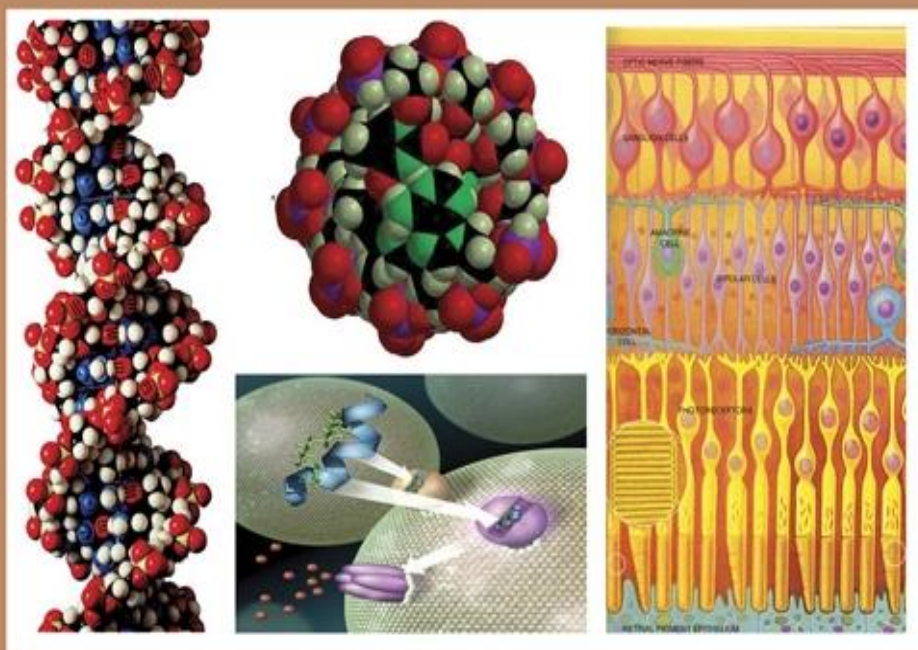




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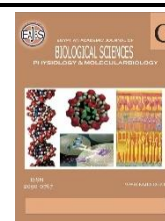
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Magnesium, A Key Element for The Management of Hypertension, Cardiovascular Complications, Retinopathy, and Diabetic Foot in Diabetes

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ABSTRACT

Magnesium is an alkaline earth metal, the eighth-most abundant mineral in the earth's crust. Most of the magnesium in the human body is found in the skeleton and teeth, at least 60-65% of the total. Almost all of the remaining amount is in tissues and muscle cells, while only 1% is in our blood. The balance of magnesium in the body is controlled by a dynamic interaction between intestinal absorption, exchange with bones, and renal excretion.

It fulfills many biological functions, including Activating muscles and nerves, creating energy in the body by activating adenosine triphosphate (ATP), helping to digest proteins, carbohydrates, and fats, serving as the building block for the synthesis of RNA and DNA.

Deficiencies in Mg status, including both hypomagnesemia and/or reduced Mg dietary intake, have been linked to an increased risk of a wide range of chronic diseases and strongly associated with developing DM2 or glucose intolerance, insulin resistance, and decreased insulin secretion.

Maximizing magnesium status through diet and supplementation appears to be a safe and useful way to stabilize and maintain adequate glucose levels and plays an important therapeutic and preventive role in diabetes and its complications.

INTRODUCTION

Magnesium is the eighth most common element in the crust of the Earth (Jahnen Dechent and Ketteler, 2012).

Magnesium (Mg²⁺) is the fourth most common mineral in the human body, after calcium (Ca²⁺), potassium (K⁺), and sodium (Na⁺), and the second most abundant intracellular cation after K⁺ (Kolte *et al.*, 2014).

Magnesium fulfills various intracellular physiological functions and has been recognized as a cofactor for >300 metabolic reactions in the body (Piovesan *et al.*, 2012; Abdullah *et al.*, 2018).

Magnesium also plays a critical role in nerve transmission, cardiac excitability, neuromuscular conduction, muscular contraction, vasomotor tone, blood pressure, and glucose and insulin metabolism (Volpe, 2016)

The normal adult body content is approximately 20-25 g and its distribution is between 60 to 70% in bones, 25 to 30% in muscles, 6 to 8% in soft tissues, and 1% in the extracellular fluid (Naithani *et al.*, 2014).

Deficiencies of Mg status including both hypomagnesemia and/or reduced dietary Mg intake have been linked to an enhanced risk to develop DM2 or glucose intolerance, insulin resistance, and decreased insulin secretion (Barbagallo and Dominguez, 2015; Milagros *et al.*, 2005)

Measuring total magnesium in serum is a convenient and affordable way to monitor changes in the state of magnesium, but it does not necessarily reflect the body's total magnesium content (Costello *et al.*, 2016; Costello *et al.*, 2016).

The recommended dietary reference intake is about 301–420 mg/day (Odusan *et al.*, 2017).

Magnesium and Hypertension:

Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg is an extremely common condition in diabetes, affecting ~20-60% of patients with diabetes (Anwer *et al.*, 2011), with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors (Ian *et al.*, 2017).

Hypertension may precede the onset of diabetes mellitus (DM) and in about 95% of cases, it is essential hypertension and the rest may be secondary type. In some cases, both hypertension and diabetes mellitus may be present at the time of initial diagnosis.

Hypertension may develop later in a diabetic subject as a feature of diabetic nephropathy (Arya, 2003).

On the other hand, hypertension, a clinical entity in which insulin resistance is common, is strongly associated with a higher risk of developing metabolic complications, including new-onset diabetes, as compared to normotension, and it may precede the development of diabetes by several years (Volpe *et al.*, 2015).

Magnesium is involved in blood pressure regulation. Every modification of the endogenous magnesium status leads to changes in vascular tonus and, as a consequence, changes in arterial blood pressure (Ueshima, 2005). Research over the decades has highlighted the crucial role of magnesium intake in the regulation of blood pressure and hypertension (Nguyen *et al.*, 2013). A substantial body of epidemiological and experimental research is linking magnesium deficiency and cardiovascular diseases such as hypertension, atherosclerosis, and stroke (Kieboom *et al.*, 2016; Rosique-Esteban *et al.*, 2018).

Magnesium plays a critical role in maintaining normal nerve and muscle function, cardiac excitability (normal heart rhythm), neuromuscular conduction, muscular contraction, vasomotor tone, normal blood pressure (Gröber *et al.*, 2015).

High Mg intake is associated with a lower risk of major cardiovascular (CV) risk factors (mainly metabolic syndrome, diabetes, and hypertension), stroke, and total cardiovascular disease (CVD). Higher levels of circulating Mg are associated with a lower risk of CVD, mainly ischemic heart disease and coronary heart disease, and stroke (Fang *et al.*, 2016).

Magnesium deficiency increases angiotensin II-mediated aldosterone synthesis and the production of thromboxane and vasoconstrictor

prostaglandins (Kostov and Halacheva 2018).

Insulin stores magnesium, but if the cell receptors are blunted and the cells grow resistant to insulin, the body can't store magnesium, so it passes out of the body through urination. If the magnesium level is too low, the smooth muscle of the blood vessels will be unable to fully relax, and this constriction raises blood pressure (hypertension) (Seriki, 2017).

Additionally, inflammation from magnesium deficiency can also lead to increased production of reactive oxygen species, which can contribute to elevating blood pressure (Nielsen, 2018).

Chronic dietary magnesium deficiency causes elevated blood pressure; initially, a hypotension phase is observed, which is due to the release of inflammatory agents, the subsequent hypertension is a result of oxidative stress and structural modifications in the vascular system (Rayssiguier *et al.*, 2010).

Magnesium deficiency may contribute to the progression of atherosclerosis by its effects on lipid metabolism, platelet aggregation, and

blood pressure, also characterized by increased triglycerides, cholesterol, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), apolipoprotein B, and triglyceride-rich lipoproteins, and a reduced High-density lipoprotein (HDL), apolipoprotein A1 and plasma lecithin-cholesterol acyltransferase activity (Swaminathan,2003).

Concomitant magnesium deficiency aggravates hypokalemia and renders it refractory to treatment by potassium. It is estimated that more than 50% of clinically significant hypokalemia has concomitant magnesium deficiency (Huang and Kuo, 2007).

Magnesium is a potent vasodilator of uterine and mesenteric arteries, and aorta, but has minimal effect on cerebral arteries. In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC). Decreased calcium-channel activity lowers intracellular calcium, causing relaxation and vasodilatation (Fig. 1) (Geiger and Wanner, 2012; Euser and Cipolla, 2009).

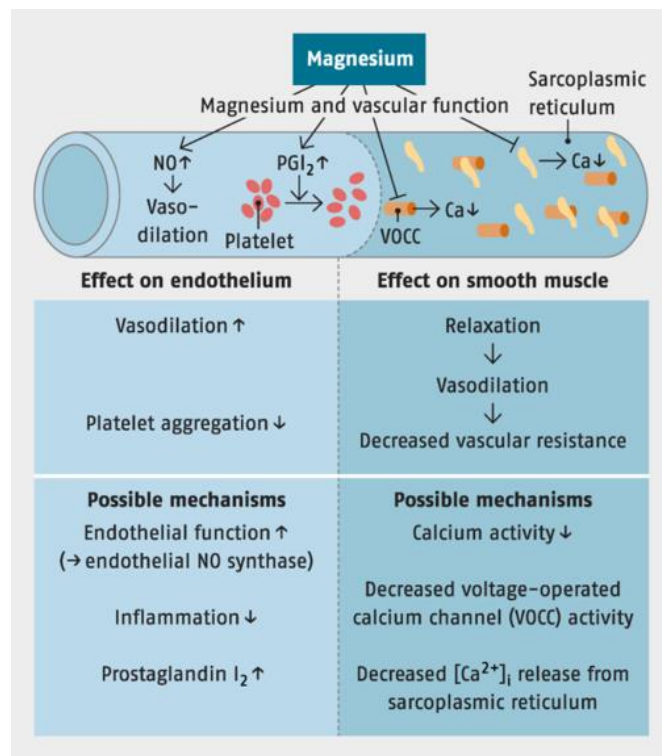


Fig.1. Magnesium and vascular function

Magnesium deficiency has been shown to decrease the activity of the Na⁺–K⁺ pump, leading to an increase in intracellular sodium and calcium, which alters the membrane potential and increased peripheral resistance, and vasospasm (DiNicolantonio,2018; Purvis and Movahed, 1992).

At the tubular level, insulin has been found to stimulate Na⁺, K⁺-ATPase activity, increase sodium transport in proximal tubules, and potentiate the antinatriuretic effects of angiotensin II (Férraille *et al.*,1999).

Glucose-induced antinatriuresis is probably due to both enhanced glucose–sodium co-transport and enhanced sodium reabsorption in the proximal tubules during hyperglycemia (Jaitovich and Bertorello,2010).

Compensatory hyperinsulinemia in insulin-resistant patients may alter the renal set point for sodium reabsorption by imposing a chronic antinatriuretic driving force on the kidney (enhanced by angiotensin II) and therefore play a critical role in the development and maintenance of high blood pressure (Horita *et al.*, 2011).

Experiments in animals have also shown increased production of prostacyclin and nitric oxide (NO) by magnesium, promoting endothelium-independent and endothelium-dependent vasodilation (Cunha *et al.*,2012).

Magnesium may have a protective effect against atherosclerosis and could play a role in promoting the growth of collateral vessels in chronic ischemia. Moreover, because it induces the synthesis of nitric oxide, this cation could be a helpful tool in hypertension as well as in preventing thrombosis (Maier *et al.*, 2004).

Hypomagnesemia selectively impaired the release of nitric oxide from the coronary endothelium. Because nitric oxide is a potent endogenous nitrovasodilator and inhibitor of platelet aggregation and adhesion,

hypomagnesemia could promote vasoconstriction and coronary thrombosis (Pearson *et al.*, 1998).

Hypomagnesemia could inhibit the protective vasodilatory and thrombolytic action of the radical in the coronary circulation and put the blood vessels at risk for ischemic events such as vasospasm and thrombosis (Severino *et al.*,2019).

In addition, alterations in calcium and magnesium metabolism have been implicated in the pathogenesis of primary hypertension (Sontia and Touyz, 2007). The influx of calcium through the outer cell membrane into smooth muscle cells and cardiomyocytes plays a crucial role in controlling the contraction of cell excitation and pulse propagation. Intracellular calcium and magnesium concentrations are controlled by reversible binding to specific calcium-binding proteins (Kosch *et al.*, 2001).

Calcium and magnesium fluxes through the outer membrane are regulated by calcium pump (calcium-magnesium-ATPase), calcium channels, and membrane binding. The cell membranes and lymphocytes of hypertensive patients showed a significant increase in calcium, a decrease in magnesium, and an increased calcium/magnesium ratio ($\text{Ca}^{2+} / \text{Mg}^{2+} > 2$) (Kisters *et al.*, 2004).

Magnesium and Diabetic Cardiomyopathy:

Patients with diabetes are at high risk of developing major cardiovascular complications, mostly including myocardial infarction, ischemic stroke, and congestive heart failure, but also microvascular complications, such as retinopathy, nephropathy, and peripheral artery disease (Kannel and McGee,1979).

Moreover, the presence of diabetes not only increases the risk of experiencing major cardiovascular events but also increases the risk of developing hypertension (Leon and Maddox, 2015).

Hypomagnesaemia is associated with hypokalemia, which causes cardiac

arrhythmias (Van de Wal-Visscher *et al.*, 2018).

Intracellular magnesium deficiency may also cause an increase in intracellular sodium and calcium which induce pathophysiological disorders in the cardiovascular system such as vasospasm, increased vasoconstrictor activity, elevation in smooth muscle and cardiac intracellular calcium concentration, formation of oxygen radicals, pro-inflammatory agents, and growth factors, and changes in membrane permeability and transport (Chetan *et al.*, 2002).

A protective role of magnesium in calcification may underlie previous observations of higher magnesium intake and lower risk of stroke, nonfatal myocardial infarction (MI), sudden cardiac death, and fatal coronary heart disease (CHD) (Hruby *et al.*, 2013).

Magnesium has vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties; thus, it is presumably a useful therapeutic agent in cardiovascular medicine (Muñoz-Castañeda, 2018).

Proposed mechanisms for the potential cardiovascular benefits of magnesium intake include improvement of glucose and insulin homeostasis or lipid metabolism; his actions as an antihypertensive, anti-dysrhythmic, anti-inflammatory, or anticoagulant agent; its antiplatelet effects; its effect on reduced vascular contractility and/or increased endothelial-dependent vasodilatation. Magnesium could lower blood pressure by acting as a calcium antagonist on smooth muscle tone, causing vasorelaxation (Houston, 2011; Watson, 2013).

Reduction in dietary magnesium intake and low magnesium in drinking water have been identified as risk factors for the development of hypertension, atherosclerosis, vasospasm, inflammatory conditions, and sudden cardiac death (Long and Romani, 2014).

Magnesium and Diabetic Retinopathy:

Diabetes retinopathy (DR) the most

common microvascular complication to cause severe vision loss and blindness and a devastating effect on the quality of life and it takes into account mental and social impact, remains a global health issue According to the World Health Organization (WHO), it is estimated that DR accounts for 4.8% of the number of cases of blindness (37 million) worldwide (Yau *et al.*, 2012; Ting *et al.*, 2016; Duh *et al.*, 2017; Pereira *et al.*, 2017).

The prevalence of DR increases with the prolonged duration of diabetes (Cade, 2008).

The coexistence of hypertensive retinopathy and diabetic retinopathy further magnifies the risk of vision loss (Long and Dagogo-Jac, 2011). Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics (Singh *et al.*, 2008).

Type 2 diabetes accounts for approximately 90 to 95% of all diagnosed cases of diabetes. Studies suggest that at the time of diagnosis, the typical patient with type 2 diabetes mellitus has diabetes for at least 4 to 7 years. 4 Among patients with type 2 diabetes mellitus, 25% are believed to have retinopathy, 9% nephropathy, and 8% neuropathy at the time of diagnosis (Sapuroo and Singh, 2017). Many types of research suggest that low serum magnesium is one of the additional risk factors for the development of microvascular complications in type 2 diabetes mellitus (Kochar and Shrotriya, 2018).

However, in addition to hyperglycemia, other factors, such as hypertension, dyslipidemia, hypomagnesemia, hemorheological changes, and increased urinary total protein levels have a remarkable influence on the severity and clinical course of diabetic retinopathy (DR) (Corcóstegui *et al.*, 2017; Shah *et al.*, 2018; Kundu *et al.*, 2013).

Diabetic retinopathy (DR) is a microvascular complication that can affect the peripheral retina, the macula, or both

and is a leading cause of visual disability and blindness in people with diabetes (Pandit and Sultana, 2012).

Diabetic retinopathy progresses from mild nonproliferative abnormalities, characterized by increased vascular permeability, to moderate and severe nonproliferative diabetic retinopathy (NPDR) (Fong *et al.*, 2004). The severity of DR varies from the non-proliferative,

which is the earlier form of retinopathy with microvascular injury characterized by microaneurysms, retinal hemorrhages, and capillary closure to the pre proliferative form characterized by the proliferation of new abnormal blood vessels on the retina or optic nerve, stimulated by angiogenic factors from ischemic retinal tissue Figure 2 (Shah and Chen 2011; Safi *et al.*, 2014; Hewapathirana, 2012).

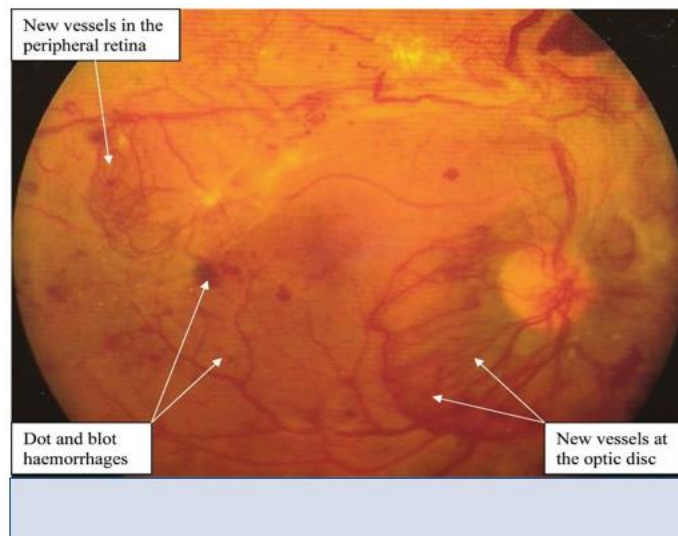


Fig. 2: Extensive new vessel formation both on the optic disc and the peripheral retina together with background dot and blot changes of background retinopathy and blot changes of background retinopathy. A small sub-hyaloid hemorrhage is seen in the top right of the retina at 12 o'clock relative to the optic disc.

Furthermore, magnesium deficiency is also a contributing factor in increased oxidative stress and inducible nitric oxide synthase (NOS) stimulation that can further contribute to the initiation and progression of ocular pathologies such as cataracts, glaucoma, and diabetic retinopathy (Agarwal *et al.*, 2014).

Hypomagnesaemia is a possible risk factor in the development of advanced retinopathy and diabetic maculopathy. These might be related to the mechanism of maculopathy which depends on leakage of microaneurysm that increases with increasing endothelial cell damage (Navin *et al.*, 2013; Haddad and Zuhair 2010; Ekici *et al.*, 2014).

Magnesium and Neuropathic Diabetic Foot Ulcers:

The diabetic foot syndrome is defined as the detection of manifestations of peripheral nerve dysfunction includes several pathologies, mainly neuropathy, infection, microvascular dysfunction, and ischemia; acting together, they contribute to the sequence of tissue necrosis, ulceration, and gangrene (Amin and Doupi, 2016; Akbari and LoGerfo, 1999).

Among all possible complications of diabetes mellitus type 2, diabetic foot syndrome (DFS) is the leading reason for hospitalization. It is reported that up to 25% of diabetic subjects are at risk of developing diabetic foot ulcers (DFU)

during their lifetime and poor wound healing is an important reason for morbidity and mortality (Volmer-Thole and Lobmann, 2016).

Mg²⁺ participates in many cellular functions, including energy production, synaptic neurotransmission, and intracellular signaling (Dribben *et al.*, 2010).

Studies have shown a strong association between low levels of serum magnesium is significantly associated with an increased risk of T2DM and various complications such as diabetic foot ulcers. The possible mechanism suggested could be the association of hypomagnesemia and risk factors for the development of diabetic foot ulcers such as polyneuropathy and platelet dysfunction (Keşkek *et al.*, 2013; Kauser *et al.*, 2014; Phuong-Chi *et al.*, 2007).

Studies postulate that serum magnesium levels may affect peripheral nerve function through axonal degeneration. First, there is growing evidence that magnesium can not only reduce the susceptibility of tissues to oxidative damage but also has indirect antioxidant capacity. In addition, it has been reported that magnesium can increase intracellular inositol levels by enhancing the affinity of the transport system for inositol, thus inhibiting further damage of the nervous system and a beneficial effect on peripheral nerve function in the patient with symptomatic diabetic neuropathy (Chu *et al.*, 2016; Clements *et al.*, 1979)

Conclusion

Over the last two decades, our understanding of the importance of Mg²⁺ ions for many cellular and body functions have increased significantly. Experimental evidence has been corroborated by the role of magnesium in clinical conditions such as diabetes and its complications. There is convincing evidence that increased consumption of nutrients containing a correct diet can help improve the quality of life by delaying and reducing the risk of metabolic diseases and, in particular, the

development of diabetes.

The beneficial effects of ingestion or magnesium status on a multitude of metabolic disorders can be explained by several mechanisms, including improvement of glucose and insulin homeostasis, oxidative stress, lipid metabolism, vascular or myocardial contractility, endothelium-dependent vasodilatation, anti-arrhythmic effects, coagulant or antiplatelet and anti-inflammatory effects. Studies have shown that adequate consumption of Mg²⁺ should be part of a healthy diet for diabetics.

Periodic determination of magnesium levels and magnesium supplementation may promote better glycemic control, a healthy lifestyle, and delay the onset of diabetes-related complications.

Longer-term prospective studies using similar amounts and types of magnesium supplementation are also needed to definitively establish a dose-response effect and the best type of magnesium to use.

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