is widely advocated by the World Health Organization.[173] The mechanisms of action underlying the effect of Mg^{2+} in the treatment of these patients are largely unknown.[35]

Mg^{2+} may reduce preeclampsia by its effect as vasodilator in the vasculature, but it cannot be excluded that Mg^{2+} also functions as an anticonvulsant through blockade of the NMDA receptor and reduces cerebral edema.[174] Recent Cochrane systematic reviews showed that $MgSO_4$ treatment in preeclamptic women reduced the risk for eclampsia by >50% (RR: 0.41, 95% CI: 0.29 – 0.58), and there was a trend towards lower maternal mortality (RR: 0.54, 95% CI: 0.26 – 1.10)(280). $MgSO_4$ demonstrated similar ratios for reduced risk for eclamptic convulsions comparable to anticonvulsant medication, with 59% compared with diazepam (RR: 0.41, 95% CI: 0.29 – 0.58) and 66% compared with phenytoin (RR: 0.34, 95% CI: 0.24 – 0.49).[175] Moreover, a recent meta-analysis of "real-world" use of $MgSO_4$ for the treatment of preeclampsia confirmed the results from the clinical trials and showed ~50% reduction of eclampsia risk in most studies.[176] Interestingly, although Mg^{2+} was successful in preventing eclampsia, it did not change the risk of death or disability for children at 18 months (RR: 1.06, 95% CI: 0.90 – 1.25) or the risk of death or disability for women at 2 years (RR: 0.84, 95% CI: 0.60 – 1.18).[177]

Hypomagnesaemia and Vascular Calcification

Vascular calcification is frequently observed in patients suffering from chronic kidney disease (CKD).[178] Calcifications are a major contributor to cardiovascular death that accounts for 50% of all deaths in CKD.[179] Vascular calcification is the consequence of a disturbed mineral metabolism including increased serum P_i levels. Increased serum levels of FGF-23 and PTH enhance the formation of calcification.[35] Low serum Mg^{2+} levels are associated with vascular calcification, and hemodialysis patients with higher serum Mg^{2+} levels show higher survival.[180] Although the mechanisms of action are not completely understood, there are two contributing factors:[35]1) Mg^{2+} prevents the formation and deposition of Ca/P nanocrystals and the development of appetite structures;[181] and 2) Mg^{2+} inhibits the trans-differentiation of the smooth muscle cells in the vessel well into osteoblast-like cells.[182] In both processes Mg^{2+} prevents vascular calcification, and thus hypomagnesemic patients are at risk. Therefore, Mg^{2+} supplementation has been proposed as P_i-binder to reduce vascular calcification in CKD patients.[35] Several studies have shown that combined administration of Ca^{2+} and Mg^{2+} is as effective as standard treatment options.[183]

In the recent CALMAG study comparing $MgCO_3/Ca(OAc)_2$ with Sevalamer-HCl in 200 hemodialysis patients, both treatments were effective in reducing serum P_i levels without increasing Ca^{2+} levels.[184]

CONCLUSION

Magnesium is one of the major mineral nutrients in the human body and it is an essential electrolyte for living organisms because of its vital role in many cellular processes. Magnesium is essential for a number of metabolic activities since it is associated with a variety of enzymes which control carbohydrate, fat, protein end electrolyte metabolism. It is also involved in several essential physiological, biochemical, and cellular processes regulating cardiovascular function. Magnesium deficiency plays an important role in the etiology of diabetes and numerous cardiovascular diseases including thrombosis, atherosclerosis, ischemic heart disease, myocardial infarction, hypertension, cardiac arrhythmias and CHF in humans. Magnesium deficiency may lead to reduced energetic metabolite production and the sense of fatigue and/or "chronic fatigue syndrome. At the vascular level, reduced magnesium concentrations are associated with endothelial dysfunction, increased vascular reactivity, increased vascular tone, and elevated blood pressure, whereas increased magnesium levels are associated with opposite effects. Magnesium has vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties. Therefore, magnesium supplementation in those patients can be of benefit in most cases. Furthermore, magnesium therapy is indicated in life-threatening ventricular arrhythmias such as Torsades de Pointes and intractable ventricular tachycardia. It is a critically important nutrient and a potentially useful therapeutic agent in cardiovascular medicine.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATIONS

RDA: Recommended Daily Allowance; **TRPM6:** Transient Receptor Potential Melastatin; **PTH:** Parathyroid Hormone; **TALH:** Thick Ascending Loop Of Henle; **ADH:** Antidiuretic Hormone; **CAD:** Coronary Artery Disease; **CHF:** Congestive Heart Failure; **MagT1:** Mg^{2+} transporter 1; **SLC:** Solute Carrier Family; **CNNM:** Cyclin M; **MRS2:** Mitochondrial RNA Splicing 2; **NIPA:** Non-imprinted in Prader-Willi/Angelman syndrome; **BMP:** Bone Morphogenetic Protein; **HIP14:** Huntingtin Interacting Protein 14; **MMgT:** Mg^{2+} Transporter; **VSM:** Vascular Smooth Muscle; **DASH:** Dietary Approaches to Stop Hypertension.

REFERENCES

1. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients. 2015;7(9):8199-226. doi: 10.3390/nu7095388, PMID 26404370.
2. Cotton F, Wilkinson G. Anorganische Chemie. Weilheim, Germany: Chemie

GmbH; 1967.
3. Weast R. Handbook of chemistry and physics. Boca Raton, FL: CRC Press; 1987.
4. Hollemann A, Wiberg E, der Anorganischen Chemie L. Berlin, Germany: De Gruyter; 1964.
5. Bodaker I, Sharon I, Suzuki MT, Feingersch R, Shmoish M, Andreishcheva E, *et al*. Comparative community genomics in the Dead Sea: an increasingly extreme environment. ISME J. 2010;4(3):399-407. doi: 10.1038/ismej.2009.141, PMID 20033072.
6. Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev. 2003;24(2):47-66. PMID 18568054.
7. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000;294(1-2):1-26. doi: 10.1016/s0009-8981(99)00258-2, PMID 10727669.
8. Gröber U. Magnesium. In: Micronutrients: metabolic tuning-prevention-therapy. 1st ed. Stuttgart, Germany: MedPharm Scientific Publishers; 2009. p. 159-66.
9. Speich M, Bousquet B, Nicolas G. Reference values for ionized, complexed, and protein-bound plasma magnesium in men and women. Clin Chem. 1981;27(2):246-8. doi: 10.1093/clinchem/27.2.246, PMID 7460276.
10. Kroll MH, Elin RJ. Relationships between magnesium and protein concentrations in serum. Clin Chem. 1985;31(2):244-6. doi: 10.1093/clinchem/31.2.244, PMID 3967355.
11. Romani A, Marfella C, Scarpa A. Cell magnesium transport and homeostasis: role of intracellular compartments. Miner Electrolyte Metab. 1993;19(4-5):282-9. PMID 8264515.
12. Romani A. Regulation of magnesium homeostasis and transport in mammalian cells. Arch Biochem Biophys. 2007;458(1):90-102. doi: 10.1016/j.abb.2006.07.012, PMID 16949548.
13. Romani AM, Scarpa A. Regulation of cellular magnesium. Front Biosci. 2000;5:D720-34. doi: 10.2741/romani, PMID 10922296.
14. de Rouffignac C, Quamme G. Renal magnesium handling and its hormonal control. Physiol Rev. 1994;74(2):305-22. doi: 10.1152/physrev.1994.74.2.305, PMID 8171116.
15. Rude RK. Magnesium metabolism and deficiency. Endocrinol Metab Clin North Am. 1993;22(2):377-95. doi: 10.1016/S0889-8529(18)30172-5, PMID 8325293.
16. Schweigel M, Martens H. Magnesium transport in the gastrointestinal tract. Front Biosci. 2000;5:D666-77. doi: 10.2741/schweigel, PMID 10922297.
17. Shechter M. Magnesium and cardiovascular system. Magnes Res. 2010;23(2):60-72. doi: 10.1684/mrh.2010.0202, PMID 20353903.
18. Mitic LL, Van Itallie CM, Anderson JM. Molecular physiology and pathophysiology of tight junctions I. Tight junction structure and function: lessons from mutant animals and proteins. Am J Physiol Gastrointest Liver Physiol. 2000;279(2):G250-4. doi: 10.1152/ajpgi.2000.279.2.G250, PMID 10915631.
19. de Baaij JH, Hoenderop JG, Bindels RJ. Regulation of magnesium balance: lessons learned from human genetic disease. Clin Kidney J. 2012;5(Suppl 1):i15-24. doi: 10.1093/ndtplus/sfr164, PMID 26069817.
20. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of magnesium in cardiovascular diseases. Cardiol Rev. 2014;22(4):182-92. doi: 10.1097/CRD.0000000000000003, PMID 24896250.
21. Touyz RM. Magnesium in clinical medicine. Front Biosci. 2004;9:1278-93. doi: 10.2741/1316, PMID 14977544.
22. Kayne LH, Lee DB. Intestinal magnesium absorption. Miner Electrolyte Metab. 1993;19(4-5):210-7. PMID 8264506.
23. Yu AS. Evolving concepts in epithelial magnesium transport. Curr Opin Nephrol Hypertens. 2001;10(5):649-53. doi: 10.1097/00041552-200109000-00016, PMID 11496060.
24. Konrad M, Weber S. Recent advances in molecular genetics of hereditary magnesium-losing disorders. J Am Soc Nephrol. 2003;14(1):249-60. doi: 10.1097/01.asn.0000049161.60740.ce, PMID 12506158.
25. Noronha JL, Matuschak GM. Magnesium in critical illness: metabolism, assessment, and treatment. Intensive Care Med. 2002;28(6):667-79. doi: 10.1007/s00134-002-1281-y, PMID 12107669.
26. Cefaratti C, Romani AM. Functional characterization of two distinct $Mg^{(2+)}$ extrusion mechanisms in cardiac sarcolemmal vesicles. Mol Cell Biochem. 2007;303(1-2):63-72. doi: 10.1007/s11010-007-9456-z, PMID 17415622.
27. Romani AM, Maguire ME. Hormonal regulation of Mg^{2+} transport and homeostasis in eukaryotic cells. Biometals. 2002;15(3):271-83. doi: 10.1023/a:1016082900838, PMID 12206393.
28. Fagan TE, Romani A. Activation of Na(+)- and $Ca^{(2+)}$-dependent $Mg^{(2+)}$ extrusion by alpha(1)- and beta-adrenergic agonists in rat liver cells. Am J Physiol Gastrointest Liver Physiol. 2000;279(5):G943-50. doi: 10.1152/ajpgi.2000.279.5.G943, PMID 11052991.
29. Kolisek M, Zsurka G, Samaj J, Weghuber J, Schweyen RJ, Schweigel M. Mrs2p is an essential component of the major electrophoretic Mg^{2+} influx system in mitochondria. EMBO J. 2003;22(6):1235-44. doi: 10.1093/emboj/cdg122, PMID 12628916.
30. Vetter T, Lohse MJ. Magnesium and the parathyroid. Curr Opin Nephrol Hypertens. 2002;11(4):403-10. doi: 10.1097/00041552-200207000-00006, PMID 12105390.
31. Classen HG, Nowitzki S. The clinical importance of magnesium. 2. The indications for supplementation and therapy. Fortschr Med. 1990;108(10):198-200. PMID 2187780.
32. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. J Card Fail. 2007;13(3):170-7. doi: 10.1016/j.cardfail.2006.11.015, PMID 17448413.
33. Altura B. Basic biochemistry and physiology of magnesium: a brief review. Mag Tr Ele. 1991;10:167-71.
34. Sica D, Frishman W. Magnesium, potassium, and calcium as cardiovascular disease therapies. 3rd ed. Minneapolis: Cardiotext Publishing; 2011. p. 177-82.
35. De Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. Physiol Rev. 2015;95(1):1-46. doi: 10.1152/physrev.00012.2014, PMID 25540137.
36. Schmitz C, Perraud AL, Johnson CO, Inabe K, Smith MK, Penner R, *et al*. Regulation of vertebrate cellular Mg^{2+} homeostasis by TRPM7. Cell. 2003;114(2):191-200. doi: 10.1016/s0092-8674(03)00556-7, PMID 12887921.
37. Jin J, Desai BN, Navarro B, Donovan A, Andrews NC, Clapham DE. Deletion of Trpm7 disrupts embryonic development and thymopoiesis without altering Mg^{2+} homeostasis. Science. 2008;322(5902):756-60. doi: 10.1126/science.1163493, PMID 18974357.
38. Bates-Withers C, Sah R, Clapham DE. TRPM7, the $Mg^{(2+)}$ inhibited channel and kinase. Adv Exp Med Biol. 2011;704:173-83. doi: 10.1007/978-94-007-0265-3_9, PMID 21290295.
39. Takezawa R, Schmitz C, Demeuse P, Scharenberg AM, Penner R, Fleig A. Receptor-mediated regulation of the TRPM7 channel through its endogenous protein kinase domain. Proc Natl Acad Sci U S A. 2004;101(16):6009-14. doi: 10.1073/pnas.0307565101, PMID 15069188.
40. Runnels LW, Yue L, Clapham DE. TRP-PLIK, a bifunctional protein with kinase and ion channel activities. Science. 2001;291(5506):1043-7. doi: 10.1126/science.1058519, PMID 11161216.
41. Desai BN, Krapivinsky G, Navarro B, Krapivinsky L, Carter BC, Febvay S, *et al*. Cleavage of TRPM7 releases the kinase domain from the ion channel and regulates its participation in Fas-induced apoptosis. Dev Cell. 2012;22(6):1149-62. doi: 10.1016/j.devcel.2012.04.006, PMID 22698280.
42. Goytain A, Quamme GA. Identification and characterization of a novel mammalian Mg^{2+} transporter with channel-like properties. BMC Genomics. 2005;6:48. doi: 10.1186/1471-2164-6-48, PMID 15804357.
43. Deason-Towne F, Perraud AL, Schmitz C. The Mg^{2+} transporter MagT1 partially rescues cell growth and Mg^{2+} uptake in cells lacking the channel-kinase TRPM7. FEBS Lett. 2011;585(14):2275-8. doi: 10.1016/j.febslet.2011.05.052, PMID 21627970.
44. Li FY, Chaigne-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, *et al*. Second messenger role for Mg^{2+} revealed by human T-cell immunodeficiency. Nature. 2011;475(7357):471-6. doi: 10.1038/nature10246, PMID 21796205.
45. Güther T, Vormann J, Förster R. Regulation of intracellular magnesium by Mg^{2+} efflux. Biochem Biophys Res Commun. 1984;119(1):124-31. doi: 10.1016/0006-291x(84)91627-9, PMID 6422934.
46. Ebel H, Hollstein M, Gunther T. Role of the choline exchanger in $Na^{(+)}$-independent $Mg^{(2+)}$ efflux from rat erythrocytes. Biochim Biophys Acta. 2002;1559(2):135-44. doi: 10.1016/s0005-2736(01)00445-x, PMID 11853680.
47. Kolisek M, Nestler A, Vormann J, Schweigel-Röntgen M. Human gene SLC41A1 encodes for the Na^+/Mg^{2+} exchanger. Am J Physiol Cell Physiol. 2012;302(1):C318-26. doi: 10.1152/ajpcell.00289.2011, PMID 22031603.
48. Goytain A, Quamme GA. Functional characterization of human SLC41A1, a Mg^{2+} transporter with similarity to prokaryotic MgtE Mg^{2+} transporters. Physiol Genomics. 2005;21(3):337-42. doi: 10.1152/physiolgenomics.00261.2004, PMID 15713785.
49. Yan Y, Tian J, Mo X, Zhao G, Yin X, Pu J, *et al*. Genetic variants in the RAB7L1 and SLC41A1 genes of the PARK16 locus in Chinese Parkinson's disease patients. Int J Neurosci. 2011;121(11):632-6. doi: 10.3109/00207454.2011.598983, PMID 21812739.
50. Wang CY, Shi JD, Yang P, Kumar PG, Li QZ, Run QG, *et al*. Molecular cloning and characterization of a novel gene family of four ancient conserved domain proteins (ACDP). Gene. 2003;306:37-44. doi: 10.1016/s0378-1119(02)01210-6, PMID 12657465.
51. De Baaij JH, Stuiver M, Meij IC, Lainez S, Kopplin K, Venselaar H, *et al*. Membrane topology and intracellular processing of cyclin M2 (CNNM2). J Biol Chem. 2012;287(17):13644-55. doi: 10.1074/jbc.M112.342204, PMID 22399287.
52. Hardy S, Uetani N, Wong N, Kostantin E, Labbé DP, Bégin LR, *et al*. The protein tyrosine phosphatase PRL-2 interacts with the magnesium transporter CNNM3 to promote oncogenesis. Oncogene. 2015;34(8):986-95. doi: 10.1038/onc.2014.33, PMID 24632616.
53. Zsurka G, Gregán J, Schweyen RJ. The human mitochondrial Mrs2 protein functionally substitutes for its yeast homologue, a candidate magnesium transporter. Genomics. 2001;72(2):158-68. doi: 10.1006/geno.2000.6407, PMID 11401429.

54. Piskacek M, Zotova L, Zsurka G, Schweyen RJ. Conditional knockdown of hMRS2 results in loss of mitochondrial $Mg^{(2+)}$ uptake and cell death. J Cell Mol Med. 2009;13(4):693-700. doi: 10.1111/j.1582-4934.2008.00328.x, PMID 18384665.
55. Yamazaki D, Funato Y, Miura J, Sato S, Toyosawa S, Furutani K, *et al*. Basolateral Mg^{2+} extrusion via CNNM4 mediates transcellular Mg^{2+} transport across epithelia: a mouse model. PLOS Genet. 2013;9(12):e1003983. doi: 10.1371/journal.pgen.1003983, PMID 24339795.
56. Kuramoto T, Kuwamura M, Tokuda S, Izawa T, Nakane Y, Kitada K, *et al*. A mutation in the gene encoding mitochondrial Mg^{2+} channel MRS2 results in demyelination in the rat. PLOS Genet. 2011;7(1):e1001262. doi: 10.1371/journal.pgen.1001262, PMID 21253565.
57. Goytain A, Hines RM, El-Husseini A, Quamme GA. NIPA1(SPG6), the basis for autosomal dominant form of hereditary spastic paraplegia, encodes a functional Mg^{2+} transporter. J Biol Chem. 2007;282(11):8060-8. doi: 10.1074/jbc.M610314200, PMID 17166836.
58. Tsang HT, Edwards TL, Wang X, Connell JW, Davies RJ, Durrington HJ, *et al*. The hereditary spastic paraplegia proteins NIPA1, spastin and spartin are inhibitors of mammalian BMP signalling. Hum Mol Genet. 2009;18(20):3805-21. doi: 10.1093/hmg/ddp324, PMID 19620182.
59. Goytain A, Hines RM, Quamme GA. Huntingtin-interacting proteins, HIP14 and HIP14L, mediate dual functions, palmitoyl acyltransferase and Mg^{2+} transport. J Biol Chem. 2008;283(48):33365-74. doi: 10.1074/jbc.M801469200, PMID 18794299.
60. Young FB, Franciosi S, Spreeuw A, Deng Y, Sanders S, Tam NC, *et al*. Low levels of human HIP14 are sufficient to rescue neuropathological, behavioural, and enzymatic defects due to loss of murine HIP14 in Hip14-/- mice. PLOS ONE. 2012;7(5):e36315. doi: 10.1371/journal.pone.0036315, PMID 22649491.
61. Goytain A, Quamme GA. Identification and characterization of a novel family of membrane magnesium transporters, MMgT1 and MMgT2. Am J Physiol Cell Physiol. 2008;294(2):C495-502. doi: 10.1152/ajpcell.00238.2007, PMID 18057121.
62. Mubagwa K, Gwanyanya A, Zakharov S, Macianskiene R. Regulation of cation channels in cardiac and smooth muscle cells by intracellular magnesium. Arch Biochem Biophys. 2007;458(1):73-89. doi: 10.1016/j.abb.2006.10.014, PMID 17123458.
63. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185-94. doi: 10.1161/CIRCEP.108.789081.
64. White RE, Hartzell HC. Effects of intracellular free magnesium on calcium current in isolated cardiac myocytes. Science. 1988;239(4841 pt 1):778-80. doi: 10.1126/science.2448878, PMID 2448878.
65. Brunet S, Scheuer T, Klevit R, Catterall WA. Modulation of CaV1.2 channels by Mg^{2+} acting at an EF-hand motif in the COOH-terminal domain. J Gen Physiol. 2005;126(4):311-23. doi: 10.1085/jgp.200509333, PMID 16157690.
66. Wang M, Tashiro M, Berlin JR. Regulation of L-type calcium current by intracellular magnesium in rat cardiac myocytes. J Physiol. 2004;555(2):383-96. doi: 10.1113/jphysiol.2003.048538, PMID 14617671.
67. Williams BA, Beatch GN. Magnesium shifts voltage dependence of activation of delayed rectifier I(K) in guinea pig ventricular myocytes. Am J Physiol. 1997;272(3 pt 2):H1292-301. doi: 10.1152/ajpheart.1997.272.3.H1292, PMID 9087604.
68. Sudo GZ, Sanguinetti MC. Intracellular [Mg++] determines specificity of K^+ channel block by a class III antiarrhythmic drug. J Pharmacol Exp Ther. 1996;276(3):951-7. PMID 8786575.
69. Westhof E, Sundaralingam M. Restrained refinement of the monoclinic form of yeast phenylalanine transfer RNA. Temperature factors and dynamics, coordinated waters, and base-pair propeller twist angles. Biochemistry. 1986;25(17):4868-78. doi: 10.1021/bi00365a022, PMID 3533142.
70. Brautigam CA, Steitz TA. Structural and functional insights provided by crystal structures of DNA polymerases and their substrate complexes. Curr Opin Struct Biol. 1998;8(1):54-63. doi: 10.1016/s0959-440x(98)80010-9, PMID 9519297.
71. Michailova AP, Belik ME, McCulloch AD. Effects of magnesium on cardiac excitation-contraction coupling. J Am Coll Nutr. 2004;23(5):514S-7S. doi: 10.1080/07315724.2004.10719392, PMID 15466954.
72. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984;108(1):188-93. doi: 10.1016/0002-8703(84)90572-6, PMID 6375330.
73. Allouche D, Parello J, Sanejouand YH. Ca^{2+}/Mg^{2+} exchange in parvalbumin and other EF-hand proteins. A theoretical study. J Mol Biol. 1999;285(2):857-73. doi: 10.1006/jmbi.1998.2329, PMID 9878449.
74. Boyman L, Mikhasenko H, Hiller R, Khananshvili D. Kinetic and equilibrium properties of regulatory calcium sensors of NCX1 protein. J Biol Chem. 2009;284(10):6185-93. doi: 10.1074/jbc.M809012200, PMID 19141619.
75. Breukels V, Konijnenberg A, Nabuurs SM, Touw WG, Vuister GW. The second $Ca^{(2+)}$-binding domain of NCX1 binds Mg^{2+} with high affinity. Biochemistry. 2011;50(41):8804-12. doi: 10.1021/bi201134u, PMID 21928827.
76. Appel LJ. Nonpharmacologic therapies that reduce blood pressure: A fresh perspective. Clin Cardiol. 1999;22(7);Suppl:III1-5. doi: 10.1002/clc.4960221502, PMID 10410298.
77. Institute of Medicine. Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: Food and Nutrition Board. National Academy Press; 1999.
78. Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, Lashevsky I. Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. Am J Cardiol. 2007;99(12):1726-32. doi: 10.1016/j.amjcard.2007.01.057, PMID 17560883.
79. Cagli K, Ozeke O, Ergun K, Budak B, Demirtas E, Birincioglu CL *et al*. Effect of low-dose amiodarone and magnesium combination on atrial fibrillation after coronary artery surgery. J Card Surg. 2006;21(5):458-64. doi: 10.1111/j.1540-8191.2006.00277.x, PMID 16948756.
80. Coleman CI, Sood N, Chawla D, Talati R, Ghatak A, Kluger J *et al*. Intravenous magnesium sulfate enhances the ability of dofetilide to successfully cardiovert atrial fibrillation or flutter: results of the Dofetilide and Intravenous Magnesium Evaluation. Europace. 2009;11(7):892-5. doi: 10.1093/europace/eup084, PMID 19351630.
81. Kinlay S, Buckley NA. Magnesium sulfate in the treatment of ventricular arrhythmias due to digoxin toxicity. J Toxicol Clin Toxicol. 1995;33(1):55-9. doi: 10.3109/15563659509020216, PMID 7837314.
82. Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Greene HL *et al*.. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). J Am Coll Cardiol. 2006;48(11):2360-96. doi: 10.1016/j.jacc.2006.09.020. PMID 17161282.
83. Kurita T, Ohe T, Shimizu W, Hotta D, Shimomura K. Early afterdepolarization in a patient with complete atrioventricular block and torsades de pointes. Pacing Clin Electrophysiol. 1993;16(1 pt 1):33-8. doi: 10.1111/j.1540-8159.1993.tb01532.x, PMID 7681173.
84. Ceremuzynski L, Gebalska J, Wolk R, Makowska E. Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. J Intern Med. 2000;247(1):78-86. doi: 10.1046/j.1365-2796.2000.00585.x, PMID 10672134.
85. Parikka H, Toivonen L, Verkkala K, Järvinen A, Nieminen MS. Ventricular arrhythmia suppression by magnesium treatment after coronary artery bypass surgery. Int J Angiol. 1999;8(3):165-70. doi: 10.1007/BF01616447, PMID 10387126.
86. Zehender M, Meinertz T, Faber T, Caspary A, Jeron A, Bremm K *et al*. Antiarrhythmic effects of increasing the daily intake of magnesium and potassium in patients with frequent ventricular arrhythmias. Magnesium in Cardiac Arrhythmias (MAGICA) Investigators. J Am Coll Cardiol. 1997;29(5):1028-34. doi: 10.1016/s0735-1097(97)00053-3, PMID 9120155.
87. Albitz R, Magyar J, Nilius B. Block of single cardiac sodium channels by intracellular magnesium. Eur Biophys J. 1990;19(1):19-23. doi: 10.1007/BF00223569, PMID 2176585.
88. Wang M, Berlin JR. Channel phosphorylation and modulation of L-type Ca^{2+} currents by cytosolic Mg^{2+} concentration. Am J Physiol Cell Physiol. 2006;291(1):C83-92. doi: 10.1152/ajpcell.00579.2005, PMID 16481369.
89. Kamp TJ, Hell JW. Regulation of cardiac L-type calcium channels by protein kinase A and protein kinase C. Circ Res. 2000;87(12):1095-102. doi: 10.1161/01.res.87.12.1095, PMID 11110765.
90. Yamaoka K, Seyama I. Modulation of Ca^{2+} channels by intracellular Mg^{2+} ions and GTP in frog ventricular myocytes. Pflugers Arch. 1996;432(3):433-8. doi: 10.1007/s004240050155, PMID 8766003.
91. Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S. Protective role of magnesium in cardiovascular diseases: a review. Mol Cell Biochem. 2002;238(1-2):163-79. doi: 10.1023/a:1019998702946, PMID 12349904.
92. Lopatin AN, Makhina EN, Nichols CG. Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. Nature. 1994;372(6504):366-9. doi: 10.1038/372366a0, PMID 7969496.
93. Vandenberg CA. Inward rectification of a potassium channel in cardiac ventricular cells depends on internal magnesium ions. Proc Natl Acad Sci U S A. 1987;84(8):2560-4. doi: 10.1073/pnas.84.8.2560, PMID 2436236.
94. Lopatin AN, Nichols CG. [K+] dependence of polyamine-induced rectification in inward rectifier potassium channels (IRK1, Kir2.1). J Gen Physiol. 1996;108(2):105-13. doi: 10.1085/jgp.108.2.105, PMID 8854340.
95. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL *et al*. Coassembly of K(V)LQT1 and mink (IsK) proteins to form cardiac I(Ks) potassium channel. Nature. 1996;384(6604):80-3. doi: 10.1038/384080a0, PMID 8900283.
96. Hirahara K, Matsubayashi T, Matsuura H, Ehara T. Intracellular Mg^{2+} depletion depresses the delayed rectifier K+ current in guinea pig ventricular myocytes. Jpn J Physiol. 1998;48(1):81-9. doi: 10.2170/jjphysiol.48.81, PMID 9538293.
97. Wilson DL, Morimoto K, Tsuda Y, Brown AM. Interaction between calcium ions and surface charge as it relates to calcium currents. J Membr Biol. 1983;72(1-2):117-30. doi: 10.1007/BF01870319, PMID 6304316.
98. Green WN, Andersen OS. Surface charges and ion channel function. Annu Rev Physiol. 1991;53:341-59. doi: 10.1146/annurev.ph.53.030191.002013, PMID 1710438.
99. Lansman JB, Hess P, Tsien RW. Blockade of current through single calcium channels by CD^{2+}, Mg^{2+}, and Ca^{2+}. Voltage and concentration dependence of calcium entry into the pore. J Gen Physiol. 1986;88(3):321-47. doi: 10.1085/

jgp.88.3.321, PMID 2428920.
100. Bara M, Guiet-Bara A. Magnesium regulation of Ca^{2+} channels in smooth muscle and endothelial cells of human allantochorial placental vessels. Magnes Res. 2001;14(1-2):11-8. PMID 11300616.
101. Serrano JR, Dashti SR, Perez-Reyes E, Jones SW. $Mg^{(2+)}$ block unmasks $Ca^{(2+)}/Ba^{(2+)}$ selectivity of alpha1G T-type calcium channels. Biophys J. 2000;79(6):3052-62. doi: 10.1016/S0006-3495(00)76540-4, PMID 11106611.
102. Yoshimura M, Oshima T, Matsuura H, Ishida T, Kambe M, Kajiyama G. Extracellular Mg^{2+} inhibits capacitative Ca^{2+} entry in vascular smooth muscle cells. Circulation. 1997;95(11):2567-72. doi: 10.1161/01.cir.95.11.2567, PMID 9184588.
103. Touyz RM, Laurant P, Schiffrin EL. Effect of magnesium on calcium responses to vasopressin in vascular smooth muscle cells of spontaneously hypertensive rats. J Pharmacol Exp Ther. 1998;284(3):998-1005. PMID 9495860.
104. Sjögren A, Edvinsson L. The influence of magnesium on the release of calcium from intracellular depots in vascular smooth muscle cells. Pharmacol Toxicol. 1988;62(1):17-21. doi: 10.1111/j.1600-0773.1988.tb01837.x, PMID 3162768.
105. Altura BM, Zhang A, Altura BT. Magnesium, hypertensive vascular diseases, atherogenesis, subcellular compartmentation of Ca^{2+} and Mg^{2+} and vascular contractility. Miner Electrolyte Metab. 1993;19(4-5):323-36. PMID 8264520.
106. Kugiyama K, Yasue H, Okumura K, Goto K, Minoda K, Miyagi H, *et al.* Suppression of exercise-induced angina by magnesium sulfate in patients with variant angina. J Am Coll Cardiol. 1988;12(5):1177-83. doi: 10.1016/0735-1097(88)92597-1, PMID 3170960.
107. Shechter M, Paul-Labrador MJ, Rude RK, Bairey Merz CN. Intracellular magnesium predicts functional capacity in patients with coronary artery disease. Cardiology. 1998;90(3):168-72. doi: 10.1159/000006839, PMID 9892764.
108. Shechter M, Bairey Merz CN, Stuehlinger HG, Slany J, Pachinger O, Rabinowitz B. Effects of oral magnesium therapy on exercise tolerance, exercise-induced chest pain, and quality of life in patients with coronary artery disease. Am J Cardiol. 2003;91(5):517-21. doi: 10.1016/s0002-9149(02)03297-6, PMID 12615252.
109. Pokan R, Hofmann P, von Duvillard SP, Smekal G, Wonisch M, Lettner K, *et al.* Oral magnesium therapy, exercise heart rate, exercise tolerance, and myocardial function in coronary artery disease patients. Br J Sports Med. 2006;40(9):773-8. doi: 10.1136/bjsm.2006.027250, PMID 16825271.
110. Nadler JL, Goodson S, Rude RK. Evidence that prostacyclin mediates the vascular action of magnesium in humans. Hypertension. 1987;9(4):379-83. doi: 10.1161/01.hyp.9.4.379, PMID 2435656.
111. Satake K, Lee JD, Shimizu H, Uzui H, Mitsuke Y, Yue H *et al.* Effects of magnesium on prostacyclin synthesis and intracellular free calcium concentration in vascular cells. Magnes Res. 2004;17(1):20-7. PMID 15083565.
112. Vaca L, Kunze DL. Depletion of intracellular Ca^{2+} stores activates a $Ca^{(2+)}$- selective channel in vascular endothelium. Am J Physiol. 1994;267(4 pt 1):C920-5. doi: 10.1152/ajpcell.1994.267.4.C920, PMID 7943286.
113. Yoshimura M, Oshima T, Matsuura H, Inoue T, Kambe M, Kajiyama G. Differential effects of extracellular Mg^{2+} on thrombin-induced and capacitative Ca^{2+} entry in human coronary arterial endothelial cells. Arterioscler Thromb Vasc Biol. 1997;17(11):3356-61. doi: 10.1161/01.atv.17.11.3356, PMID 9409333.
114. Yang ZW, Gebrewold A, Nowakowski M, Altura BT, Altura BM. $Mg^{(2+)}$-induced endothelium-dependent relaxation of blood vessels and blood pressure lowering: role of NO. Am J Physiol Regul Integr Comp Physiol. 2000;278(3):R628-39. doi: 10.1152/ajpregu.2000.278.3.R628, PMID 10712282.
115. Pearson PJ, Evora PR, Seccombe JF, Schaff HV. Hypomagnesemia inhibits nitric oxide release from coronary endothelium: protective role of magnesium infusion after cardiac operations. Ann Thorac Surg. 1998;65(4):967-72. doi: 10.1016/s0003-4975(98)00020-4, PMID 9564911.
116. Gawaz M, Ott I, Reininger AJ, Neumann FJ. Effects of magnesium on platelet aggregation and adhesion. Magnesium modulates surface expression of glycoproteins on platelets *in vitro* and *ex vivo*. Thromb Haemost. 1994;72(6):912-8. doi: 10.1055/s-0038-1648983, PMID 7740463.
117. Gawaz M, Reininger A, Neumann FJ. Platelet function and platelet-leukocyte adhesion in symptomatic coronary heart disease. Effects of intravenous magnesium. Thromb Res. 1996;83(5):341-9. doi: 10.1016/0049-3848(96)00144-2, PMID 8873343.
118. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, *et al.* Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39(2):257-65. doi: 10.1016/s0735-1097(01)01746-6, PMID 11788217.
119. Shechter M, Merz CN, Rude RK, Paul Labrador MJ, Meisel SR, Shah PK, *et al.* Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. Am Heart J. 2000;140(2):212-8. doi: 10.1067/mhj.2000.107553, PMID 10925332.
120. Rukshin V, Azarbal B, Shah PK, Tsang VT, Shechter M, Finkelstein A, *et al.* Intravenous magnesium in experimental stent thrombosis in swine. Arterioscler Thromb Vasc Biol. 2001;21(9):1544-9. doi: 10.1161/hq0901.094493, PMID 11557686.
121. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients. 2015;7(9):8199-226. doi: 10.3390/nu7095388, PMID 26404370.
122. Classen HG, Gröber U, Kisters K. Drug-induced magnesium deficiency. Med Monatsschr Pharm. 2012;35(8):274-80. PMID 22970526.
123. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003;23(2):168-75. doi: 10.1161/01.atv.0000051384.43104.fc, PMID 12588755.
124. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell. 2001;104(4):545-56. doi: 10.1016/s0092-8674(01)00241-0, PMID 11239411.
125. Hans CP, Chaudhary DP, Bansal DD. Magnesium deficiency increases oxidative stress in rats. Indian J Exp Biol. 2002;40(11):1275-9. PMID 13677631.
126. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. Am J Cardiol. 2003;91(3A):7A-11A. doi: 10.1016/s0002-9149(02)03144-2, PMID 12645638.
127. Bernardini D, Nasulewic A, Mazur A, Maier JA. Magnesium and microvascular endothelial cells: a role in inflammation and angiogenesis. Front Biosci. 2005;10:1177-82. doi: 10.2741/1610, PMID 15769616.
128. Ferrè S, Baldoli E, Leidi M, Maier JA. Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB. Biochim Biophys Acta. 2010;1802(11):952-8. doi: 10.1016/j.bbadis.2010.06.016, PMID 20600865.
129. Wiles ME, Wagner TL, Weglicki WB. Effect of acute magnesium deficiency (MgD) on aortic endothelial cell (EC) oxidant production. Life Sci. 1997;60(3):221-36. doi: 10.1016/s0024-3205(96)00619-4, PMID 9000647.
130. King JL, Miller RJ, Blue JP, O'Brien WD, Erdman JW. Inadequate dietary magnesium intake increases atherosclerotic plaque development in rabbits. Nutr Res. 2009;29(5):343-9. doi: 10.1016/j.nutres.2009.05.001, PMID 19555816.
131. Altura BT, Altura BM. Endothelium-dependent relaxation in coronary arteries requires magnesium ions. Br J Pharmacol. 1987;91(3):449-51. doi: 10.1111/j.1476-5381.1987.tb11235.x, PMID 3496933.
132. Teragawa H, Matsuura H, Chayama K, Oshima T. Mechanisms responsible for vasodilation upon magnesium infusion *in vivo*: Clinical evidence. Magnes Res. 2002;15(3-4):241-6. PMID 12635879.
133. Altura BM, Altura BT. Vascular smooth muscle and prostaglandins. Fed Proc. 1976;35(12):2360-6. PMID 823050.
134. Joffres MR, Reed DM, Yano K. Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study. Am J Clin Nutr. 1987;45(2):469-75. doi: 10.1093/ajcn/45.2.469, PMID 3812346.
135. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J *et al.* Prospective study of nutritional factors, blood pressure, and hypertension among US women. Hypertension. 1996;27(5):1065-72. doi: 10.1161/01.hyp.27.5.1065, PMID 8621198.
136. 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(12):1616-21. doi: 10.1016/j.amjcard.2006.07.040, PMID 17145221.
137. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM *et al.* A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336(16):1117-24. doi: 10.1056/NEJM199704173361601, PMID 9099655.
138. Abbott LG, Rude RK. Clinical manifestations of magnesium deficiency. Miner Electrolyte Metab. 1993;19(4-5):314-22. PMID 8264519.
139. Parikka H, Toivonen L, Naukkarinen V, Tierala I, Pohjola-Sintonen S, Heikkilä J *et al.* Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infarction. Eur Heart J. 1999;20(2):111-20. doi: 10.1053/euhj.1998.1238, PMID 10099907.
140. Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS *et al.* Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. Circulation. 2013;127(1):33-8. doi: 10.1161/CIRCULATIONAHA.111.082511, PMID 23172839.
141. Gottlieb SS, Baruch L, Kukin ML, Bernstein JL, Fisher ML, Packer M. Prognostic importance of the serum magnesium concentration in patients with congestive heart failure. J Am Coll Cardiol. 1990;16(4):827-31. doi: 10.1016/s0735-1097(10)80329-8, PMID 2212365.
142. Abbott RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H, *et al.* Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). Am J Cardiol. 2003;92(6):665-9. doi: 10.1016/s0002-9149(03)00819-1, PMID 12972103.
143. Ford ES. Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. Int J Epidemiol. 1999;28(4):645-51. doi: 10.1093/ije/28.4.645, PMID 10480691.
144. Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. Am J Clin Nutr. 2007;85(4):1068-74. doi: 10.1093/ajcn/85.4.1068, PMID 17413107.
145. Rukshin V, Shah PK, Cercek B, Finkelstein A, Tsang V, Kaul S. Comparative

antithrombotic effects of magnesium sulfate and the platelet glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide in a canine model of stent thrombosis. Circulation. 2002;105(16):1970-5. doi: 10.1161/01.cir.0000014612.88433.62, PMID 11997285.

146. Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2010;160(3):464-70. doi: 10.1016/j.ahj.2010.06.012, PMID 20826254.
147. Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation. 2000;102(19):2353-8. doi: 10.1161/01.cir.102.19.2353, PMID 11067788.
148. Shechter M, Merz CN, Paul-Labrador M, Meisel SR, Rude RK, Molloy MD *et al.* Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease. Am J Cardiol. 1999;84(2):152-6. doi: 10.1016/s0002-9149(99)00225-8, PMID 10426331.
149. Abraham AS, Eylath U, Weinstein M, Czaczkes E. Serum magnesium levels in patients with acute myocardial infarction. N Engl J Med. 1977;296(15):862-3. doi: 10.1056/NEJM197704142961509, PMID 846497.
150. Singh RB, Pella D, Neki NS, Chandel JP, Rastogi S, Mori H, *et al.* Mechanisms of acute myocardial infarction study (MAMIS). Biomed Pharmacother. 2004;58;Suppl 1:S111-5. doi: 10.1016/s0753-3322(04)80018-0, PMID 15754848.
151. Shiga T, Wajima Z, Inoue T, Ogawa R. Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. Am J Med. 2004;117(5):325-33. doi: 10.1016/j.amjmed.2004.03.030, PMID 15336582.
152. Rasmussen HS, McNair P, Norregard P, Backer V, Lindeneg O, Balslev S. Intravenous magnesium in acute myocardial infarction. Lancet. 1986;1(8475):234-6. doi: 10.1016/s0140-6736(86)90773-7, PMID 2868254.
153. Smith LF, Heagerty AM, Bing RF, Barnett DB. Intravenous infusion of magnesium sulphate after acute myocardial infarction: effects on arrhythmias and mortality. Int J Cardiol. 1986;12(2):175-83. doi: 10.1016/0167-5273(86)90239-1, PMID 2427458.
154. Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester intravenous Magnesium Intervention Trial (LIMIT-2). Lancet. 1992;339(8809):1553-8. doi: 10.1016/0140-6736(92)91828-v, PMID 1351547.
155. Shechter M, Hod H, Marks N, Behar S, Kaplinsky E, Rabinowitz B. Beneficial effect of magnesium sulfate in acute myocardial infarction. Am J Cardiol. 1990;66(3):271-4. doi: 10.1016/0002-9149(90)90834-n, PMID 2195862.
156. Fourth international study of infarct survival. ISIS4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Collab Group Lancet. 1995;345:669-85.
157. Seelig MS, Elin RJ, Antman EM. Magnesium in acute myocardial infarction: still an open question. Can J Cardiol. 1998;14(5):745-9. PMID 9627532.
158. Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the magnesium in Coronaries (MAGIC) Trial: a randomised controlled trial. Lancet. 2002;360(9341):1189-96. doi: 10.1016/s0140-6736(02)11278-5, PMID 12401244.
159. Li J, Zhang Q, Zhang M, Egger M. Intravenous magnesium for acute myocardial infarction. Cochrane Database Syst Rev. 2007;(2):CD002755. doi: 10.1002/14651858.CD002755.pub2, PMID 17443517.
160. Zwillinger L. Über die Magnesiumwirkung auf das Herz. Klin Wochenschr. 1935;14(40):1429-33. doi: 10.1007/BF01778848.
161. Topol EJ, Lerman BB. Hypomagnesemic torsades de pointes. Am J Cardiol. 1983;52(10):1367-8. doi: 10.1016/0002-9149(83)90611-2, PMID 6650429.
162. Ho KM. Intravenous magnesium for cardiac arrhythmias: jack of all trades. Magnes Res. 2008;21(1):65-8. PMID 18557136.
163. Cook RC, Yamashita MH, Kearns M, Ramanathan K, Gin K, Humphries KH. Prophylactic magnesium does not prevent atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg. 2013;95(2):533-41. doi: 10.1016/j.athoracsur.2012.09.008, PMID 23141526.
164. De Oliveira GS, Knautz JS, Sherwani S, McCarthy RJ. Systemic magnesium to reduce postoperative arrhythmias after coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2012;26(4):643-50. doi: 10.1053/j.jvca.2012.03.012, PMID 22560953.
165. Hoshino K, Ogawa K, Hishitani T, Isobe T, Etoh Y. Successful uses of magnesium sulfate for torsades de pointes in children with long QT syndrome. Pediatr Int. 2006;48(2):112-7. doi: 10.1111/j.1442-200X.2006.02177.x, PMID 16635167.
166. Hassan TB, Jagger C, Barnett DB. A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. Emerg Med J. 2002;19(1):57-62. doi: 10.1136/emj.19.1.57, PMID 11777881.
167. Blackfan K, Hamilton B. Uremia in acute glomerular nephritis. Boston Med Surg J. 1925;193(14):617-29. doi: 10.1056/NEJM192510011931401.
168. Widman L, Wester PO, Stegmayr BK, Wirell M. The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study. Am J Hypertens. 1993;6(1):41-5. doi: 10.1093/ajh/6.1.41, PMID 8427660.
169. Ferrara LA, Iannuzzi R, Castaldo A, Iannuzzi A, Dello Russo A, Mancini M. Long-term magnesium supplementation in essential hypertension. Cardiology. 1992;81(1):25-33. doi: 10.1159/000175772, PMID 1477853.
170. Dickinson HO, Nicolson DJ, Campbell F, Cook JV, Beyer FR, Ford GA, *et al.* Magnesium supplementation for the management of essential hypertension in adults. Cochrane Database Syst Rev. 2006;(3):CD004640. doi: 10.1002/14651858.CD004640.pub2, PMID 16856052.
171. Jee SH, Miller ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. Am J Hypertens. 2002;15(8):691-6. doi: 10.1016/s0895-7061(02)02964-3, PMID 12160191.
172. Rosanoff A, Plesset MR. Oral magnesium supplements decrease high blood pressure (SBP>155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis. Magnes Res. 2013;26(3):93-9. doi: 10.1684/mrh.2013.0343, PMID 24134861.
173. Zuspan FP. Treatment of severe preeclampsia and eclampsia. Clin Obstet Gynecol. 1966;9(4):954-72. doi: 10.1097/00003081-196612000-00010, PMID 5955334.
174. Euser AG, Cipolla MJ. Magnesium sulfate for the treatment of eclampsia: a brief review. Stroke. 2009;40(4):1169-75. doi: 10.1161/STROKEAHA.108.527788, PMID 19211496.
175. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev. 2010;(11):CD000025. doi: 10.1002/14651858.CD000025.pub2, PMID 21069663.
176. McDonald SD, Lutsiv O, Dzaja N, Duley L. A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use. Int J Gynaecol Obstet. 2012;118(2):90-6. doi: 10.1016/j.ijgo.2012.01.028, PMID 22703834.
177. The magpie trial. A randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. B.J.O.G. 2007;114:289-99.
178. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116(1):85-97. doi: 10.1161/CIRCULATIONAHA.106.678342, PMID 17606856.
179. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, *et al.* Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17(7):2034-47. doi: 10.1681/ASN.2005101085, PMID 16738019.
180. Ishimura E, Okuno S, Yamakawa T, Inaba M, Nishizawa Y. Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. Magnes Res. 2007;20(4):237-44. PMID 18271493.
181. Cheng PT, Grabher JJ, LeGeros RZ. Effects of magnesium on calcium phosphate formation. Magnesium. 1988;7(3):123-32. PMID 2846970.
182. Kircelli F, Peter ME, Sevinc Ok E, Celenk FG, Yilmaz M, Steppan S, *et al.* Magnesium reduces calcification in bovine vascular smooth muscle cells in a dose-dependent manner. Nephrol Dial Transplant. 2012;27(2):514-21. doi: 10.1093/ndt/gfr321, PMID 21750166.
183. Hutchison AJ, Wilkie M. Use of magnesium as a drug in chronic kidney disease. Clin Kidney J. 2012;5(Suppl 1):i62-70. doi: 10.1093/ndtplus/sfr168, PMID 26069822.
184. De Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, *et al.* Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrol Dial Transplant. 2010;25(11):3707-17. doi: 10.1093/ndt/gfq292, PMID 20530499.

Cite this article: Melaku LS. Molecular Physiology of Magnesium in Cardiovascular System and Pathobiology of Hypomagnesaemia in Cardiovascular Diseases. Int J Clin Exp Physiol. 2022;9(2):63-74.