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**REVIEW ARTICLE**

# Role of Magnesium Sulphate in Kidney and Coronary Artery Disease

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**ABSTRACT:**

**Background**: The body uses magnesium for a wide range of physiological processes in both health and illness. Magnesium has an impact on energy production, electrolyte balance, and oxygen uptake in relation to muscle function. Magnesium needs are higher when participating in sports, especially during intense workouts when sweating a lot increases magnesium requirement. Reduced serum magnesium levels are linked to hypertension, Type 2 diabetes mellitus (T2DM), and metabolic syndrome; a lower chance of having the metabolic syndrome is associated with higher blood magnesium levels. Therefore, some people find that taking magnesium supplements is beneficial. It also seems that consuming more magnesium lowers the risk of high blood pressure. However, research on the use of magnesium with and without reperfusion therapy for coronary artery disease has shown contradictory findings. The question of whether magnesium should be administered as a first-line treatment was the subject of a protracted debate.

**Conclusions:** In patients with myocardial infarction, intravenous magnesium cannot currently be suggested because the results of the most recent trials have not demonstrated any difference in outcome. Nonetheless, magnesium is indicated in torsade de pointes patients and has been effectively administered to patients with life-threatening ventricular arrhythmias or digoxin-induced arrhythmias.

**Keywords:** Magnesium sulphate; Coronary artery disease; Kidney.

## INTRODUCTION:

Magnesium is one of the most common electrolytes in the human body. The average adult human body has 25 grams of magnesium, 60–65% of which is contained in the skeleton and most of which is found in the intracellular spaces of muscle and soft tissues. The two main mechanisms that control the magnesium balance are renal excretion and intestine absorption from food. Magnesium is essential for blood pressure (BP), bone integrity, neuromuscular transmission, cardiac excitability, muscle contraction, vasomotor tone, and the metabolism of glucose and insulin. It is a cofactor for more than 300 bodily metabolic processes **[1]**.

The majority of senior people do not consume the average amount of magnesium required by the diet, according to recent studies. Total body magnesium is dependent on food intake. Elderly people are susceptible to hypomagnesemia not just from a diet deficient in magnesium but also from comorbidities and medications that raise magnesium excretion in the urine **[2]**. The Hypomagnesemia is thought to affect 2% of people in the general population, but it can affect up to 53% of people in high-risk groups such those who have chronic heart failure **[3]**. Serum magnesium is still evaluated somewhat rarely, despite the fact that hypomagnesemia can have both short-term and long-term consequences**[4]**. Recent studies have connected low serum magnesium levels to endothelial dysfunction, inflammation, and anomalies in the regulation of vascular tone. It is believed that these mechanisms contribute to the development of atherosclerosis, which might worsen coronary heart disease (CHD) **[5].** Additionally, magnesium is well known for preserving the energy balance and electrical stability of cardiomyocytes **[6].** Hypomagnesemia may potentially increase the risk of sudden cardiac death (SCD), as low serum magnesium levels have been linked to atrial and ventricular arrhythmias **[5]**.

There is limited and conflicting evidence linking the relationship between dietary magnesium intake and serum magnesium levels

and the frequency of ischemic heart disease episodes and stroke **[7].**

Intracellular magnesium concentrations vary from 5 to 20 mmol/L depending on the type of tissue, with the highest concentrations seen in skeletal and cardiac muscle **[8].** Magnesium is distributed almost equally among the sarcoplasmic reticulum, mitochondria, and nucleus of a cell. Merely 0.5–1.2 mmol/L are available for free access, while the remaining 4-5 mmol/L are complexed with ATP (Mg21-ATP) and other phosphometabolites in the cytosol **[9].**

Because ATP is produced by magnesium-dependent oxidative phosphorylation and because magnesium is needed for the hydrolysis and transfer of phosphate groups in all ATP-dependent processes, magnesium is essential for the production of cellular energy. Therefore, magnesium is essential for several metabolic processes, including as glycolysis, transcription and synthesis of DNA, protein synthesis, intracellular signaling, ion channel modulation that produces intracellular ion currents, and membrane voltage determination **[10].**

According to recent studies, 42% of hospitalized patients had hypomagnesemia. Only 7% of these individuals have their magnesium levels tested, according to doctors. A study including patients in the intensive care unit revealed that 53% of the patients had lower-than-normal mononuclear cell magnesium levels. Although less than 1% of magnesium resides extracellularly, serum magnesium may not always adequately reflect the complete body reserves of magnesium because it is typically evaluated in clinical situations. Serum magnesium levels may really be normal even when the body's overall magnesium content has decreased **[8].**

The retention of an oral or intravenous magnesium load can be used in experimental settings to estimate total body magnesium stores. Nevertheless, this method is time-consuming and requires continuous urine collection for the whole day**[11].**

Serum magnesium levels are frequently not as reliable as intracellular magnesium levels as a measure of the body's overall magnesium concentration. The most precise test for magnesium is blood mononuclear cell magnesium **[12].**

Additionally, there is a higher relationship between intracellular mononuclear magnesium concentration and cardiac magnesium status. Magnesium has a variety of roles in the cellular and molecular pathophysiology of cardiovascular issues. First, magnesium causes adenosine triphosphatase (ATPase) to become active. The Na+–K+ pump needs ATPase as its energy source in order for cell membranes to work correctly. In rat models, it has been shown that a magnesium deficiency inhibits the Na+–K+ pump, raising intracellular sodium levels and altering membrane potential **[8].**

## HYPOMAGNESEMIA

Hypomagnesemia, or abnormal magnesium levels, can induce disruptions in almost all organ systems and potentially deadly consequences, such as ventricular arrhythmia, coronary artery vasospasm, and sudden death **[2].**

### Causes

### GASTROINTESTINAL LOSSES

The digestive system absorbs magnesium through both active and passive paracellular transport. A fixed percentage of ingested magnesium is absorbed via the straightforward diffusion pathway, and absorption rises with increasing luminal concentrations. The apical membrane magnesium entry channels known as transient receptor potential melastatin-6 and 7 (TRPM6/7) work together to facilitate active magnesium transport. These saturable, high-affinity transporters are crucial for the absorption of magnesium in situations where luminal contents are low because they enable adaptation to low intake **[13].**

### Dietary deprivation

A certain amount of magnesium is found in gastrointestinal secretions, and potential losses are uncontrolled and ongoing. Consequential losses are minimal, but severe dietary restriction can cause progressive magnesium deficiency. A relatively moderate magnesium deficiency sets the stage for hypomagnesemia since there is minimal fast exchange of extracellular magnesium with the considerably greater reserves found in bone and cells **[15].**

### Gastrointestinal tract losses

Hypomagnesemia may be caused by magnesium losses from the upper and lower gastrointestinal tracts. Nonetheless, diarrhea rather than vomiting is more frequently the cause of magnesium deficiency. This is due to the fact that lower tract secretions have a substantially higher magnesium concentration (up to 15meq/l compared to roughly 1 mEq/l for upper tract). Hypomagnesemia is frequently observed in the following conditions: small intestinal bypass surgery, acute or chronic diarrhea, and malabsorption and steatorrhea **[15].**

### Primary familial hypomagnesemia

A hereditary condition marked by a specific impairment in the absorption of magnesium manifests as hypocalcemia in newborns that responds to the supplementation of magnesium. Although autosomal recessive inheritance has also

been reported, the disorder appears to have an X-linked recessive heredity in some individuals. When the TRPM6 gene is mutated, the autosomal recessive form is produced. Because TRPM6 is also found in the renal tubule, some patients with this illness have both improper renal magnesium squandering and decreased intestinal magnesium absorption. Since the passive absorption channel is unharmed, high-dosage oral treatment may be beneficial **[16].**

**Pancreatitis**

Acute pancreatitis can present with hypomagnesemia. The mechanism that is probably in charge of saponification of calcium and magnesium in necrotic fat **[17].**

**RENAL LOSSES**

The loop of Henle and the distal nephron, which are situated beyond the proximal tubule, are where the majority of magnesium's renal tubular reabsorption takes place, in contrast to most other ions. Urine magnesium losses in these segments can result in hypomagnesemia, which can be caused by a variety of inherited or acquired mechanisms. The mechanism that is probably in charge of saponification of calcium and magnesium in necrotic fat **[18].**

**Loop of Henle**

Magnesium reabsorption in the loop of Henle is accomplished by passive transport through paracellular channels driven by the lumen positive potential. Consequently, decreased magnesium transport in this segment is linked to interference with either paracellular permeability or Na–K–Cl transport **[18].**

**Loop diuretics and Bartter syndrome**

The Na-K-Cl cotransporter is inhibited by diuretics, which lowers the amount of magnesium (and calcium) reabsorption. Because of the simultaneous ECF volume reduction, which favors proximal salt, water, and magnesium reabsorption, the degree of hypomagnesemia is often modest. Not all forms of Bartter syndrome exhibit hypomagnesemia for unknown causes. Some variations of the illness can show hypomagnesemia due to type 3 mutations in the CLCNKB gene, which codes for the renal chloride channel ClC-Kb**[19].**

**Hypercalcemia**

In cases with hypercalcemia, the thick ascending limb of the loop of Henle functionally competes with magnesium for transport, which may cause mild hypomagnesemia. The thick ascending limb's basolateral calcium-sensing receptor (CaSR) mediates another process. When calcium attaches to the CaSR, it blocks the apical potassium channel and produces prostaglandins. As a result, the paracellular absorption of calcium and magnesium is reduced, and the reabsorption of NaCl is suppressed. Furthermore, activation of the CaSR reduces the thick ascending limb's paracellular permeability to calcium and magnesium, which lowers reabsorption **[20].**

**Alcohol**

One study found that 30% of hospitalized alcoholic patients had hypomagnesemia. Eighteen of the 38 hypomagnesemia patients showed excessive magnesium excretion in their urine **[21].**

**Uncontrolled diabetes mellitus**

In those with uncontrolled diabetes mellitus, insulin correction of the hyperglycemia restores hypomagnesemia, which seems to be associated with increased excretion of magnesium in the urine **[22].**

**Hypermagnesemia**

When magnesium is not administered or there is no renal failure, hypermagnesemia is an unusual issue. When it happens, the patient usually has no symptoms and the spike in plasma magnesium content is small (<3 mEq/L, 3.6 mg/dL, or 1.5 mmol/L). On the other hand, when the plasma magnesium content rises above 4 mEq/L (4.8 mg/dL or 2 mmol/L), clinical signs could appear **[23].**

**Causes:**

Hemolysis: Since erythrocytes have a magnesium concentration that is about three times higher than serum's, hemolysis can raise the amount of magnesium in plasma. Hypermagnesemia is only anticipated in cases of severe hemolysis **[24].**

Kidney insufficiency: magnesium excretion is hampered when creatinine clearance is less than 30 milliliters per minute. However, unless magnesium intake is increased, hypermagnesemia is not a major characteristic of renal insufficiency **[25].**

Adrenal insufficiency, hypothyroidism, hyperparathyroidism, diabetic ketoacidosis, and lithium intoxication are additional diseases that may predispose to mild hypermagnesemia **[26].**

**ROLE OF MAGNESIUM IN CORONARY ARTERY DISEASE**

***A) Impact of Magnesium on Vascular Tone***

Magnesium (Mg), the second most prevalent intracellular cation, is an essential component of several important metabolic activities, including every ATP transfer event. Magnesium directly affects vascular tone, baseline tension, and vascular sensitivity to vasoconstrictor drugs through both endothelium independent and endothelium dependent processes, even though it is not directly engaged in the biochemical process of contraction **[27].**

By affecting the concentrations and availability of calcium ions at critical sites, magnesium acts as a

physiological blocker of calcium channels. Because magnesium is a cofactor for the relaxation generated by acetylcholine in the endothelium, variations in extracellular magnesium can influence the formation and release of nitric oxide (NO), which can alter the tone of arterial smooth muscle **[27].**

Since magnesium reduces the amount of calcium released into and out of the sarcoplasmic reticulum and protects the cell from excess calcium during ischemia, it is believed to be nature's physiological antagonist of calcium channels. Magnesium lowers pulmonary and systemic vascular resistance, which also lowers blood pressure and slightly raises cardiac index. **[28].**

Elevated extracellular magnesium levels enhance the dilation effect of several endogenous vasodilators, including as potassium, adenosine, and some prostaglandins, as well as exogenous vasodilators, like isoproterenol and nitroprusside. This results in a decrease in arteriolar tone and tension in various arteries. Consequently, magnesium may have a small inhibitory effect on systolic blood pressure by reducing afterload and unloading the ischemic ventricle **[29].**

Research has demonstrated that intravenous magnesium, most likely due to its ability to reduce coronary artery spasm, increases regional myocardial blood flow and suppresses exercise-induced angina pectoris in individuals with variant angina. **[30].**

***B) Impact of Magnesium on Lipid Metabolism***

Although little is known, magnesium's role in lipid control is fascinating. For the two enzymes involved in lipid metabolism, lipoprotein lipase and lecithin-cholesterol acyltransferase (LCAT), magnesium is a necessary cofactor **[27].**

***C) Anticoagulant/Antiplatelet Properties of Magnesium***

Some studies found that the clotting time of freshly obtained, unclotted human plasma was prolonged by the addition of a little amount of magnesium. In the past, magnesium sulfate was frequently used as a muscle relaxant, and it was observed that after such treatment, the patients' postmortem blood was discovered to be unclotted **[30].**

Another study revealed that magnesium inhibits human blood coagulation. When magnesium was administered topically and parenterally, Adams and Mitchel discovered that it raised the concentration of ADP, which was necessary to start thrombus development at human mild injury sites, and inhibited thrombus formation **[27].**

Elevated levels of plasma magnesium prevent thrombus formation and blood coagulation in vivo, minimize platelet aggregation, decrease the production of the platelet agonist thromboxane A2, and impede the inflow of thrombin-stimulated calcium **[28].**

Acute arterial thrombosis, which plays a significant role in the aetiology of AMI and the problems associated with coronary balloon angioplasty and stenting, is mostly dependent on platelet activation. Studies have shown that magnesium can inhibit platelet-stimulating factors like thromboxane A2 or increase the synthesis of platelet-inhibitory factors such prostacyclin, hence limiting platelet activation (PGI2) **[29].**

In healthy participants, intravenous magnesium therapy reduced ADP-induced platelet aggregation by 40% and fibrinogen binding, or glycoprotein IIb-IIIa complex GMP-140 surface expression, by 30%. Therefore, both in vitro and in vivo, magnesium at therapeutic doses efficiently reduces platelet activity **[28].**

The median platelet-dependent thrombosis was considerably reduced by 35% following oral magnesium treatment; however, individuals who received a placebo showed no significant improvement in this regard. It was found that magnesium medication had an antithrombotic effect even when aspirin therapy was used 100% of the time. P-selectin expression, platelet aggregation, serum lipid levels, and monocyte-derived tissue factor procoagulant activity were not significantly affected by magnesium therapy **[27].**

***D) Impact of Magnesium on Endothelial Function***

Variations in endothelial function have been observed often in type 2 diabetes mellitus and hypertension, and they have been associated with an increased risk of vascular diseases in both conditions, suggesting that they are an early indicator of atherosclerosis **[31].**

We found that high-resolution ultrasound was used both before and following the six-month trial period to evaluate endothelium-independent nitroglycerin (glyceryl trinitrate) induced vasodilation and endothelium-dependent brachial artery flow mediated vasodilation. This was done in a randomized, double-blind, placebo-controlled research **[30].**

Sublingual cells' intracellular magnesium levels were measured by X-ray dispersion. Oral magnesium therapy dramatically raised intracellular magnesium levels after the intervention as compared to a placebo. Across the board, there was a strong correlation between the baseline flow-mediated vasodilation and

intracellular magnesium levels. We showed for the first time that magnesium intervention significantly increased flow-mediated endothelium-dependent vasodilation following the intervention; this was not the case with placebo **[28].**

Hypomagnesaemia specifically decreased the release of NO from coronary endothelium, according to a recent study. Hypomagnesaemia has been proposed as a potential cause of coronary thrombosis and vasoconstriction because NO is an effective endogenous nitro vasodilator that also inhibits platelet adhesion and aggregation **[29].**

According to certain findings, endothelial cells are more susceptible to free radical damage and oxidative injury when magnesium deficit exists. Additionally, demonstrate that an in vivo magnesium deficit causes an equivalent rise in erythrocyte oxidative stress sensitivity) Figure 3)**[27].**

**Mechanism of magnesium induced coronary dilatation:**

Numerous theories have been proposed to explain how magnesium causes coronary dilatation in the heart. Extracellular magnesium functions as a physiological calcium blocker to prevent calcium from entering vascular smooth muscle cells, as demonstrated by earlier research. According to recent research, co-infusion of calcium and magnesium decreases the vasodilatory effects of magnesium infusion alone, indicating that the antagonistic actions of calcium and magnesium are what create the dilation induced by magnesium **[32].**

Another theory is that magnesium activates adenylate cyclase, which in turn regulates the synthesis of adenosine 3',5'-monophosphate.23 26 Thus, magnesium infusion or coronary artery dilatation may lead to an increase in coronary smooth muscle cells' synthesis of adenosine 3',5'-monophosphate **[33].**

Numerous investigations have demonstrated that prostacyclin, the vasodilator generated by the vascular endothelium, plays a role in magnesium's vasodilatory effect. Prostacyclin release varies greatly between and among individuals, according to research, despite some having contradictory results. Thus, although several observations are needed to ascertain the precise amount of prostacyclin produced by magnesium infusion, it is likely that endothelial prostacyclin release plays a role in the vasodilatory action of the infusion **[34].**

Without altering the cardiac index, the hemodynamic impact of magnesium supplementation was linked to a minor but noteworthy drop in mean arterial pressure (from 91 to 87 mm Hg), suggesting a mild vasodilator effect. Oral magnesium aspartate hydrochloride intake has been linked to similar changes in blood pressure, while parenteral magnesium salts have been demonstrated to reduce systemic vascular resistance in CHF patients **[32].**

It is believed that a magnesium deficit increases vascular tone by blocking prostaglandin-mediated vasodilatation and amplifying neurohormonal vasoconstriction **[33].**

Mg directly affects vascular tone, baseline tension, and vascular reactivity to vasoconstrictor medications via both endothelium-dependent and -independent pathways, without directly participating in the contraction's biochemical process **(Ma et al., 1995). 35**

Mg affects calcium ion availability and concentrations at key sites, acting as a physiological calcium channel blocker. Because magnesium is a cofactor for the relaxation generated by acetylcholine in the endothelium, variations in extracellular magnesium can influence the formation and release of nitric oxide (NO), which can alter the tone of arterial smooth muscle **[34].**

**Anti-ischemic Effects of Mg**

Numerous investigations have demonstrated that cytoplasmic Ca2+ excess is the consequence of cardiac ischemia followed by reperfusion. Mg2+ protects cells during cardiac ischemia in the following ways; By functioning as an antagonist of Ca2+, it lowers Ca2+ excess. Preserving magnesium-salt cellular adenosine triphosphatase (ATP), which protects energy-dependent cellular functions. Diminishing the high oxygen demand caused by catecholamines and reducing heart rate, contractility, and systemic afterload to minimize myocardial oxygen consumption. Preventing oxidative damage to the myocardium after an ischemia **[36].**

It is not unexpected that Mg2+ therapy has been extensively studied in the setting of acute MI given these effects of Mg2+. The first randomized, double-blind, placebo-controlled study was called the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) to demonstrate how well intravenous magnesium treatment lowers early mortality in acute MI. 2,316 patients with suspected acute MI were randomly assigned to either intravenous MgSO4 or a placebo.

In the MgSO4 group, there was a 25% drop in the frequency of left ventricular failure and a 24% relative reduction in 28-day mortality. Intravenous magnesium sulfate (MgSO4) is a simple, safe, and widely utilized treatment for

acute MI, according to the study's findings. It functions independently of thrombolytic or antiplatelet medication, but its efficacy in reducing early mortality is comparable to that of the latter **[37].**

However, the Fourth International Study of Infarct Survival (SIS-4) and Magnesium in Coronaries (MAGIC), two further large-scale investigations, were unable to demonstrate the beneficial effects of magnesium treatment on acute MI patients. In the ISIS-4 trial, 114,115 58,050 Randomization was used to assign patients with suspected acute MI to receive intravenous MgSO4, oral controlled-release mononitrate, or captopril. The study found that the MgSO4 group had a greater incidence of cardiogenic shock, CHF, and 35-day death. Regardless of whether the patients in the therapy group received thrombolysis or not, no benefit was seen in any of the major subgroups. Apart from standard care, According to a recent meta-analysis of all randomized controlled trials comparing intravenous magnesium with placebo in patients with acute MI, (1) magnesium is unlikely to reduce mortality in patients already receiving thrombolytic therapy; (2) when used at a high dose (≥75 mmol); (3) magnesium may reduce the incidence of hypotension, bradycardia, and flushing; and (4) the relationship between low-dose treatment (<75 mmol) and ventricular fibrillation, ventricular tachycardia, and severe arrhythmia requiring medical attention remain unclear regarding the impact of magnesium on mortality **[38].**

Overall, there is little evidence to support routine intravenous magnesium therapy in patients with acute MI based on existing clinical data. But before completely discarding this inexpensive therapy, it might be worthwhile to reevaluate the potential therapeutic role of Mg2+ in acute MI in additional clinical trials given its experimentally demonstrated cardioprotective effects, promising animal study results, relatively cheap cost, ease of administration, and generally good tolerability **[36].**

**Antiarrhythmic Effects**

The treatment and/or prevention of cardiac arrhythmias is arguably the most often recognized and utilized application of magnesium dioxide in cardiovascular medicine. Mg2+ works to prevent arrhythmias by adjusting the excitability of the heart muscle. The effect of Mg2+ on cardiac voltage-dependent Na+ channels has not been thoroughly studied, despite the fact that the participation of voltage-dependent Na+, Ca2+, and K+ channels in the pathophysiology of cardiac arrhythmias and the formation of ventricular action potentials is well recognized. Currents across individual cardiac Na+ channels were measured using inside-out patches derived from ventricular myocytes of guinea pigs. The findings demonstrated that whereas (Mg2+) had no effect on inward currents, it did, in a concentration- and voltage-dependent manner, reduce the amplitude of outward currents. This implies that the main effect of (Mg2+) on the voltage-dependent Na+ channels is primarily limited to an open channel blocking effect and that there is little to no direct allosteric modulatory action **[39].**

Mg2+ primarily modifies the voltage-dependent L-type Ca2+ channels (LCa) to stabilize the cardiac membrane. It is well established that variations in (Mg2+) have an impact on LCa through modifications to its amplitude, kinetics of activation and inactivation, and modulation by elements such phosphorylation, which eventually results in a reduction in Ca2+ entry through these channels. High (Mg2+) causes a decrease in LCa amplitude, while low (Mg2+) causes an increase. Changes in channel gating can result in (Mg2+)-induced current amplitude decreases through a change in the channel's availability and/or voltage-dependent inactivation. Raising (Mg2+) has been shown to both accelerate and enhance the pace at which the Ca2+ current decays; allosterically induced inactivation explains this action. High (Mg2+) this results in a leftward shift in the voltage-dependent steady state inactivation, most likely as a result of internal charges being screened by (Mg2+) **[40].**

The degree of phosphorylation of the LCa affects how much Mg2+ affects amplitude of the LCa. The LCa current amplitude is enhanced by phosphorylation through the protein kinase A–dependent pathway, which also amplifies the inhibitory effect of Mg2+. On the other hand, the Mg2+ impact is diminished when phosphatases or protein kinase inhibitors dephosphorylate the channels **[41].**

Rather than deriving from changes in the quantity of cyclic adenosine monophosphate or channel phosphorylation, Mg2+ seems to directly affect the phosphorylated channel or channel dephosphorylation. When Mg2+ binds to phosphorylated channels, conformational changes that would otherwise result in more frequent opening are blocked. However, ATP-bound Mg2+ (Mg2+-ATP) is necessary for phosphorylation of LCa mediated by PKC or protein kinase A. Guanosine triphosphate (GTP) and magnesium dioxide (Mg2+) work together to inhibit LCa. It has been shown that LCa channels can be blocked

by GTP and other guanine di- or trinucleotides without the need for G proteins **[42].**

While Mg2+ and GTP can both bind to LCa directly, their different charges prohibit them from attaching to each other allosterically. Mg2+ and GTP both have independent binding sites. Under basal conditions, the majority of LCa bind Mg2+ and/or GTP and stay in an unavailable state. Depletion of (Mg2+) relieves the Mg2+ block because the blocking device in the C-terminal region of the α-subunit of LCa can no longer block the channel when Mg2+ is missing. But when GTP is present, the depletion of (Mg2+) permits GTP to bind to LCa and carry out its inhibitory action, keeping the channels in an inactive state **[43].**

In addition to voltage-dependent LCa and Na+ channels, magnesium can influence the delayed rectifier K+ and inward rectifier Na+ channels that are expressed in cardiac cell membranes. Compared to ventricular conduction cells or atrial and ventricular contractile cells, nodal cells exhibit less inward rectifier K+ channels (IK1). IK1 current is the primary factor affecting cardiac cells' resting membrane potential **[44].**

Strong inward rectification is known to be caused by intracellular organic cations known as polyamines blocking voltage-dependently. The most powerful inducers of inward rectification are the polyamines spermine and spermidine, but (Mg2+) also has a significant effect. Moreover, extracellular K+ influences this high voltage-dependent rectification, so that increased extracellular K+ levels alleviate the rectification caused by polyamines or Mg2+. The delayed rectifier K+ (IK) current, the repolarization phase of the cardiac action potential is driven by a component that is made up of quickly activating (IKr) and slowly activating (IKs) elements. It is mediated by two distinct channel proteins, HERG and KvLQT1, respectively. Elevated (Mg2+) decreases IK current in mammalian cardiac myocytes, while decreasing (Mg2+) has the reverse effect **[40].**

50–60% of the current is suppressed by modest increases in (Mg2+) within the physiological range of 0.3 to 1.0 mM. It has been hypothesized that the modulatory effects of (Mg2+) on IK are independent of channel phosphorylation because these effects are seen in both nonstimulated and cyclic adenosine monophosphate-treated cells. Finally, it does not seem that the open channel blocking effect shown on the IK1 channels is the cause of the (Mg2+) modulation of these channels as both outward and inward current through IK is modulated independently of voltage. Instead, it has been suggested that the IK channels' binding site for (Mg2+) may control how readily or slowly these channels open **[40].**

It is evident from Mg2+'s physiological effects on cardiac ion channels that Mg2+ affects the production and conduction of cardiac impulses, which is why it is essential for the etiology and treatment of cardiac arrhythmias **[45].**

**Mg and HF:**

Those with heart failure who had hypermagnesemia (serum magnesium level ≥0.89 mmol/L) had a 38% and 35% higher risk of dying from cardiovascular illnesses and other causes, respectively, than those who had normomagnesemia, according to a systematic review and meta-analysis. On the other hand, hypomagnesemia (serum magnesium less than 0.74 mmol/L) did not seem to have any obvious consequences. The risk of CV death was almost doubled by hypermagnesemia levels between 1.05 and 1.09 mmol/L **[46].**

The detrimental effects of hypermagnesemia in HF patients may be better understood by considering the following explanation: First, in people with normal hearts, altered oxido-redox states frequently cause changes in ion channel characteristics that can lead to proarrhythmic disorders and a worse prognosis. Due to the fact that magnesium ions compete with calcium ion-inactivating and -activating sites on cardiac myocytes' type II isoform ryanodine receptor channels, as was observed in earlier rat model studies, hypermagnesemia may have an impact on both cardiac diastolic relaxation and systolic contraction **[47].**

These anomalies may be enhanced by structural cardiac changes in failing heart individuals. Secondly, it seems that hypermagnesemia affects acetylcholine release and reduces muscle motor end-plate sensitivity to acetylcholine. It may cause myocardial depression, vasodilation, and severe arrhythmias (such as bradycardia, extended PR, QRS, QT interval, and total heart block), all of which can lead to hypotension. Furthermore, as a powerful predictor of both pump failure and sudden mortality in heart failure patients, the extended corrected QT interval (QTc>440ms) is significant. Third, hypermagnesemia is linked to advanced age and renal impairment, both of which are previously linked to death in patients with heart failure. As a result, hypermagnesemia may either directly affect mortality or act as a mediator between those factors. Finally, the high frequency

of hypomagnesemia (varying from 7% to 52%) in patients with congestive heart failure should increase public awareness of this illness and encourage aggressive treatment to prevent its side effects, including cardiac arrhythmia, congestive HF, and other CV events, compared to people who are hypermagnesemic. When compared to their hypermagnesemic counterparts, hypomagnesemic heart failure patients have a better prognosis, which could be explained by this rigorous therapy **[46].**

**Role of Mg in kidney**

the kidney has a vital role in maintaining a normal concentration of Mg. Furthermore, when the glomerular filtration rate falls, the kidney's ability to excrete Mg decreases accordingly in chronic kidney disease (CKD), there is a tendency towards hypermagnesemia, but it depends on the severity of the disease. For example, in CKD stages 1–3, an increase in fractional Mg excretion compensates for the loss of renal function, and, as a consequence, Mg levels remain within normal ranges. However, in advanced CKD (stages 4–5), compensatory systems are not sufficient, and the fraction of filtered Mg excreted increases as a result of impaired tubular reabsorption [25]. This becomes more evident when the glomerular filtration rate drops below 10 mL/min. In other words, the compensatory increase in fractional excretion of Mg is inadequate to prevent and increase serum Mg concentrations **[48]**.

CKD patients in treatment with dialysis have both ionized and total Mg concentrations that tend to be higher than normal but always depend on the degree of residual kidney function. However, patients with end-stage renal disease who are on treatment with dialysis usually have normal levels or can sometimes present hypomagnesemia. This could be a consequence of the diet, drug side effects or dialysate Mg concentration. Additionally, it is common for CKD patients to have impaired intestinal Mg absorption compared to healthy individuals **[49]**.

**Role of Mg in CAD**

Magnesium (Mg) is an abundant cation and micronutrient that plays many crucial roles in the body by activating enzymes, contributing to energy production, and regulating concentrations of calcium and related biomarkers. Serum total Mg has traditionally been used to assess Mg status in both research and clinical settings. Low serum Mg has been associated with increased risk of many outcomes, including increased incidence of cardiovascular disease (CVD), hypertension, and diabetes in observational studies. In meta-analyses of randomized controlled trials, Mg supplementation has inconsistently been associated with reductions in blood pressure and reductions in fasting glucose concentrations among individuals with diabetes. The strongest evidence that serum Mg *may* be causally related to CVD risk comes from a recent Mendelian randomization study, in which genetically predicted higher serum Mg was associated with lower risk of coronary artery disease (CAD). The association between low Mg and CVD may arise through numerous physiological pathways, such as elevated blood pressure, chronic inflammation, hyperglycemia, or impaired vasomotor tone and peripheral blood flow **[50]**.

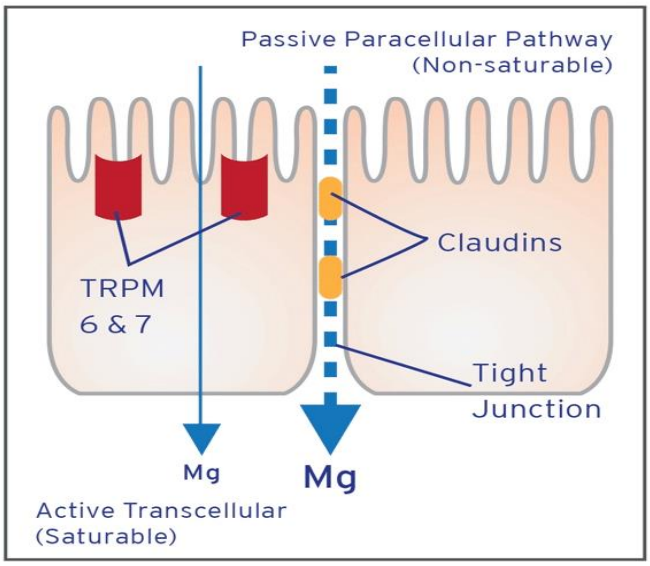


**Figure 1**: the magnesium's intestinal absorption. A saturable transcellular pathway (left) in which TRPM6 and TRPM7 actively transport magnesium into the GI epithelial cells, where it is effluxed through a Na + /Mg 2+ exchanger, or a paracellular pathway (right) in which magnesium crosses the tight junctions of the

intestinal epithelium with the assistance of magnesium-associated claudin proteins, are the two ways that magnesium is absorbed **[14].**

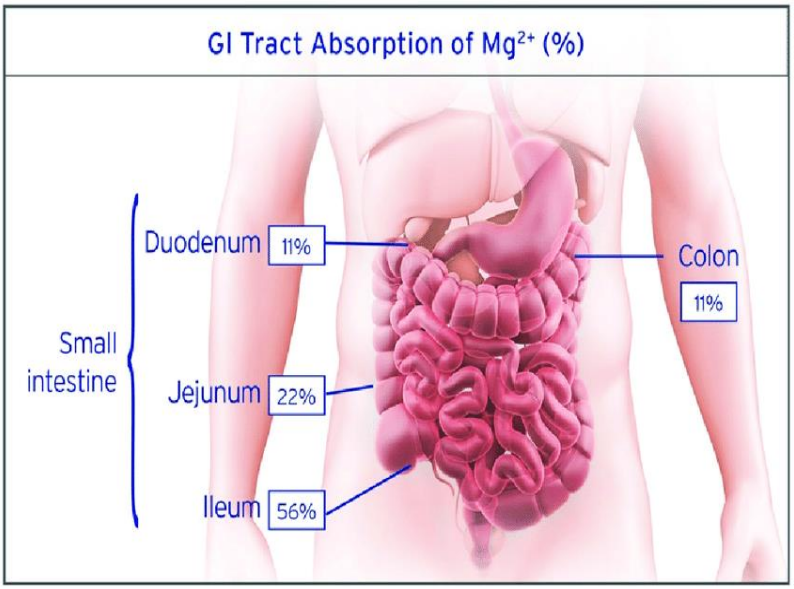


**Figure 2**: The GI tract's percentage of magnesium absorption. The distal section of the small intestine absorbs the majority of magnesium. 56% are absorbed by the ileum, 22% by the jejunum, 11% by the duodenum, and 11% by the colon **[14]**.

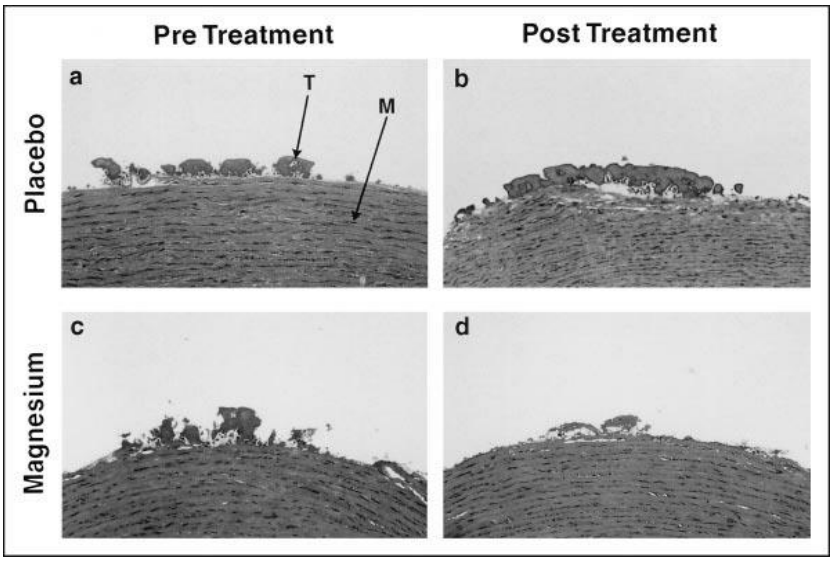


**Figure 3:** An example histologic slice (hematoxylin-phloxine-safranin stain) from a patient obtained before (a) and after (b) receiving a placebo and before (c) and after (d) getting magnesium supplementation for three months. The PDT was deposited (T) on porcine aortic medium (M) **[27].**

## CONCLUSIONS:

In patients with myocardial infarction, intravenous magnesium cannot currently be suggested because the results of the most recent trials have not demonstrated any difference in outcome. Nonetheless, magnesium is indicated in torsade de pointes patients and has been effectively administered to patients with life-threatening ventricular arrhythmias or digoxin-induced arrhythmias

## CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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