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Exploring the Positive Impact of Magnesium on Cardiovascular Diseases: A Comprehensive Review

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Abstract:
Magnesium plays a critical role in cardiovascular health, being essential for various biochemical processes and maintaining physiological balance. Deficiency in magnesium is linked to conditions such as arrhythmias, hypertension, coronary artery disease and pregnancy-related disorders like preeclampsia and eclampsia. This study aims to investigate the role of magnesium in these cardiovascular conditions and highlight its therapeutic potential.
Aim of the Study:
The aim of this study is to comprehensively review the role of magnesium in cardiovascular diseases, including arrhythmias, hypertension, coronary artery disease, preeclampsia and eclampsia, with an emphasis on its physiological mechanisms, therapeutic applications, and potential clinical benefits.
Material and Methods:
A literature review was conducted using PubMed as the primary database. The search terms included: "magnesium", "cardiovascular diseases", "arrhythmia", "hypertension", "coronary artery disease", "preeclampsia" and "eclampsia".
Conclusions:
Magnesium deficiency contributes to various cardiovascular conditions, particularly arrhythmias, hypertension, coronary artery disease and pregnancy-related complications.

Its therapeutic effects are primarily linked to ionic modulation, vasodilation, and anti-inflammatory properties, emphasizing the importance of magnesium in cardiovascular disease prevention and treatment.

Keywords: magnesium, cardiovascular diseases, arrhythmia, hypertension, coronary artery disease, preeclampsia, eclampsia

Introduction:

Magnesium (Mg^{2+}) is a vital nutrient indispensable for all forms of life, playing a critical role in various physiological processes [1]. This mineral is the fourth most abundant in the human body and functions as a key electrolyte, crucial for maintaining physiological balance [2]. In healthy individuals, serum magnesium levels typically range between approximately 0.6 and 1.2 mmol/L [3], and consistent intake is necessary to prevent deficiency, though defining an exact optimal intake remains complex due to variability in recommended daily allowances [2]. Magnesium serves as a cofactor in numerous biochemical reactions, supporting functions such as protein synthesis, cellular energy production, DNA and RNA synthesis, and mitochondrial membrane stabilization. Additionally, it is fundamental to sustaining normal nerve and muscle function, neuromuscular conduction, cardiac excitability, and vasomotor tone, all of which are essential to cardiovascular health [4]. Magnesium deficiency has been associated with a range of chronic health issues; excluding cardiovascular diseases, it is linked to conditions such as migraines, Alzheimer's disease, stroke, and type 2 diabetes [4]. Although major studies on magnesium supplementation have shown inconsistent results regarding its benefits, they have also highlighted potential negative effects associated with magnesium overload. Therefore, there are currently no clear recommendations for routine magnesium supplementation, except when hypomagnesemia is confirmed or suspected as a cause of cardiac arrhythmias [5].
This review aims to elucidate the role of magnesium in cardiovascular diseases.

State of knowledge:

1. **Arrhythmias**

Magnesium has long been used in treating arrhythmias, with studies examining its role in arrhythmia pathophysiology and treatment. Hypomagnesemia is associated with both supraventricular and ventricular arrhythmias, although the link is complex, as patients with normal serum magnesium levels may still have a reduced total body magnesium due to its primary intracellular location [6].
Intravenous magnesium, administered as magnesium chloride ($MgCl_2$) or magnesium sulfate ($MgSO_4$), has shown effectiveness in treating cardiac arrhythmias. The anti-arrhythmic effect of intravenous magnesium was first observed by Zwillinger in 1935, where $MgSO_4$ successfully restored sinus rhythm in patients with digitalis-induced tachyarrhythmias [7].
Magnesium contributes to the regulation of various ionic channels, including those for sodium, potassium, and calcium. It reduces the rapid inward current of the delayed rectifier potassium channel, showing its antiarrhythmic effects by modulating action potential duration and myocardial excitability.

Mg2+ infusion slows atrioventricular nodal conduction and prolongs PR and QRS intervals. It also extends the refractory periods of the atria and ventricles, reducing proarrhythmic conditions such as triggered automaticity and reentry circuits. In contrast, Mg2+ deficiency is associated with a prolonged QT interval, which may lead to ventricular arrhythmias like Torsade de Pointes (TdP) [8,9].

Magnesium sulfate is effective in managing patients with long QT syndrome in TdP and is recommended by guidelines (Level of Evidence: B) [6, 10]. However, magnesium is not likely to be effective in patients with a normal QT interval [10].

Beyond ventricular arrhythmias, magnesium continues to be explored for its role in the management of atrial fibrillation, Premature Atrial Contractions, Supraventricular Tachycardia and Ventricular Tachycardias (other than the "torsade") [12]. Furthermore, the role of magnesium in prevention of postoperative arrhythmias is also under investigation [12,13,14].

2. Hypertension

Hypertension is a complex, multifaceted condition and ranks among the most common health issues in today's world. In individuals at high risk, it can result in severe complications such as coronary artery disease and congestive heart failure [15].

Magnesium plays a crucial physiological role as a regulator of vascular tone by enhancing relaxation responses and counteracting agonist-induced vasoconstriction [16]. This modulation of vascular tone is linked to magnesium's competitive action with calcium. Intracellular magnesium can lower the concentration of intracellular calcium in vascular smooth muscle cells, leading to vasodilation, which is believed to be the mechanism through which magnesium affects blood pressure [16]. Additionally, high extracellular magnesium levels have been shown to reduce endothelin-1 expression while increasing prostacyclin (PGI_2) levels, further promoting vasodilation [17]. Magnesium also stimulates the production of nitric oxide and alters vascular responses to vasoactive agonists [18,19].

One contributing factor is the higher risk of magnesium deficiency in this population due to various mechanisms [15], which has been linked to elevated blood pressure [16,17,18,19]. Epidemiological and experimental studies have demonstrated an inverse correlation between serum magnesium levels and blood pressure, suggesting that magnesium deficiency may play a role in the development of hypertension [19,20]. Low serum magnesium levels are thus frequently associated with increased blood pressure, emphasizing their importance in managing vascular health [16,17,18,19].

3. Coronary Artery Disease (CAD)

Ischemic heart disease remains one of the leading causes of death and disability worldwide [21]. The role of magnesium in cardiovascular health is multifaceted. Due to its significant anti-inflammatory properties, magnesium contributes to an improved lipid profile, reduction of free oxygen radicals, and enhanced endothelial function.

Additionally, it inhibits platelet aggregation, thus preventing blood clotting, and exerts a potent vasodilatory effect. These characteristics collectively position magnesium as a crucial element in the development and management of CAD, as it enhances multiple aspects of vascular function in this condition [9,17, 22].

Over the last years, numerous studies have shown that low serum magnesium levels and inadequate dietary intake of magnesium are linked to an increased risk of CAD [17,23,24,25,26]. While observational studies can indicate associations, large-scale clinical trials are necessary to confirm the safety, efficacy, and optimal dosing of magnesium.

4. Preeclampsia and Eclampsia

Eclampsia is a common complication of preeclampsia (PE) patients and can be life-threatening for both the mother and the fetus. Hence, timely intervention and appropriate management of this detrimental condition are extremely crucial. MgSO4 is the drug of choice for treating and preventing eclampsia [27].

The precise molecular mechanisms by which magnesium deficiency contributes to PE are not fully understood. The anticonvulsant mechanism of magnesium sulfate in PE treatment is thought to involve multiple actions on the central nervous system, vascular endothelium, and neuromuscular junction [27]. In the central nervous system, $MgSO_4$ induces generalized depression through voltage-dependent blockade of N-methyl-D-aspartate (NMDA) receptors, while at the neuromuscular junction, it reduces calcium conductance, acetylcholine release, and motor endplate excitability [27]. Furthermore, magnesium is believed to have functions as a calcium antagonist, which helps lower blood pressure by reducing peripheral vascular resistance. Magnesium deficiency leads to reduced production of nitric oxide and endothelial prostaglandins, resulting in vasoconstriction and elevated blood pressure [27,28].

Magnesium sulfate has been shown to be relatively effective for treating eclampsia and preeclampsia and the treatment is widely advocated by the World Health Organization [17,29]. Studies consistently confirm the beneficial effects of magnesium, demonstrating its effectiveness and value in clinical practice [30,31].

Conclusions:

Magnesium plays an essential role in cardiovascular health, with its deficiency potentially contributing to various conditions, including arrhythmias, hypertension, CAD, and pregnancy-related disorders such as preeclampsia and eclampsia. In arrhythmias, magnesium's modulation of ionic channels helps extend refractory periods and reduce arrhythmic potential, proving particularly effective in managing Torsade de Pointes. Its vasodilatory effects in hypertension are achieved by competing with calcium in vascular smooth muscle cells, promoting relaxation and blood pressure reduction. Additionally, its anti-inflammatory, antiplatelet, and vasodilatory actions contribute to its protective effect in CAD. In preeclampsia and eclampsia, magnesium sulfate remains the preferred treatment due to its mechanisms involving NMDA receptor blockade and inhibition of calcium conductance. However, despite some benefits, studies on magnesium supplementation have shown inconsistent results, with concerns about magnesium overload leading to adverse effects. Therefore, routine supplementation is not recommended unless hypomagnesemia is confirmed or suspected, particularly in the case of cardiac arrhythmias.

Disclosures:
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