

Magnesium: Effect on ocular health as a calcium channel antagonist

Magnezyum: Kalsiyum kanal antagonisti olarak göz sağlığı üzerindeki etkileri

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ABSTRACT

Magnesium is the physiologic calcium channel blocker, involving in many different metabolic processes by maintaining cell membrane function, modulating smooth muscle contraction and influencing enzymatic activities. Magnesium has been shown to increase blood flow to tissues by modifying endothelial function via endothelin-1 (ET-1) and nitric Oxide (NO) pathways. Magnesium also exhibits neuroprotective role by blocking N-methyl-D-aspartate (NMDA) receptor related calcium influx and by inhibiting the release of glutamate, hence protects the cell against oxidative stress and apoptosis. Both increase in blood flow and its neuroprotective effect make magnesium a good candidate for glaucoma studies. Magnesium has been shown to decrease oxidative stress and apoptosis in retinal tissue and to have retinal ganglion cell sparing effect. A series of studies has been conducted about magnesium could decrease insulin resistance in diabetic patients, ease glycemia control and prevent diabetic retinopathy. Magnesium is found to be critically important in maintaining normal ionic homeostasis of lens. Magnesium deficiency has been shown to cause increased lenticular oxidative stress and ionic imbalance in the lens so trigger cataractogenesis. *J Clin Exp Invest* 2013; 4 (2): 244-251

Key words: Magnesium, calcium channel blockage, glaucoma, neuroprotection, diabetic retinopathy, cataract

ÖZET

Magnezyum hücre zar fonksiyonlarını, düz kas kontraksiyonlarını ve enzimatik reaksiyonları etkileyerek pek çok metabolik sürece katılan fizyolojik bir kalsiyum kanal blokörüdür. Magnezyumun Endothelin-1 (ET-1) ve Nitrik Oksit (NO) yolları vasıtasıyla endotel fonksiyonlarını modifiye ederek dokulara kan akımında artışa neden olduğu gösterilmiştir. Magnezyum aynı zamanda N-metil-D-aspartat (NMDA) reseptör ilişkili kalsiyum içe akımını bloke ederek ve glutamat serbestleşmesini önleyerek nöroprotektif rol oynamakta ve hücreleri oksidatif stres ve apoptoza karşı korumaktadır. Hem kan akımında artışa neden olması hem de nöroprotektif etkileri magnezyumu glaukom çalışmaları için iyi bir hedef molekül yapmaktadır. Magnezyumun retinada oksidatif stresi ve apoptozu azalttığı ve ganglion koruyucu etkileri olduğu gösterilmiştir. Bir takım çalışmalarda aynı zamanda magnezyumun diabetik hastalarda insulin resistansını azalttığı, glisemik kontrolü kolaylaştırdığı ve retinopatiyi önlediği gösterilmiştir. Magnezyumun lensteki iyon dengesinin sağlanmasında kritik önemi belirlenmiştir. Magnezyum eksikliğinin lenticüler oksidatif stresi arttırdığı ve iyon dengesini bozarak katarakt oluşumuna neden olduğu gösterilmiştir.

Anahtar kelimeler: Magnezyum, kalsiyum kanal blokajı, glaukom, nöroproteksiyon, diabetik retinopati, katarakt

INTRODUCTION

Magnesium is an essential trace element for human life, and is also the second most common cation in the intracellular space. It plays a key role to function for many enzymes as a cofactor, including kinases. Magnesium is related to the stability of cell walls, and many magnesium containing enzymes are involved in metabolic processes. So that magnesium is required for carbohydrate, protein and fat metabolism, maintenance of normal cell membrane func-

tion, synthesis of nucleic acid, and maintenance of energy metabolism [1-3].

Magnesium is a nature's calcium blocker [4,5]. In addition to direct action on calcium blockage of vascular smooth muscle, magnesium affects endothelial functions which have an impact on vascular tone and blood flow regulation. Magnesium reduces vascular tone and increases blood flow by modulating production of vasoactive agents such as endothelin-1 (ET-1) and nitric oxide (NO) and respon-

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siveness to these agents [6]. Elevated magnesium levels prevents ET-1 induced contractile responses by inhibition of ET-1's production and its hypertrophic effect [7,8]. Endothelium-dependent vasodilation mediated by NO is induced with magnesium by modifying formation and release of NO [9-11]. Indeed, magnesium therapy may improve endothelial function in patients with diabetes and coronary artery diseases [12,13]. Magnesium tends to increase blood flow, and decreases vascular resistance in various vascular beds [6,9,12,14]. Hence magnesium has been shown to inhibit vasospasm in subarachnoid hemorrhages [15] and also induces vasodilation in pre-eclampsia clinically [16].

Magnesium has gained attention as an accepted neuroprotective agent. Glutamate is the major excitatory neurotransmitter in the vertebrate central nervous system. Excessive exposure with by glutamate may destroy neuronal tissue, through N-methyl-D-aspartate (NMDA)-mediated excitotoxicity [17,18]. Glutamate induces accumulation of excessive intraneuronal calcium via overactivation of NMDA receptors, and thus leads to apoptotic cell death as a result of increased production of intracellular reactive oxygen species [19,20]. Glutamate excitotoxicity is thought to be involved in the duration times of various number of neuronal diseases including ischemic and traumatic brain injury, Alzheimer and Parkinson's disease, and glaucoma by changing their form from acute to chronic [21,22]. Magnesium may prevent glutamate induced neurotoxicity by blocking NMDA receptor related calcium influx and by inhibiting the release of glutamate, hence magnesium protect the cell against oxidative stress and apoptosis [23-25]. Indeed, other potential neuroprotective mechanism attributed for magnesium is considered to be increasing blood flow dependent of vasodilator effect on calcium channel blockade [15,26,27].

Necessity in terms of eye tissue development

Very little is known about ocular diseases related to magnesium deprivation in clinical practice. A number of experimental animal studies have shown that magnesium has a vital role in development and function of eye. Magnesium deficiency has been correlated with multifocal necrosis in retinal pigment epithelium as well as photoreceptor outer segment deformation and pyknotic-apoptotic changes in photoreceptor cell nuclei, probably as a result of magnesium and calcium distribution imbalance in retinal tissue [28]. Magnesium may protect the cells against the effects of glutamate, peroxynitrite, oxygen radicals and the other pathways of calcium

related excitotoxicity. Magnesium influences superoxide dismutase activity in retinal tissue [29]. Magnesium is required for enzyme activity and membran integrity in retinal tissue as well as all human tissues. Magnesium is involved in all kinase reactions. It means that almost all enzymatic reactions that involve adenosine triphosphate (ATP) definitely require magnesium. Both disturbed metabolism and antioxidation pathway may contribute to magnesium deficiency induced retinal damage. Hypomagnesemia has been associated with pigmentary retinal degenerations like Kearns-Sayre syndrome and retinitis pigmentosa [30,31]. Interestingly, visual field progression has been stabilized after magnesium replacement in retinitis pigmentosa [31]. Magnesium also exists at high concentrations in retinal photoreceptors and has some physiologic activity on vision [32-34]. Caddell proposed a hypothesis that magnesium deficiency may be one of causative factors for the pathogenesis of retinopathy of prematurity as well as high arterial oxygen pressure, because magnesium deficiency results in impairment of both vasodilator activity and protection from oxidative injury [35]. Magnesium deprivation during developmental phase may cause myelination disorders and multifocal necrosis in optic nerve [36]. Magnesium also may be necessary for maintenance of corneal surface health which is important for protection from infections and dryness. Cornea has showed some structural changes if magnesium is missing in the developmental cycle, including decreased microvilli in the epithelial cells, nuclear changes like apoptosis in the epithelial and endothelial cells through abnormal ATP activity and abnormal ion transport [37].

Putative therapeutic effect in glaucoma

Glaucoma is characterized by progressive retinal ganglion cell loss with a complex pathogenesis. Intraocular pressure (IOP) is considered the main risk factor of glaucoma, and IOP lowering therapies plays essential role in glaucoma progression control. However, glaucomatous damage may proceed progressively despite keeping IOP at the level of low teens [38], and also there is a concept of normal tension glaucoma (NTG) with IOP that is consistently at or below 21 mmHg, as known. Accordingly, the factors other than IOP may contribute to pathogenetic mechanism at least sensitizing the ganglion cell for IOP-induced damage. Vascular dysregulation deserves attention for this issue. Vascular dysregulation is caused by imbalance between vasoconstriction and vasodilatation at microcirculatory level. Vascular dysregulation induces perfusion instability, and then leads to isch-

emia, reperfusion injury and oxidative stress. Local disturbed autoregulation in ocular tissues is thought to be as a part of primary vascular dysregulation syndrome which is caused by general dysfunction of endothelium and autonomic nervous system as seen in whole body [39-42]. Vascular tone is regulated locally by endothelium derived vasoactive agents such as ET-1 and NO. A number of studies have demonstrated the increased plasma ET-1 levels in glaucoma patients, which could contribute to glaucoma pathogenesis particularly in NTG [43-45]. Indeed, increased ET-1 level was associated with glaucoma progression despite normal IOP level [46]. ET-1 induces contraction of retinal and optic nerve head vessels, which is dependent on an influx of extracellular calcium through voltage-gated calcium channels, and then resulting in decreased ocular blood flow and ischemia [47-52]. Efficacy of ET-1 can be inhibited by calcium channel blockade. So that calcium channel blockers were evaluated for the management of glaucoma. In this sense, some calcium channel blockers have shown a positive effect on ocular blood flow and visual field in NTG [50,53,54]. But many systemic side effects such as hypotension, bradycardia, conduction disturbances and decrease in cardiac output can be seen during the calcium channel blocker intake, resulting in a restriction in the use for chronic diseases such as NTG [55].

Magnesium acts as a natural physiologic calcium antagonist with minimal side effects. Magnesium-induced favorable vascular effects have been demonstrated in many organ systems and previously discussed [12,13,26]. Therefore, these could explain how magnesium may have potential therapeutic effect in some diseases associated with perfusion abnormality via local microcirculatory disturbances and decreased blood flow such as NTG. Gaspar et al. [56] evaluated the effect of oral magnesium therapy in 10 glaucoma patients (6 with open angle glaucoma and 4 with NTG with normal or drug normalized IOP). All patients had a cold-induced digital vasospasm. 121.5 mg of magnesium was given twice daily for 1 month and video-nailfold-capillaroscopy was used to evaluate peripheral capillary blood flow. At the end of 4 weeks of treatment, both peripheral blood flow and visual field were improved, as the former was statistically significant and the latter not. They concluded that magnesium seemed to have a beneficial effect on the visual field in glaucoma patients [56]. Similarly, Aydın et al. [57] investigated the efficacy of oral magnesium supplementation on visual field perimetry indices and ocular blood flow in pure NTG by

a prospective controlled randomized clinical trial. Fifteen NTG patients were received 300 mg oral magnesium for 1 month and blood flow velocity of orbital vessels such as ophthalmic, posterior ciliary and central retinal arteries were measured by color Doppler imaging. After 1 month of magnesium therapy, the improvement in visual field mean deviation and pattern standard deviation were found statistically significant in the study group compared with control group. They did not report any significant change in ocular blood flow parameters provided by color Doppler imaging. Authors speculated that other mechanisms than increased blood flow could be responsible for the improvement in the visual field [57].

The known facts about impact of magnesium on the ocular blood flow are limited. Elevated extracellular concentrations of magnesium inhibit ET-1-induced contraction in porcine ciliary arteries. However, complete inhibition was achieved only with very high concentrations of magnesium, sufficient to provoke cardiac arrest [58]. Magnesium influences vascular tonus in dose-dependent manner via calcium antagonistic effect non-competitively. It was shown that non-toxic lower dose could be quite enough for visual improvement in NTG, higher concentrations may not be needed. The 300 mg/day oral magnesium intake may have an effect on more distal vasculature (particularly the capillaries) which cannot be revealed by color Doppler analysis [57]. More likely, the perfusion anomaly caused by vascular dysregulation at microcirculatory level is regulated by magnesium without the need of increased blood flow of orbital vessels, in a mechanism which possibly related to calcium antagonistic effect. This impact can be explained by regulation of endothelial function by magnesium. Magnesium therapy may also improve endothelial function [12,13]. In addition to reverse interaction with ET-1, magnesium induces endothelium-dependent vasodilation mediated by endothelial NO [9,10]. NO, derived from nitric oxide synthase-3 in vascular endothelium, contributes to regulation of local circulatory disturbances, and may be neuroprotective by causing vasodilation and increased blood flow in the glaucoma patients [59,60].

Repeated reperfusion injury which occurs as a result of perfusion instability via vascular dysregulation induces glutamate retention in retinal tissue. Glutamate is the principal excitatory neurotransmitter in retina as discussed before [61]. Elevated glutamate has been demonstrated in vitreous of glaucoma patients [21]. Exposure to chronic low dose glutamate could damage retinal ganglion cells [18].

Glutamate induced excitotoxicity is predominantly managed by NMDA subtype of glutamate receptor.

Overstimulation of NMDA receptors leads to excessive calcium influx through NMDA receptors and voltage-gated calcium channels, and then a number of enzymes become inappropriately activated to promote apoptotic cell death [19]. Calcium influx into retinal ganglion cells through NMDA receptors seems to have major value in producing permanent damage, and may be a critical step that can be interfered. NMDA receptor antagonists such as memantine and MK-801 and dihydropyridine derived calcium channel antagonists have been shown to attenuate NMDA related neurotoxicity in retinal ganglion cells [17,18,62]. As a physiological calcium channel blocker, magnesium may be a good alternative in terms of neuroprotection of retinal ganglion cells with minimal side effects. Magnesium ions proceed to regulate conductance of the NMDA channels by blocking the pores in a voltage dependent manner, and to limit neuronal calcium influx [63]. Elevated magnesium levels can also inhibit influx of calcium non-competitively at NMDA receptors [64,65]. Calcium mediated neurotoxicity depends on the activation of distinct signaling pathways resulting in free radical generation, which is also triggered by NMDA receptor. Magnesium deficiency may promote oxidative injury. Magnesium can prevent retinal ganglion cells from oxidative injury by combined effects on NMDA receptor activity, glutathione synthesis and lipid peroxidation [66,67]. Magnesium also influences superoxide dismutase activity in retinal tissue [19]. Magnesium is required for glutathione biosynthesis and its depletion has been associated with decreased antioxidant properties [68,69]. Oxidative stress is involved in glaucoma pathogenesis [70]. Overproduction of NO by neuronal and inducible NO synthesis acts as neurodestructive agent because of the production of peroxynitrites [59]. Reduced oxidative load intervened by magnesium may also contribute to attenuate progression of glaucoma.

In conclusion, some evidence supports that magnesium can prevent the loss of neuron in glaucoma via an undefined mechanism. Only two studies have shown meritorious effect of magnesium on visual fields clinically. Further studies are required to confirm these findings, and to reveal the underlying pathways.

Association of diabetic retinopathy

Clinical and experimental evidences suggest that magnesium may reduce the risk of diabetic retinopathy in patients with diabetes. Magnesium may play

an important role in the maintenance of glucose metabolism and insulin homeostasis. Dietary magnesium intake and serum magnesium level have been inversely correlated with fasting serum insulin level and positively correlated with markers of insulin sensitivity [71,72]. A graded inverse relationship between serum magnesium level and incidence of type 2 diabetes has been shown prospectively by the Atherosclerosis Risk in Communities Study, and low serum magnesium levels were found to be an independent predictive factor for the incidence of diabetes [73]. Further studies tended to confirm similar association so that plasma magnesium concentration in diabetic patients is lower than non-diabetic patients [74-77]. The mechanisms of how magnesium could affect insulin resistance or reduce diabetic complications like diabetic retinopathy are not defined yet. Magnesium acts as a natural calcium antagonist [4]. Elevated cytosolic free calcium concentration causes the deficiency of insulin actions on glucose uptake, and leads to worsen hyperglycemia [78,79]. Magnesium may regulate insulin actions through interfering the effect of calcium. Otherwise many enzymes of carbohydrate metabolism require magnesium as a cofactor [80]. Low intracellular magnesium concentrations result in a defective tyrosine-kinase activity and alter insulin sensitivity by disrupting signaling pathway interaction at receptorial or postreceptorial phase [81-84]. It is also likely that magnesium can improve insulin actions through altering directly enzyme function involving in glucose metabolism. Hyperglycemia may get worse because of low magnesium-induced insulin resistance. All these evidences suggest that magnesium may have effect on pathogenesis and treatment of diabetic retinopathy. Plasma magnesium concentration of diabetic patients with retinopathy has been shown to tend to be lower when compared with diabetic patients without retinopathy [76,77,85-87]. Hypomagnesemia has also been linked to the most severe degree of retinopathy [76,85,87]. One prospective study demonstrated an inverse relationship between plasma magnesium level and both development and progression of diabetic retinopathy at the end of long term follow up. A similar relationship remained unchanged after adjusting for the potential confounding effects of hemoglobinA1c and disease duration [87]. In contrast to these observations, some studies have not found similar association, and supported that there was no consistent association between serum level of magnesium and diabetic retinopathy [88-90]. Lastly, conflicting reports can be seen on this issue. In terms of development and progression of diabetic retinopathy, the fact that whether serum magnesium is only an

indicator or a causative factor has not been yet understood. Although magnesium probably plays a role to break down insulin resistance in peripheral target tissues, to what extent this influence might be effective for preventing retinopathy is a matter of debate. Magnesium may be protector against diabetic retinopathy, but it is clear that further evaluation is needed to reveal true etiologic association between magnesium and diabetic retinopathy if there is.

Magnesium: Have a role in cataractogenesis?

Magnesium, a common cation that plays an important role as a cofactor for numerous enzymes, is closely linked with calcium, sodium and potassium homeostasis. The integrity of lens both structurally and functionally largely depends on the maintenance of intracellular and extracellular ionic homeostasis. Magnesium is found to be critically important in maintaining normal ionic homeostasis of lens. Two main enzymes, sodium potassium adenosine triphosphatase (Na⁺ K⁺ ATPase) and calcium adenosine triphosphatase (Ca²⁺ ATPase), which seem very important to lens active ion transport mechanism use magnesium as a cofactor and are largely magnesium dependent [91].

Role of magnesium in the onset and progression of cataract has been evaluated by various researchers. It was found that the ionic imbalance in age related cataract is mainly associated with decreased magnesium and potassium and increased calcium and sodium [92]. Also magnesium supplementation has been shown to have a preventive role in Shumiya cataract rats [93]. It is clearly indicated that magnesium deficiency is correlated with high calcium levels in the lens. Probably the oxidative stress resulting from magnesium deficiency play a role to increase lens calcium concentration and finally result in cataractogenesis [94]. Magnesium deficiency has been shown to cause increased oxidative stress and trigger cataractogenesis by increasing inducible NO synthase (iNOS) expression and NO release. Pretreatment of rats with NO synthase inhibitors has been shown to prevent onset of selenite-induced cataract and reduce lens calcium content [95]. Culture of human lens epithelial cells in magnesium deficient medium shows 6 fold increase in expression of iNOS as compared to those cultured in medium with normal magnesium concentration. Also treatment of culture medium with iNOS inhibitors attenuate increased release of NO [96]. In another study it was shown that treatment with magnesium taurate also delays the onset and progression of cataract in galactose fed rats. This effect was attributed to the restorage of the lens calcium/

magnesium ratio and the reduction of the lenticular oxidative stress [97].

Magnesium deficiency causes increased lenticular oxidative stress, alterations in function of ATPases resulting in ionic imbalances consist of reduced intracellular potassium and increased calcium and sodium levels. Increased sodium causes cellular swelling and increased calcium causes conversion of soluble proteins into insoluble ones. All these changes finally result in cataractogenesis. Although current literature provides evidence for the association of magnesium deficiency with cataract, its role can be thought as an associated factor with several other factors.

CONCLUSION

Magnesium is of critical importance in regulating intracellular enzymatic functions including those of ocular tissue. The role of magnesium in several ocular diseases has been studied widely. The association of magnesium levels with ocular pathologies such as glaucoma, diabetic retinopathy and cataract may primarily attributed to its highly important role as a cofactor for membrane associated ATPases, vessel smooth muscle modulating effects and also role in oxidative stress regulation mechanisms. The review of current literature supports the need of further investigations to evaluate the role of magnesium as a supportive approach in various ocular diseases.

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