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Effect of Magnesium on reducing Insulin resistance in the cardiovascular system

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Abstract

Alterations in the levels of essential ions in the body can lead to numerous diseases. One such critical ion is magnesium (Mg^{2+}). Extensive research has highlighted the significant role of Mg in bodily functions, raising hopes that this ion may contribute to the treatment of various chronic and severe diseases. With the rise of modern lifestyles, insulin resistance (IR) and cardiovascular diseases (CVD) have become increasingly prevalent. Furthermore, studies indicate that insulin resistance is a key factor in the progression of CVD. Researchers, recognizing the relationship between Mg ions and these two conditions, are conducting investigations to identify effective therapeutic approaches for their treatment or symptom alleviation. Broadly, it can be concluded that multiple factors, including metabolic compounds and cellular genes, contribute to the development of insulin resistance. By tracing the signaling pathways associated with these factors, Mg emerges as a significant component in certain segments of these pathways, underscoring its importance in the onset of these conditions. Additionally, Mg may positively influence cardiovascular health and directly impact these diseases. This article aims to provide a concise overview of research findings on the efficacy of Mg in reducing insulin resistance within the cardiovascular system and to discuss emerging therapeutic approaches for these conditions.

Keywords: Insulin resistance, Magnesium, Cardiovascular diseases, Diabetes.

Introduction

Magnesium (Mg) is the eighth most abundant element in the Earth's crust. It is classified in Group 2 (alkaline earth metals) of the periodic table, with a relative atomic mass of 24.305, a melting point of 648.8°C, and a boiling point of 1,090°C. Approximately 99% of the body's total Mg is stored in bones, muscles, and non-muscular soft tissues. Intracellular Mg concentrations range from 5 to 20 mmol/L. Of this, 1–5% exists in an ionized form, while the remainder is bound to proteins, negatively charged molecules, and adenosine triphosphate (ATP). Extracellular Mg constitutes approximately 1% of the body's total Mg and is primarily found in serum and red blood cells.[1]

Cardiovascular diseases (CVD) were responsible for 17.9 million deaths globally in 2019. By 2030, this figure is projected to exceed 22.2 million, establishing CVD as the leading cause of mortality worldwide.[2] Insulin, a critical hormone, regulates the metabolism of carbohydrates, lipids, and proteins, while also contributing to cellular growth and differentiation.[2] Insulin resistance (IR), a hallmark of type 2 diabetes mellitus (T2DM), is characterized by impaired glucose metabolism, where tissues exhibit reduced sensitivity to insulin despite normal or elevated circulating insulin levels.[3,4] In IR, insulin-sensitive tissues -such as skeletal and cardiac muscle, adipose tissue, liver, and vascular smooth muscle- lose their ability to respond effectively to insulin, resulting in disrupted glucose metabolism.[2,4,5]

Insulin resistance and its effects

IR poses a significant global health risk. Closely associated with metabolic syndrome (MetS), IR is linked to Western lifestyles characterized by high-calorie diets,

limited physical activity, and excessive stress.[2] IR is implicated in the development of various conditions, including CVD, MetS, obesity, cancer, and T2DM.[4] IR impairs glucose utilization, leading to compensatory hyperinsulinemia due to increased insulin production by pancreatic β-cells. This condition may arise from a reduced number of insulin receptors (INSRs) or mutations that decrease insulin's binding affinity to its receptors. Consequently, plasma insulin concentrations rise compensatory, which can further exacerbate IR by downregulating INSRs and desensitizing insulin receptor signaling pathways. IR is primarily driven by diminished sensitivity of INSRs to insulin. Glucose intolerance and IR are key contributors to diabetes-related complications, collectively driving hyperglycemia, reduced glucose uptake in muscles, increased hepatic glucose production, and impaired insulin secretion by β-cells in the pancreatic islets of Langerhans. IR is associated with a spectrum of diseases, including CVD, MetS, obesity, cancer, and T2DM.[3–5]

Insulin Resistance in the Cardiovascular System

A strong association exists between the risk of CVD and IR. Researchers have identified a direct link between IR and atherosclerosis. A prospective study involving 2,938 patients established IR as a primary risk factor for CVD. A meta-analysis of 65 studies, encompassing 516,325 participants, demonstrated that IR, assessed using the Homeostatic Model Assessment (HOMA), is a robust predictor of CVD. Utilizing the Archimedes model in a representative population of non-diabetic young adults aged 20–30 years, it was concluded that preventing IR could avert approximately 42% of myocardial infarctions over a simulated 60-year follow-up period. Numerous other studies further support the association between CVD and IR. Several molecular mechanisms underlie the relationship between IR and CVD, including the role of IR in vascular dysfunction, hypertension, and macrophage accumulation in the development of atherosclerosis.[6]

Findings indicate that patients with heart failure (HF) and IR are less likely to exhibit improvements in ejection fraction (EF). IR has been strongly correlated with the severity and adverse outcomes of HF. According to studies based on the New York Heart Association functional classification, IR significantly increases with reduced exercise capacity.[7]

Insulin Signaling Pathways in the Cardiovascular System

As previously noted, HF is more prevalent in diabetic patients, contributing to myocardial contractile dysfunction through increased atherosclerosis and hypertension. However, clinical and laboratory studies have demonstrated that diabetes can directly impact cardiac structure and function, independent of hypertension or coronary artery disease, leading to a condition termed diabetic cardiomyopathy. This condition is characterized by ventricular dysfunction, hypertension, and atherosclerosis, observed in the whole heart, cardiac tissue, and isolated myocytes from diabetic patients.[8]

Multiple mechanisms contribute to this condition, including defective expression of proteins in the mammalian target of rapamycin (mTOR) pathway, impaired insulin metabolism, and myofibrillar abnormalities.[8] Dysfunction in insulin signaling within the heart is a central factor in the pathophysiology of diabetic cardiomyopathy-related disorders. Disruptions in insulin signaling pathways can impair critical pathways such as mTOR. Cardiomyocyte growth is associated with increased protein synthesis or reduced protein degradation.[8]

Insulin shares signaling pathways with various growth hormones, including insulin-like growth factor 1 (IGF-1) and neurohormonal hypertrophic agonists such as angiotensin II (Ang II). These hormones can activate mitogen-activated protein kinase (MAPK) or phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB/Akt) signaling pathways, which promote cell growth, protein synthesis, and inhibition of protein degradation.[8] Under normal conditions, activation of the PI3K/PKB/Akt pathway by insulin and IGF-1 contributes to fetal and postnatal cardiac growth. However, in adulthood, certain physiological (e.g., exercise) and pathological (e.g., hypertension, valvular dysfunction) conditions are associated with chronic activation of the PI3K/PKB/Akt or MAPK pathways, contributing to myocardial hypertrophy.[8]

Cardiac hypertrophy is defined as an increase in heart mass.[9] Pathological cardiac hypertrophy, which occurs during disease states such as hypertension, is a key risk factor for heart failure and is associated with increased interstitial fibrosis, cell death, and cardiac dysfunction.[9] In contrast, physiological cardiac hypertrophy, such as that observed in response to chronic exercise (e.g., "athlete's heart"), is reversible and characterized by normal cardiac morphology and normal or enhanced cardiac function, without fibrosis or apoptosis.[9]

The signaling pathways involved in physiological and pathological hypertrophy are not identical, despite sharing some signaling elements. The PI3K/PKB/Akt axis appears to be more closely associated with physiological

hypertrophy, whereas MAPK signaling, in conjunction with protein kinase C (PKC) and calcineurin-NFAT pathways, contributes to pathological hypertrophy, typically induced by Ang II. The action of PKB/Akt depends on the mTOR/P70S6K pathway, as rapamycin, an mTOR inhibitor, is sufficient to prevent myocardial hypertrophy induced by cardiac-specific PKB/Akt overexpression. The critical role of mTOR in cardiac hypertrophy highlights the potential of AMP-activated protein kinase (AMPK) as a strategy to prevent hypertrophic development. The behavior of mTOR varies depending on pathological conditions: it can regulate β-cell adaptation to hyperglycemia but may also exacerbate complications. However, chronic inhibition of the mTOR pathway can induce diabetes. Additionally, in cardiac muscle cells, mTOR inhibition may lead to IR by disrupting AKT signaling, which impairs glucose transport across the plasma membrane. Recent studies have shown that chronic hyperinsulinemia activates Ang II signaling, which is implicated in pathological hypertrophy.[8]

Type 2 Diabetes Mellitus

Diabetes is classified into type 1 and type 2 based on the underlying cause of hyperglycemia. T2DM comprises a heterogeneous group of disorders typically characterized by varying degrees of IR in insulin-target tissues, impaired insulin secretion, and increased glucose production.[3] In individuals with IR, cells require elevated insulin levels to facilitate proper glucose uptake. The pancreas compensates by increasing insulin secretion to maintain blood glucose within the normal range. However, prolonged hyperinsulinemia may overburden the pancreas, reducing its insulin secretory capacity and ultimately contributing to the development of T2DM.[10]

Effects of Diabetes on the Cardiovascular System

Heart failure (HF) is a prevalent complication of diabetes, with diabetes recognized as an independent risk factor for HF. Studies indicate that the risk of HF is twofold higher in men and fivefold higher in women with diabetes compared to non-diabetic individuals. Furthermore, vascular complications of diabetes are present in 30–40% of HF patients, supporting a strong association between diabetes and HF.[11] Diabetes is not only linked to HF but also to ischemic heart disease and metabolic disorders, including glucose toxicity and lipotoxicity. Cardiac dysfunction in the absence of coronary artery disease, hypertension, or valvular disease is termed diabetic cardiomyopathy. Hyperglycemia and hyperinsulinemia associated with diabetes result in capillary damage, myocardial fibrosis, myocardial hypertrophy, and mitochondrial dysfunction.[11]

Role of Mg in the Body

Mg is essential for the activity of numerous enzymes, including those involved in ATP-generating reactions. It plays a critical role in regulating muscle contraction, blood pressure, insulin metabolism, cardiac excitability, vasomotor tone, nerve transmission, and neuromuscular conduction. Research has associated hypomagnesemia with several chronic conditions, including Alzheimer's disease, IR, T2DM, hypertension, cardiovascular diseases (e.g., stroke), migraine headaches, and attention-deficit/hyperactivity disorder (ADHD).[12]

Mg and Insulin Resistance

It has long been hypothesized that Mg may influence insulin secretion. Epidemiological studies have reported a high prevalence of hypomagnesemia and reduced intracellular Mg concentrations in diabetic patients. Mg serves as an essential cofactor for multiple enzymes involved in carbohydrate metabolism. It enhances insulin sensitivity by promoting autophosphorylation of insulin receptors and regulating tyrosine kinase activity on these receptors.[1] Mg deficiency alters prostaglandin synthesis, resulting in decreased levels of vasodilatory prostaglandins (e.g., prostacyclin I2) and increased levels of vasoconstrictive prostaglandins (e.g., thromboxane A2 [TXA2]) and lipoxygenase products such as 12-hydroxyeicosatetraenoic acid. These changes promote platelet aggregation, release of growth factors, and direct vasoconstriction. Dietary Mg deficiency increases urinary thromboxane levels and enhances angiotensin-induced aldosterone synthesis, effects that are associated with reduced insulin action. This suggests that Mg deficiency may be a common factor linking IR and cardiovascular disease (CVD).[13]

Mg deficiency can contribute to IR in various tissues, including muscle, liver, and the cardiovascular system, through multiple mechanisms.[13] Phosphorylation of the insulin receptor and downstream signaling kinases in insulin-target cells is dependent on intracellular Mg concentrations. Maintaining normal Mg levels is critical for proper insulin secretion and function. In individuals with T2DM, oral Mg supplementation and appropriate dietary patterns improve insulin sensitivity and metabolic control, leading to reduced IR and alleviation of diabetes-related complications.[14] A study demonstrated that Mg supplementation in diabetic mice enhanced insulin sensitivity and reduced IR by increasing insulin receptor expression, affinity, and signaling.[14] Mg optimizes insulin secretion from β-cells by regulating glucokinase activity

and ATP-sensitive potassium (K-ATP) channels. Mg deficiency impairs glucokinase activity and insulin secretion, ultimately contributing to insulin deficiency and IR. Adequate intracellular Mg is also required for autophosphorylation of the insulin receptor's β-subunit, a critical step in initiating the PI3K/Akt signaling pathway. Insufficient Mg levels reduce the activity of this pathway, decreasing insulin sensitivity. Furthermore, Mg plays a pivotal role in regulating the PI3K/Akt/GLUT4 pathway. Mg deficiency inhibits GLUT4 stabilization on the cell surface in muscle and adipose tissues, impairing peripheral glucose uptake. Additionally, Mg deficiency promotes the production of pro-inflammatory cytokines, such as TNF-α and IL-6, which directly phosphorylate IRS-1, disrupting insulin signaling and exacerbating IR.[15]

Mg and Type 2 Diabetes

Mg serves as a second messenger in insulin function. As previously noted, insulin itself is a critical regulatory factor in blood glucose control.[16] A meta-analysis demonstrated that Mg supplementation improves glycemic control in patients with T2DM. Additionally, hypertension affects 70% of individuals with diabetes, a prevalence twice that of non-diabetic individuals. Previous studies have also linked hypertension, hyperinsulinemia, and CVD. Another study found that hypertension and T2DM exert a synergistic negative effect on health, contributing to the development of other chronic diseases.[17] Numerous reports have identified reduced levels of free intracellular Mg in individuals with essential hypertension or T2DM. IR is recognized as a factor associated with hypertension, CVD, atherosclerosis, or a combination of these conditions. Limited evidence also suggests that Mg may play a role in insulin-mediated glucose uptake. Consequently, low levels of free intracellular Mg may represent a significant link to IR, hypertension, and accelerated CVD.[13]

Mg and Cardiovascular Health

Recent studies have reported beneficial effects of Mg on cardiovascular health. Specifically, one study identified an inverse association between Mg intake and CVD risk, while a clinical trial demonstrated that Mg supplementation improved vascular endothelial function, resulting in relatively greater flow-mediated vasodilation compared to a placebo group. These findings suggest that Mg enhances coronary blood flow by acting on vascular endothelium.[17] Evidence also indicates that low Mg reserves increase the risk of cardiac arrhythmias, a contributing factor to complications associated with myocardial infarction. Population-based studies further demonstrate that higher blood Mg levels are associated with a reduced risk of coronary artery disease. Additionally, nutritional research suggests that increased Mg intake lowers the risk of stroke.[18]

In one study, serum Mg levels and dietary Mg intake were lower in Black individuals compared to White individuals. Furthermore, mean serum Mg levels were significantly lower in participants with CVD, hypertension, or diabetes compared to those without these conditions. In participants without CVD, serum Mg levels exhibited an inverse correlation with fasting serum insulin, glucose, systolic blood pressure, and smoking. According to the study's findings, dietary Mg intake reduced fasting serum insulin, high-density lipoprotein, plasma cholesterol, and both systolic and diastolic blood pressure.[19] IR in the cardiovascular system impairs insulin-dependent vasodilation, disrupts endothelial function, and alters vascular reactivity. The PI3K/Akt signaling pathway, a primary insulin signaling pathway, is responsible for nitric oxide (NO) production via endothelial nitric oxide synthase (eNOS) in endothelial cells, promoting vasodilation. In IR, this pathway is impaired, while the MAPK pathway, which mediates vasoconstrictive and inflammatory responses, remains intact or becomes hyperactive. This imbalance leads to vascular dysfunction and contributes to many CVD-related disorders. As Mg is a vital cofactor for numerous enzymatic reactions, including those involved in ATP utilization and insulin receptor signaling, its deficiency in the cardiovascular system exacerbates IR by disrupting insulin signaling pathways (e.g., PI3K/Akt/eNOS), reducing NO production, and increasing vascular smooth muscle tone and inflammation. Hypomagnesemia also contributes to endothelial dysfunction, arterial stiffness, and hypertension, thereby aggravating cardiovascular diseases.[20] Table 1 addresses IR in the cardiovascular system and the role of Mg in its mitigation.

Table 1. Insulin resistance in the cardiovascular system and the role of Magnesium in reducing CVD

Subject	Effect
Insulin resistance in the cardiovascular system	Impaired vasodilation, increased inflammation, and abnormal vascular reactivity
Role of magnesium	Improved insulin signaling via PI3K/Akt/eNOS pathway, increased NO, reduced inflammation, enhanced endothelial function

Impact of Nitric Oxide on the development of IR

Endothelial cells not only provide the physical lining of blood vessels but also secrete various factors that influence vascular diameter, platelet function, and coagulation. Insulin plays a significant role in multiple aspects of endothelial function, including the enhancement of NO production.[21] The primary pathway for NO synthesis is mediated by the nitric oxide synthase (NOS) enzyme family, which catalyzes the NADPH- and O_2-dependent oxidation of L-arginine to L-citrulline, producing NO in the process. NO synthesis also depends on the availability of cofactors such as flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), tetrahydrobiopterin (BH4), and the heme prosthetic group. While IR is strongly associated with endothelial dysfunction, pharmacological studies, gain-of-function studies, and loss-of-function studies have clearly demonstrated critical roles for NO in regulating obesity and IR. To date, supplementation with the NOS substrate L-arginine and inhibition of NOS enzymes have been the most common pharmacological approaches used to investigate the regulation of body composition and insulin sensitivity.[22]

Evidence suggests that early stages of IR may be characterized by increased basal NO activity and enhanced activity of non-NO vasodilators, such as endothelium-derived hyperpolarizing factor (EDHF), resulting in reduced arterial stiffness. However, reduced NO bioavailability or impaired NO-mediated vasodilatory mechanisms associated with the progression of IR to type 2 diabetes may lead to increased arterial stiffness, contributing to the development of CVD. Thus, in the early stages of IR, increased NO and EDHF activity may represent compensatory mechanisms for initial vascular injury. The renin-angiotensin system is activated in diseased vascular beds through the regulation of two angiotensin II (Ang II) receptors: type 1 (AT1R) and type 2 (AT2R). Increased AT1R-mediated activity in central arteries contributes to heightened arterial stiffness and is elevated in IR states. AT2R activity is also increased in early IR and may contribute to the observed increase in basal NO activity. Consequently, AT1R blockade may represent a valuable therapeutic approach for early IR.[23]

Evidence also indicates that the development of microvascular disease in diabetes is associated with reduced basal NO levels and impaired non-NO-mediated vasodilatory mechanisms. This is particularly significant, as the onset of microvascular disease in diabetic patients is associated with a 40-fold increase in mortality in those with clinical nephropathy (urinary albumin excretion ≥300 mg/day) compared to those without nephropathy. In type 1 diabetes, no differences in endothelial function or basal NO levels have been observed between patients without microvascular disease and non-diabetic controls.[23]

Overall, the combined vasodilatory effects of increased basal NO levels and enhanced AT2R expression in IR likely contribute significantly to the increased arterial compliance observed in the early stages of IR. These effects may represent an initial response to vascular injury, some of which is induced by increased AT1R expression. Thus, AT1R blockade may be a beneficial treatment for IR due to its threefold effect: inhibiting the deleterious vascular effects of AT1R, increasing AT2R expression, and enhancing Ang II formation with non-opposing AT2R activation.[23]

Impact of IR on Smooth Muscle Function

In IR, pathways stimulating eNOS are diminished, impairing vasodilatory responses to insulin and cholinergic agonists. The ability of insulin to counteract tumor necrosis factor-alpha (TNFα)-mediated Akt dephosphorylation in endothelial cells is also lost. Free fatty acids, which are elevated in IR states, inhibit eNOS activity and reduce NO production. Insulin stimulates endothelin-1 release, which is increased in IR states. Endothelin-1, a potent vasoconstrictor, also inhibits insulin signaling via PIP-3 kinase and competes with NO, leading to endothelial dysfunction. Meanwhile, the metabolic effects of insulin, mediated through the MAPK pathway, remain intact. These mitogenic effects of insulin on endothelial smooth muscle cell proliferation likely contribute to atherosclerosis [21].

Mg Deficiency: A Key Factor in Cardiovascular Diseases

Evidence suggests that Mg deficiency may play a significant role in CVD.[13] Mg is a critical physiological regulator of vascular tone, enhancing vascular relaxation responses. The effects of Mg as a vascular regulator often result from a competitive interaction with calcium (Ca). Alterations in intracellular Mg status lead to changes in vascular tone and, consequently, arterial blood pressure. Mg plays a vital role in blood pressure regulation by modulating vascular tone and reactivity. Even minor changes in both extracellular and intracellular Mg concentrations exert significant effects on vascular tone, contractility, reactivity, and growth.[24] Existing evidence indicates that Mg deficiency may be a key factor in the progression of CVD, including hypertension and atherosclerosis. In healthy individuals, induced Mg deficiency can exacerbate stress-induced hypertension.

Numerous studies have reported hypomagnesemia in individuals with essential hypertension or T2DM. Additionally, limited evidence suggests that Mg may contribute to insulin-mediated glucose uptake. Thus, low levels of free intracellular Mg may represent a critical link between IR, hypertension, and accelerated CVD.[13]

Mg and Myocardial Health

Mg ions are essential for the structural and functional integrity of the myocardium. Mg deficiency induces cardiac necrosis and increases susceptibility to cardiotoxic agents, while Mg administration prevents these conditions. Recent research suggests that hypomagnesemia may be an underlying biochemical mechanism in the development and progression of myocardial lesions. Other studies have demonstrated that Mg depletion affects coronary blood flow, blood clotting, and atherogenesis.[25] Loss of myocardial Mg is one of the earliest changes observed in various animal models of cardiomyopathy, including those induced by coronary artery occlusion, asphyxia, and hemorrhagic hypotension. The timing of hypoxia induction influences the extent of Mg loss from cardiac muscle. Myocardial Mg loss was first demonstrated 11 hours after two-stage coronary occlusion. Less pronounced Mg loss was observed in hearts analyzed six days post-coronary occlusion. Approximately one-third of myocardial Mg loss occurs 40 minutes after temporary occlusion, a phenomenon not observed one hour after permanent occlusion in canine hearts. An initial Mg reduction was also demonstrated in guinea pig hearts exposed to anoxic chambers. Dogs with myocardial hypoxia secondary to hemorrhagic hypotension exhibited greater myocardial Mg loss between 135 and 180 minutes post-hemorrhage.

In human cases, ventricular muscle from patients who died of myocardial infarction showed significantly lower Mg content, particularly in infarcted regions, compared to non-infarcted regions and hearts from patients who died of other causes. In one study, hearts obtained within two hours of death were thoroughly examined macroscopically and microscopically. Mg content in left ventricular muscle was measured using atomic absorption spectrophotometry. The mean myocardial Mg content in hearts from sudden deaths due to trauma was 85.44 milliequivalents per kilogram of dry weight. Cardiac muscle with acute infarction exhibited an average 42% reduction in Mg content, while non-infarcted regions of the same hearts showed a 19% reduction. This latter reduction was comparable to cases of sudden coronary death without detectable infarction. No significant differences in skeletal muscle Mg levels were observed between control and coronary groups.[25]

Effects of Mg Deficiency on Cellular Calcium Levels

Mg deficiency can lead to alterations in cellular Ca levels. Increased intracellular calcium has been reported to contribute to IR. Consequently, Mg deficiency may reduce insulin activity by elevating free calcium levels, thereby increasing vascular tone and contributing to CVD.[13] Oral Mg acts as a natural calcium channel blocker and enhances NO production, thereby improving endothelial dysfunction and promoting both direct and indirect vasodilation.[26]

Impact of Mg on Hypertension

Hypertension remains a primary contributor to CVD, affecting approximately 1 billion individuals worldwide. Observational epidemiological data and clinical trials indicate that a diet rich in Mg, providing at least 500–1,000 mg per day, reduces blood pressure. Mg plays a critical role in regulating vascular tone and the progression of atherosclerosis.[26]

Hypomagnesemia may be a key factor in the progression of CVD, hypertension, and atherosclerosis. Studies on isolated vessels demonstrate that reduced Mg levels significantly enhance responses to angiotensin II (Ang II) and norepinephrine. Conversely, increased Mg concentrations significantly attenuate pressor responses under experimental conditions. Recent studies also indicate that diet- or diabetes-induced intracellular free Mg deficiency is associated with increased platelet aggregation, which can be ameliorated by Mg supplementation. Mg may lower blood pressure, in part, by enhancing the production of vasodilatory compounds such as prostacyclin (prostaglandin I2). However, the effects of Mg on the production of vasoconstrictors and prostaglandins, such as thromboxane A2 (TXA2), remain poorly understood.[13]

Cytosolic Mg regulates Ca channel activity and reduces free intracellular calcium concentrations in smooth muscle and platelets. Mg can mitigate the predetermined effects of Ang II. Additionally, Mg administration in endothelial cells or humans stimulates the production of the vasodilatory prostacyclin. These actions of Mg also contribute to modulating platelet aggregation in both healthy and diabetic individuals. Experimental studies have demonstrated that Mg administration can reduce atherosclerosis progression in animal models and decrease overall mortality from acute myocardial infarction by up to 54%. In a series of studies, pharmacological Mg administration was used to investigate its effects on the concentration of the potent vasoconstrictor TXA2 and platelet aggregation. The

results indicate that Mg acutely reduces urinary TXA2 levels and attenuates Ang II-induced pressor responses.[13]

Table 2 illustrates the effects of Mg intake on key indicators associated with cardiovascular diseases.

Table 2. Effects of Magnesium intake on some important indicators related to cardiovascular disease (CVD)

Indicator	Effect of Magnesium Intake	Percentage or Magnitude of Change
Cardiovascular Disease (CVD) Risk	Decrease	35% ↓
Systolic Blood Pressure (SBP)	Decrease	3.5 mmHg ↓
C-Reactive Protein (CRP) Level	Decrease	22% ↓
Cardiac Mortality Risk	Decrease	13% ↓
Arterial Stiffness	Decrease	~10% ↓
HDL Level	Increase	~8% ↑
LDL/HDL Ratio	Decrease	~12% ↓

Conclusions

As the severity of IR increases in patients, the risk and intensity of CVD also rise, with individuals exhibiting IR showing more pronounced CVD symptoms compared to others. Mg is recognized as a critical element in improving bodily functions, and its deficiency increases the risk of several chronic diseases, including CVD. Moreover, Mg has been observed to significantly alleviate symptoms of IR and CVD in various patient populations. Given the serious public health burden posed by CVD, T2DM, and IR in modern societies, influenced by contemporary lifestyles, and considering the beneficial effects of Mg in the prevention, treatment, and mitigation of adverse outcomes of these conditions, as well as the correlation between bodily Mg levels and disease severity, Mg appears to be a promising therapeutic agent for reducing IR in the cardiovascular system and, consequently, alleviating CVD complications.

Practical points in Biochemistry/Nutrition:

► Given the link between magnesium levels and both insulin resistance and cardiovascular diseases, ensuring adequate magnesium intake may serve as a valuable complementary strategy for preventing and managing these conditions.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Magnesium: Mg^{2+}; insulin resistance: IR; cardiovascular diseases: CVD: adenosine triphosphate: ATP: type 2 diabetes mellitus: T2DM; metabolic syndrome: MetS; insulin receptors: INSRs; Homeostatic Model Assessment: HOMA; heart failure: HF; ejection fraction: EF; mammalian target of rapamycin: mTOR; insulin-like growth factor 1: IGF-1; angiotensin II: Ang II; mitogen-activated protein kinase: MAPK; phosphatidylinositol 3-kinase/protein kinase B: PI3K/ PKB; protein kinase C: PKC; AMP-activated protein kinase: AMPK; attention-deficit/hyperactivity disorder: ADHD; thromboxane A2: TXA2; nitric oxide: NO; endothelial nitric oxide synthase: eNOS; nitric oxide synthase: NOS; flavin adenine dinucleotide: FAD; flavin mononucleotide: FMN; tetrahydrobiopterin: BH4; endothelium-derived hyperpolarizing factor: EDHF; angiotensin II: Ang II; tumor necrosis factor-alpha: TNFα; thromboxane A2: TXA2.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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