Mini Review

Thekkuttuparambil A. Ajith[1]

Possible therapeutic effect of magnesium in ocular diseases

[1] Department of Biochemistry, Amala Institute of Medical Sciences, Amala Nagar, Thrissur 680 555, Kerala, India, E-mail: taajith@rediffmail.com

Abstract:
Magnesium (Mg^{2+}) is one of the major elements required to maintain normal metabolism and ionic balances in ocular tissues. The physiological role of Mg^{2+} is mediated through maintaining the Na^{+}-K^{+}-ATPase on membrane, favoring energy-generating reactions, replication of DNA and protein synthesis. Despite the wide availability of this element, hypomagnesemia has been associated with many human ailments. Recent studies highlighted the association of hypomagnesemia and, thereby, supplementation of Mg^{2+} in the management of eye diseases. Glaucoma, senile cataract and diabetic retinopathy were associated with low level of extracellular Mg^{2+}. The neurovascular protective effects of Mg^{2+} mediated through activation of endothelial nitric oxide synthase and inhibition of endothelin-1 eventually result in vasodilatation of retinal vessels. Mg^{2+} can maintain the lens sodium pump activity and antioxidant status and block the calcium channels and release of glutamate in nerve endings. Furthermore, it can prevent the apoptosis of retinal ganglion cells. All these effects contribute to its being a pharmacological agent against ocular diseases. However, clinical trials are scant. This article discusses the role of Mg^{2+} as a possible therapeutic agent in the management of glaucoma, cataract and diabetic retinopathy.

Keywords: cataract, diabetic retinopathy, glaucoma magnesium, oxidative stress

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Introduction

Magnesium (Mg^{2+}) has long been considered as one of the major elements required in human body to maintain normal metabolism and health. It functions as a coenzyme in several enzyme catalyzed reactions and involved in the maintenance of ionic equilibrium in the cells. Among the total Mg^{2+} present in the body, 50–60% is present in bone and the remaining is distributed in muscles and nonmuscular soft tissues [1]. Green leafy vegetable, pumpkin seed, almond, avocado, figs, black beans, banana, yogurt and dark chocolate are the major sources of this essential element. The serum normal reference level of Mg^{2+} in adult is 0.70–0.95 mmol/L (1.7–2.3 mg/dL). Certain pathological conditions such as diabetes mellitus, obesity, hypertension and metabolic syndrome are associated with a decreased level of extracellular Mg^{2+} [2], [3], [4], [5]. Gröber et al. reviewed the beneficial effects from the supplementation of Mg^{2+} in the management of migraine, cardiovascular disease, Alzheimer's disease, insulin resistance and diabetes mellitus type 2, asthma, eclampsia and preeclampsia and attention-deficit hyperactivity disorder [6], [7]. Various Mg^{2+} preparations such as magnesium sulfate, magnesium taurate, magnesium oxide, magnesium citrate, magnesium chloride, magnesium aspartate or gluconate are available for the administration. Among these, Mg^{2+} complexes with organic molecules like citrate, aspartate or gluconate are showing high bioavailability [8]. The Mg^{2+} deficiency has been suggested in ocular diseases such as glaucoma, cataract and diabetic retinopathy [9]. However, clinical trials are scant to prescribe it for the management of these eye diseases. Therefore, a discussion on the role of Mg^{2+} in eye disease is essential to promote further research in this area. This article discusses the role of Mg^{2+} in eye disease and its possible therapeutic role in glaucoma, senile cataract and diabetic retinopathy.

Physiological role of magnesium in ocular tissues

In the eye, Mg^{2+} is present mainly in cornea, lens, retina, vitreous body and in the anterior chamber [10]. This major intracellular cation is distributed in the cytosol as well as in subcellular organelles [11]. In the corneal

Thekkuttuparambil A. Ajith is the corresponding author.

surface, it is important for preventing dryness and, thus, renders protection from infections [12]. A high level of Mg^{2+} exists in photoreceptors in retina and lens [11]. In the lens, Mg^{2+} level in the periphery is found higher than the axial regions [13]. As it is a major cofactor for the normal cellular metabolism to produce ATP, Mg^{2+} is found to be involved in regulating the intracellular ionic balance and, thus, maintained the functional and structural integrity of many ocular tissues. The effect is mediated through maintaining the activity of membrane associated ATPase such as Na^+/K^+ ATPase and calcium-dependent ATPase [10], [14]. The normal levels of Mg^{2+}, calcium, sodium and potassium in the lens are 5.5, 0.32, 20 and 60 μmol/g fresh lens weight, respectively [15]. Thus, physiologically, a low calcium and sodium with an increased potassium level is observed in the human lens, which is found to be altered during the deficiency of Mg^{2+} [16]. Therefore, calcium homoeostasis, ionic balances and appropriate antioxidant status are required for maintaining the lens transparency. In retinal neurons, Mg^{2+} act as a neuroprotective agent by inhibiting the elevated inducible nitric oxide synthase (iNOS) activity, and in the lens, it can maintain the antioxidant status. Furthermore, Mg^{2+} is a physiological blocker of calcium channel and *N*-methyl-D-aspartate (NMDA) receptors, a voltage-dependent channel in the retinal ganglion cells (RGC) [17], [18].

Potential therapeutic application of magnesium supplements in ocular diseases

Effect in glaucoma

Glandular and surface epithelia of the cornea, conjunctiva, lacrimal gland and accessory lacrimal glands of the ocular surface system is found to be linked functionally by the vascular, endocrine and immune systems [19]. Most of the eye diseases including glaucoma are associated with a disturbed ocular blood flow to retina, optic nerve, iris, choroid and trabecular meshwork due to a primary or secondary vascular defect [20], [21]. Though the exact mechanism has not yet been elucidated, vasospasm was found to be associated with the incidence of glaucoma [22]. An increased oxidative stress is possible during the disturbed blood flow as well as following the ischemia-reperfusion injury. The free oxygen radicals such as superoxide anion and nitric oxide (NO•) produced during the unstable ocular blood flow can lead to oxidative damage in the RGC [23]. The excess NO• along with superoxide anion favors the formation of peroxynitrite, which is the main culprit for the endothelial as well as neuronal damages [24]. The oxidation including the nitrosylation of gap junction protein in ganglion cell will augment the damage further [24]. The disturbed blood flow and oxidative stress can release the potent vasoactive peptide endothelin-1 (ET-1) from the endothelial cells, which induces the vasoconstriction of microcirculatory vessels supplied by ophthalmic branches. Furthermore, ET-1 can induce the proliferation of optic nerve head astrocytes as evidenced from the study using the cultured human optic nerve head astrocytes [25]. Elevated ET-1 is found to increase the risk for primary open angle glaucoma and normal tension glaucoma (NTG) [26], [27].

Correlation of optic nerve sheath diameter with the intraocular pressure (IOP) was also reported in patients with glaucoma [28]. Oxidative stress can damage the trabecular mesh work and, thereby, elevate the IOP in glaucoma [29], [30]. Oxidative stress can induce the ocular surface inflammation as evidenced in dry eye disease and is involved in the apoptotic death of RGC, which will be mediated through phosphoinositol-3 kinase/Akt/mitogen activated protein kinase pathway [31], [32]. Influx of calcium through the voltage-gated calcium channels into the mitochondria of nerves finally activates the caspase-3 to execute apoptosis of RGC. Glutamate, an excitatory neurotransmitter, was also found to be toxic to RGC, which is mediated through its effect on NMDA receptor and influx of calcium [33]. Hence, the use of calcium channel blockers along with maintaining a normal ocular blood flow is essential to alleviate the oxidative stress and inflammation.

The exact role of Mg^{2+} in the management of glaucoma has not yet been completely elucidated. Mg^{2+} is considered as a neurovascular protective agent. As a natural calcium channel blocker, Mg^{2+} can prevent the influx of calcium into the nerves with no adverse effect on the cardiovascular system [34]. Improvement in the visual field was reported in NTG when 300 mg of Mg^{2+} citrate was administered orally for 1 month [35]. Another study conducted in a small number of patients with primary open angle glaucoma and NTG found that Mg^{2+} at 121.5 mg twice a day for a month improved the visual fields [36].

The improved visual field can be ascribed to the increased ocular blood flow favored by Mg^{2+} therapy. Mg^{2+} present in the aqueous and vitreous humor has a direct vasodilator effect on the central retinal and posterior ciliary arteries [37]. Furthermore, Mg^{2+} supplementation was found to decrease the production of ET-1 in the arterial endothelial cells [38]. The extracellular Mg^{2+} is found to be significant for the function of endothelial NOS of small blood vessels and, thus, the release of physiologically effective level of NO• [39]. The release of NO• with the decrease in ET-1 level along with calcium channel blockade might contribute to the beneficial effect of Mg^{2+} in glaucoma therapy. However, more clinical trials are required to confirm its role as a therapeutic agent in glaucoma.

Effect in cataract

Age-related cataract is another major cause of blindness worldwide. The opacification of lens during aging is one of the major contributing factors for senile cataract due to cumulative modifications of the lens protein, crystalline. Such structural modification of crystalline can result in its aggregation, which gradually loses its transparency and becomes opaque [40]. Oxidative stress due to activation of iNOS in epithelial cells can generate excess NO• and contribute to the cataractogenesis [41], [42]. The excess NO• level can decline the Na^+-K^+ ATPase activity eventually leading to the development of cataract [42], [43]. An influx of calcium into the lens activates the calpain, a calcium-dependent enzyme, and mediates the proteolysis of lens proteins, alpha (A and B chain) and beta B1 crystallin [44], [45]. An ionic imbalance due to an increase of calcium and sodium with the lowering of potassium was observed in the human senile cataractous lens [18].

Extracellular Mg^{2+} deficiency in turn lowers its level in the lens, which can be thus associated with the progression of lens opacification. Study in human lens epithelial cells demonstrated that Mg^{2+} deficiency was associated with iNOS-mediated enhanced NO• production and increased oxidative stress in the lens [16]. Deficiency of Mg^{2+} can reduce the ATP level, which finally results in the accumulation of Na^+ and Ca^{2+} [18]. The alterations in lenticular redox status with an ionic imbalance can be explained for the basis of the association of Mg^{2+} deficiency and cataract [46]. Mg^{2+} in the lens is important for the synthesis of reduced glutathione (GSH) and antioxidant enzymes such as superoxide dismutase and catalase. An experimental model of cataract proved that Mg^{2+} taurate administration is able to restore the normal antioxidant status in the lens [47]. Choudhary et al. demonstrated that Mg^{2+} supplementation at 3 and 6 mg/kg/day increased the Na^+K^+-ATPase and Ca^{2+}-ATPase activity in the lens and rendered protection against cataractogenesis in experimental animals [48]. In galactose-fed rats, the topical application of liposomal Mg^{2+} taurate reduced the oxidative stress by improving the GSH level and catalase activities. The effect was found to be mediated by increasing the Na^+K^+-ATPase and Ca^{2+}-ATPase activities and decreasing the calpain II activity [49]. Despite few studies, well designed randomized clinical trials are limited to explore the beneficial effect of Mg^{2+}.

Effect in diabetic retinopathy

Hypomagnesemia is commonly found in diabetic patients and patients with retinopathy [50], [51]. Studies demonstrated that free radicals released during hyperglycemia in diabetes contribute to oxidative stress in the retina and its capillary endothelial cells, which is closely associated with the development of diabetic retinopathy [52], [53], [54]. In association to the oxidative stress, the retinal mitochondria dysfunction has also been observed in diabetes [55]. Mg^2-rich diet can reduce the risk of diabetes by about 34% [56]. Similarly, diabetic retinopathy was decreased by about 20% for every 0.1 mmol/L increase in serum Mg^{2+} [57]. The effect may be mediated through its inhibitory effect on iNOS, calcium channel blockade, maintaining the GSH level and superoxide dismutase activity [58]. Therefore, Mg^{2+} supplementation has been suggested in diabetic patients who are proven to have hypomagnesemia.

Conclusion and future perspectives

The biological effects of magnesium such as direct vasodilatation of the retinal vessels, activation of endothelial nitric oxide synthase, blocking of calcium channels and release of glutamate in nerve endings, maintaining the sodium pump activity and mitochondrial energy production are all contributing to its pharmacological effect in ocular disease (Figure 1). Several clinical studies highlighted the importance of magnesium in the management of hypertension and diabetes. Most of the studies recommend a higher dose supplementation such as 434 or ≥370 mg/day to reduce hypertension [2], [59]. While supplementing magnesium in the form of magnesium chloride at 638 mg/day for 3 months could improve the insulin levels and insulin resistance [60], [61]. Though the beneficial effects of magnesium in hypertension and diabetes (known risk factors for ocular diseases) are established, clinical trials on the effect of magnesium in ocular diseases has not yet been conducted as well.

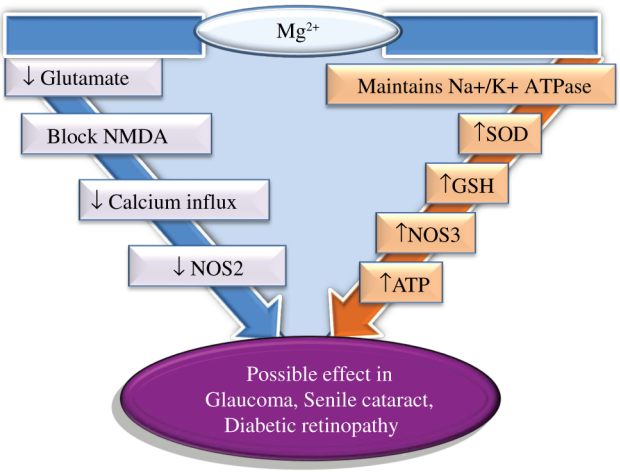

Figure 1: Magnesium (Mg^{2+}) inhibits the release of glutamate from the nerve endings and blocks its receptor *N*-methyl-D-aspartate (NMDA), which lower the influx of calcium and render neuronal protection.
Magnesium has an inhibitory effect on calcium channels and induces nitric oxide synthase in the epithelial cells (NOS_2). These effects are beneficial in maintaining the sodium pump (Na^+/K^+ ATPase) in nerves, enhancing the lens superoxide dismutase (SOD) and endothelial nitric oxide synthase (NOS3) activity, reducing glutathione (GSH) and energy (ATP) level in lens that can contribute to the possible effect of magnesium in the management of ocular diseases.

The recommended daily intake of magnesium for men is 400–420 and 310–320 mg/day for women [62]. Magnesium complexes with organic molecules such as citrate, aspartate or gluconate are showing high bioavailability [8]. Supplementations of magnesium with a serum concentration of 4.2–6.3 mg/dL (1.74–2.61 mmol/L) may result diarrhea, gastrointestinal disturbances, hypotension, confusion, lethargy, muscle weakness, disturbances in normal cardiac rhythm and deterioration of kidney function [14], [63]. Severe hypermagnesemia may also lead to cardiac arrest [64]. Therefore, measuring the magnesium level in the serum and co-morbidities like diabetes, hypertension or the prolonged use of proton pump inhibitors need to be considered [64], [65]. Furthermore, supplementation of magnesium may interfere with other drugs. Itoh et al. demonstrated that the bioavailability of risedronate, a bisphosphonate, was reduced by a high level of magnesium, whereas hypomagnesemia is a known predisposing condition for the appearance of digitalis toxicity [66], [67], [68]. Similarly, co-administration of magnesium hydroxide or carbonate with an antibiotic, ciprofloxacin, can affect the dissolution rate of ciprofloxacin from the tablets, which may affect its absorption [69]. The ability of magnesium to attenuate epithelial oxidative stress and neuronal inflammation suggests its possible role in the management of ocular diseases. Despite a few trials of short-term duration and small sample size, a detailed study on the effect of magnesium in ocular diseases is warranted.

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