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Review

Magnesium deficiency: Does it have a role to play in cataractogenesis?

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ABSTRACT

Magnesium is one of the most important regulatory cation involved in several biological processes. It is important for maintaining the structural and functional integrity of vital ocular tissues such as lens. Presence of high magnesium content especially in the peripheral part of lens as compared to aqueous and vitreous humor has been observed. Magnesium plays significant role as a cofactor for more than 350 enzymes in the body especially those utilizing ATP. Membrane associated ATPase functions that are crucial in regulating the intracellular ionic environment, are magnesium-dependent. Moreover, the enzymes involved in ATP production and hydrolysis are also magnesium-dependent. Magnesium deficiency by interfering with ATPase functions causes increased intracellular calcium and sodium and decreases intracellular potassium concentration. Furthermore, magnesium deficiency is associated with increased oxidative stress secondary to increased expression of inducible nitric oxide synthase and increased production of nitric oxide. Thus the alterations in lenticular redox status and ionic imbalances form the basis of the association of magnesium deficiency with cataract. In this paper we review the mechanisms involved in magnesium homeostasis and the role of magnesium deficiency in the pathogenesis of cataract.

1. Introduction

Magnesium is an important cation that plays significant role as a cofactor for more than 350 enzymes in the body, especially those utilizing high energy phosphate bonds such as ATPases (Wolf and Cittadini, 2003; Yang et al., 2006; Cowan, 2002). Besides being involved in maintaining the genomic stability, processes of synthesis, transcription, and translation (Yang et al., 2006; Vernon, 1988; Sreedhara and Cowan, 2002), it also regulates activity of several ion channels. Magnesium homeostasis is closely linked with calcium, sodium and potassium homeostasis and therefore any disturbances in magnesium homeostasis are bound to be associated with calcium, sodium and potassium homeostasis and vice versa. Clearly, the consequences of disturbances in magnesium homeostasis may seriously affect the cellular and molecular functions and may form the basis of several pathological conditions. Ocular tissue especially the lens is as susceptible to changes in magnesium homeostasis as any other organ in the body. The structural and functional integrity of the lens which is of primary importance in transmitting the light to retina largely depends on the maintenance of intracellular and extracellular ionic homeostasis. In this review we summarize the knowledge available from currently available literature with regards to the mechanisms of magnesium homeostasis and association of magnesium deficiency states with cataract. Literature search was made using Pubmed search engine. Several key word like magnesium, calcium, ocular, ophthalmic, cataract were used. Full texts of all research papers in English and Russian language were read and abstracts in English language were read for those published in other languages. A total of 114 references are included in this paper published during 1960–2011.

2. Magnesium homeostasis and its regulation

Regulation of magnesium homeostasis involves maintenance of normal distribution and total magnesium contents in different body compartments. Physiological homeostatic mechanisms of the body regulate the body magnesium contents and distribution unless the pathological conditions bring about alterations in normal homeostasis.

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2.1. Normal body magnesium contents and distribution

Adult human body contains about 15 mmol of magnesium per kg bodyweight. About 50% of total pool of magnesium is in the bones, less than 50% is in the muscles and soft tissue (about 28% is in striated muscles) (Moskalev, 1985; Okazaki, 1988; Wacker and Vallee, 1958). About 1% of magnesium is in extracellular fluid and about 0.3% is in serum (in the ionized form) (Revúsová and Dzúrik, 1984) with a physiological range of 0.75–1 mmol/l. One third of serum magnesium is bound to plasma proteins, preferentially to albumin and to a lesser extent to globulins (Kroll and Elin, 1985; Lau et al., 1985). In healthy individuals average concentration of serum magnesium is rather stable, whereas concentration of total magnesium is affected by circadian variations and the lowest values are observed between 6:00 and 10:00 in the morning (Elin et al., 1994; Graham et al., 1960).

2.2. Dietary magnesium requirements

The usual diet quite varies in magnesium content and provides 2–7.5 mg magnesium/kg body weight (Vormann, 2003). During recent years dietary reference intakes for magnesium have been revised and current recommended intakes of magnesium for adults are between 300 and 420 mg/day. Normal American or European diet may maintain normal level of magnesium in the body (Rude, 1998; Spasov, 2000) and dietary magnesium deficiency occurs rather rarely. However, rapid growth and pubertal period as well as pregnancy and lactation require higher magnesium intake (Mitrović and Jovanović, 2002).

2.3. Physiological basis of the regulation of magnesium homeostasis

The extracellular magnesium level depends on the balance between intestinal absorption and renal excretion. Within physiological ranges, decrease in magnesium intake is counterbalanced with increase in intestine magnesium absorption and decrease in renal magnesium excretion.

Gastrointestinal tract absorbs not more than 30% of ingested magnesium and this absorption primarily occurs in the ileum and colon. In severe magnesium depletion, significantly more magnesium can be absorbed. Absorption involves passive (paracellular) and active (transcellular) transport mechanisms (Quamme et al., 1994).

Kidney is the main regulator of magnesium homeostasis. Decrease or increase in magnesium intake by individuals with normal renal function results in decreased or increased urinary excretion of magnesium respectively (Shils, 1969; Heaton, 1969). However, there are daily and circadian changes of this parameter (Johansson, 1979; Sjögren et al., 1987). Control of magnesium homeostasis mainly occurs at the level of nephron in kidneys. About 80% of total magnesium is filtered through the glomerular membrane (Brunette and Crochet, 1975; Le Grimellec et al., 1975). At the rate of glomerular filtration of 125 ml/min the amount of filtered magnesium is about 140 mmol per day. Kidney reabsorbs about 80–99% of this filtered magnesium and 1–20% is excreted in urine (Quamme et al., 1994). Proximal tubules reabsorb 5–15%, the thick ascending limb of Henle's loop absorbs 70–80%, and the distal tubule reabsorbs about 5–10% of filtered magnesium. Although the distal tubule reabsorbs only 10% of magnesium filtered through the glomerule, this is a significant amount, representing about 60–70% of magnesium entering this segment from the Henle's loop (Quamme and de Rouffignac, 2000). Only insignificant amount of magnesium is reabsorbed in collecting tubules so that the tubular segments of this part of nephron play an important role in determining final urinary excretion of magnesium (Quamme and de Rouffignac, 2000; Quamme, 1989; Quamme et al., 2000). Magnesium reabsorption in the loop occurs within the cortical thick ascending limb by passive means driven by the transepithelial voltage through the paracellular pathway.

The thick ascending limb of Henle's loop mediates transcellular reabsorption of NaCl while generating a lumen-positive voltage that drives passive paracellular reabsorption of divalent cations (Ca^{2+} and Mg^{2+}). Disturbance of paracellular reabsorption leads to divalent cations wasting in patients with the rare inherited disorder of familial hypercalciuric hypomagnesemia with nephrocalcinosis. Recent work has shown that the claudin family of tight junction proteins (claudin-16/paracellin-1 and claudin-19) form paracellular pores and determine the ion selectivity of paracellular permeability (Cole and Quamme, 2000; Günzel and Yu, 2009; Haisch et al., 2011).

Unlike the thick ascending limb of the loop of Henle, magnesium reabsorption in the distal tubule is transcellular and active in nature (Quamme and de Rouffignac, 2000). Critical role in this process belongs to the members of the melastatin-related subfamily of transient receptor potential (TRP) ion channels, TRPM6 and TRPM7, gatekeepers of human magnesium metabolism. Recently, genetic studies in patients with primary hypomagnesaemia and secondary hypocalcaemia have identified TRPM6 as the first component involved directly in epithelial magnesium reabsorption. TRPM7, the closest homologue of TRPM6, has a central role in Mg^{2+} uptake in vertebrate cells since TRPM7-deficient cells become Mg^{2+} deficient and are not viable. TRPM7 has been characterized functionally as a constitutively active ion channel permeable for a variety of cations including calcium and magnesium and regulated by intracellular concentrations of magnesium and/or magnesium–nucleotide complexes. Both proteins share the unique feature of cation channels fused to serine/threonine kinase domains (Schlingmann et al., 2007; Chubanov and Gudermann, 2005).

Many hormones and nonhormonal factors influence renal magnesium reabsorption to variable extent in the cortical thick ascending limb and distal tubule. Moreover, nonhormonal factors may have important implications on hormonal controls of renal magnesium conservation. Parathyroid hormone, calcitonin, glucagon, and antidiuretic hormone act through a common second messenger, adenosine 3′,5′-cyclic monophosphate, to limit magnesium excretion by enhancing active magnesium transport in the cortical thick ascending limb (Quamme and de Rouffignac, 2000; Quamme et al., 2000; Dai et al., 2001). Adaptation of magnesium transport with dietary magnesium restriction or excess dietary intake occurs in both the cortical thick ascending limb and distal tubule. The identification of an extracellular Ca^{2+}/Mg^{2+}-sensing receptor located on the peritubular side of the cortical thick ascending limb and distal tubule cells explains this phenomenon. Loop diuretics, such as furosemide and bumetanide, diminish salt absorption in the cortical thick ascending limb whereas the distally acting diuretics, amiloride and chlorothiazide stimulate magnesium reabsorption within the distal convoluted tubule. Finally, metabolic acidosis, potassium depletion or phosphate restriction can diminish magnesium reabsorption within the loop and distal tubule (Quamme and de Rouffignac, 2000; Quamme et al., 2000; Dai et al., 2001). Magnesium deficiency may arise together with and contribute to the persistence of potassium deficiency and cases of magnesium deficiency accompanying the magnesium-dependent or -independent potassium deficiency are not uncommon among the general population.

2.4. Disturbances of magnesium homeostasis: causes and associated diseases

Magnesium deficiency appears as a result of altered functional state of the body, in some pathological conditions such as diabetes

mellitus (de Valk, 1999; Emoto et al., 2007), alcoholism (Johnson, 2001), cardiovascular diseases (Iezhitsa, 2005; Seelig, 2000; Purvis and Movahed, 1992), kidney diseases (Navarro et al., 2007; Okuno et al., 2007; Moiseeva et al., 2006), severe form of diarrhea and vomiting (Dørup, 1993), stress (Seelig, 1994), effects of some iatrogenic factors as well as therapy with some drugs (loop and distal diuretics (Devane and Ryan, 1981; Greenberg, 2000), cardiac glycosides (Young et al., 1991), aminoglycosides (Kes and Reiner, 1990), cysplatin (Lajer and Daugaard, 1999), amphotericin B (Barton et al., 1984)). Genetic defects of magnesium transporting systems, which function in intestinal and renal tubular epithelial cells, also cause impairments of magnesium homeostasis (Cole and Quamme, 2000; Warnock, 2002; Knoers et al., 2003; Schlingmann et al., 2004). Evidence suggests that a deficit of magnesium is closely interrelated to potassium deficiency. Importance of magnesium deficiency as a cause of potassium depletion has gained clinical attention (Rude, 1989).

2.5. Lens homeostasis: role of magnesium

Magnesium is critically important in maintaining normal mineral homeostasis of lens. It is well known that imbalances in magnesium concentration can occur with intra- and extracellular calcium concentration modifications (Baldwin and Bentley, 1980). In the normal lens, the intracellular level of free calcium is in the micromolar range, whereas the extracellular calcium level is in the millimolar range, creating a transmembrane gradient (Hightower, 1985). In rat, bovine, dog, and rabbit lenses, the concentration of total calcium was found to be approximately 0.2 mM, at least an order of magnitude lower than that found in the aqueous humor (Hightower et al., 1980). Lenticular magnesium level is much greater than that in the bathing aqueous and vitreous humors. The magnesium concentration in the peripheral part of the lens is about four times greater than that in the inner 'nuclear' regions (Wallach et al., 1967). Exchanges of magnesium between the lens and its bathing fluids are very slow; under control conditions the lens appears to be virtually impermeable to magnesium (Wallach et al., 1967). In the study of McGahan (McGahan et al., 1983), exposure of lens to metabolic inhibitors, depolarizing concentrations of potassium, ouabain or replacement of Na^+ with Li^+ had little effect on the magnesium content of the lens. Incubation of lenses in solutions containing EDTA or following freezing and thawing suggested that much of the magnesium is present in a bound form (about 35% of the lenticular magnesium).

Increased intracellular calcium levels can have a deleterious effect on lens metabolism (Hightower, 1985). The low intracellular calcium concentration is maintained by calcium-activated, magnesium-dependent adenosine triphosphatase (Ca^{2+}-ATPase) (Borchman et al., 1989), which extrudes cytosolic calcium across the plasma membrane or into subcellular organelles in the lens (Duncan et al., 1993). In the study of Borchman (Borchman et al., 1988) the Ca^{2+}-ATPase was routinely determined in both rabbit and bovine lenses and in pooled specimens. The pattern of stimulation of ATPase activity by a range of calcium concentrations was found to be similar in membrane preparations of epithelium and cortex, from rabbit and bovine lenses. Calcium-ATPase was undetectable in the lens nuclear region of both species. Studies of ion channels in the lens indicate that the calcium channel is closed under normal physiological conditions (Cooper et al., 1986). It has been suggested that lens cells have a Na^+/Ca^{2+} exchange mechanism to transport calcium out of the cell (Tomlinson et al., 1991). It is likely that there is a small passive inward leak of calcium, which is balanced by a Ca^{2+}-ATPase.

Sodium–potassium transport is another important electrolyte transport mediated by magnesium dependent sodium, potassium adenosine triphosphatase (Na^+,K^+-ATPase). Earlier study of Paterson (Paterson, 1969; Paterson and Delamere, 2004) revealed that the anterior region of the lens is specialized for energy-dependent Na–K transport mediated by Na^+,K^+-ATPase. It turns out, however, that anteriorly located fiber cells have an Na^+,K^+-ATPase activity that does not differ very much from the activity in posterior fibers; Na^+,K^+-ATPase activity in both regions is low (Delamere and Dean, 1993). However, Na^+,K^+-ATPase activity is considerably higher in the anterior, epithelial monolayer. Lens epithelial cells seem to be specialized to maintain a high Na^+,K^+-ATPase activity. Moreover, the extensive cell coupling in the fiber mass enables energy-dependent sodium and potassium transport by the epithelium to contribute to ion regulation for the underlying fibers that have much lower Na^+,K^+-ATPase (Paterson and Delamere, 2004).

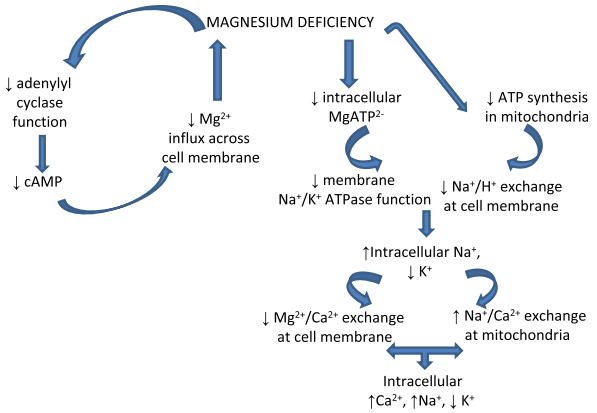

Fig. 1. Intracellular ionic changes in presence of magnesium deficiency.

Since ATPase function seems to be potentially so important to the lens, role of magnesium in Na^+,K^+-ATPase and Ca^{2+}-ATPase activities may perhaps be significant in lens active ion transport mechanisms. (Fig. 1).

3. Magnesium and cataract

3.1. Magnesium deficiency in onset and progression of cataract

Cataract is the leading cause of blindness and occurs because of the loss of optical homogeneity and transparency of lens. Changes in the intracellular ionic concentrations of cataractous lens have been described by various researchers. The ionic imbalance in age-related cataract has been shown to be significantly associated with decreased magnesium and potassium coupled with increased calcium and sodium (Dilsiz et al., 2000). These ionic imbalances develop due to membrane changes and lead to lens opacification. Among all, role of magnesium in the onset and progression of cataract has widely been evaluated using various animal models.

3.2. Magnesium supplementation delays onset of cataract in vivo

Magnesium supplementation has been shown to have a preventive role in cataract development in Shumiya cataract rats. The Shumiya cataract rats are the hereditary cataractous rat strains that were established by Shumiya and Nagase (Shumiya and Nagase, 1988). These rats develop perinuclear and nuclear lens opacities spontaneously by the age of 11–12 weeks and are considered a good representation of human senile cataract (Shumiya, 1995). One of the studies showed that the development of cataract in these rats was delayed by administration of deep-sea drinking water containing 200 mg/l of magnesium ion along with

calcium (71 mg/l), sodium (74 mg/l), potassium (69 mg/l) and other minerals. Similar observation was also made when these rats were fed with magnesium water containing 200 mg/l magnesium only. Further increase in magnesium concentration in fed water did not protect against cataract development. The calcium contents of the lenses in rats receiving magnesium supplemented water, at week 15 were found to be significantly low even after development of cataract as compared to the controls (developed cataract at 11–12 weeks) that were fed with purified water at the same time (Nagai et al., 2006a,b).

In another study, Shumiya cataract rats aged 5–15 weeks were fed with low magnesium (Magnesium oxide 50 mg/l), standard magnesium (Magnesium oxide 500 mg/l) or high magnesium diet (Magnesium oxide 5000 mg/l). It was observed that low magnesium diet accelerated development of cataract but there was no significant difference in the onset of lens opacities between standard magnesium diet and high magnesium diet fed rats. In rats fed with low magnesium diet, lens opacification started at the age of 10 weeks and was mature at 12 weeks as compared to rats on standard or high magnesium diet for which corresponding ages were 11 and 13 weeks respectively. At 15 weeks of age, the calcium contents of low magnesium fed rat lenses were significantly high as compared to those with standard or high magnesium diet. In addition, the rats on high magnesium diet had low body weight as compared to two other groups and this effect was attributed to the laxative effect of magnesium oxide (Nagai et al., 2007).

The above-mentioned studies clearly indicate a positive correlation of magnesium deficiency with increased calcium content in the lens. The underlying mechanisms to explain this correlation have also been studied by several researchers. The oxidative stress resulting from magnesium deficiency seems to play a key role in initiating the cascade of events leading to increased lens calcium concentration and finally culminating into cataractogenesis.

3.3. Magnesium deficiency triggers increased iNOS expression and release of NO

The high amounts of free radicals are normally generated in lens due to chronic exposure to ultraviolet light and high metabolic rate of lens epithelial cells but because of the existence of efficient lenticular antioxidant defenses, the oxidative damage to lens components is kept in check. Excessive production of free radicals such as H_2O_2 and nitric oxide (NO) and reduced antioxidant capacity such as superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) predispose to oxidative damage (Formicki and Stawarz, 2006). NO has been shown to play a critical role as it produces nitrogen free radicals such as NO^+, NO^-, NO_2, N_2O_3, and $ONOO^-$ which are capable of causing oxidative damage. The NO is produced from L-arginine and the reaction is catalyzed by the enzyme nitric oxide synthase (NOS). One of the isoform of NOS, inducible NOS (iNOS), is expressed in response to various stimuli such as cytokines and leads to production of excessive quantities of NO. The NO levels in aqueous humor have been shown to be significantly high in patients with cataract and the rise was shown to be correlated to age and maturity of cataract (Kao et al., 2002). Örnek et al. (2003) showed increased nitrite (a metabolite of NO) contents in human lenses with posterior subcapsular cataract. Pretreatment of rats with inhibitors of the NOS has been shown to prevent onset of selenite-induced cataract, reduce lens calcium and increase GSH contents (Ito et al., 2001).

The studies show that magnesium deficiency triggers the cataractogenesis by increasing the iNOS expression and release of NO. Culture of human lens epithelial cells (HLEC) in medium deficient of magnesium (Mg^{2+} 0.21 nM) causes 6 fold increase in expression of iNOS mRNA, 24 h after culture, as compared to those cultured in medium containing normal magnesium concentration (Mg^{2+} 0.77 nM). Release of NO from cells cultured in magnesium deficient medium reached peak after 6 h of incubation and thereafter a plateau was maintained. Treatment of medium with diethyldithiocarbamate (a free radical scavenger) and aminoguanidine (inhibitor of iNOS) attenuated increased release of NO (Nagai et al., 2007) (Fig. 2).

3.4. Magnesium deficiency-induced NO release causes ATP depletion

NO has previously been shown to cause depletion of cellular ATP by interfering with several key enzymatic function in the pathways to generate ATP (Okuma et al., 1998; Yasuda et al., 1998). Similar effects of excessive NO production have been observed in lens. The ATP level in HLEC, cultured in magnesium deficient medium increased during initial 6 h of incubation and thereafter reduced significantly at 24 h as compared to those cultured in medium containing normal magnesium concentration. Addition of disulfiram and aminoguanidine to magnesium deficient medium increased ATP levels by 2 fold (Nagai et al., 2006b). Exposure of lens to NO *in vitro* has also been shown to significantly reduce the ATP in the lens (Varma and Hegde, 2007). Interestingly, the lens ATP contents of UPL rats also start decreasing at the age of 39 days and marked reduction in lens ATP has been observed at the age of 46 and 53 days (Nabekura et al., 2004). UPL rats, derived from *Sprague Dawley* rats, are also useful hereditary models of cataract. The cataractous opacities in these rats develop within 8–10 weeks after birth. The cataract in these rats resembles closely to human senile cataract because except for the ocular abnormality all other biological parameters including the life span is same as for normal rats (Tomohiro et al., 1993, 1996a,b, 1997). Significantly low ATP levels have also been reported in the lenses of human senile cataract patients as compared to those with normal lens (Maraini et al., 1967) (Fig. 2).

3.5. Magnesium deficiency alters membrane associated ATPase functions and increases intracellular calcium

The mechanisms involved in producing intracellular ionic imbalances in presence of magnesium deficiency have been studied extensively. Magnesium is one of the most important cofactor involved in several metabolic enzymatic reactions, particularly those involving ATP. ATP in its active form exists in anionic form and in combination with magnesium as $MgATP^{2-}$. The plasma membrane Na^+,K^+-ATPase is responsible for active transport of Na^+ out of the cell in exchange for K^+ thus maintaining a high intracellular potassium concentration. Reduced Na^+,K^+-ATPase (Bara et al., 1993) functions result in an increase in membrane permeability to potassium, leading to inability of cells to maintain the normally high intracellular concentration of potassium. As a result, the cells lose potassium, which is excreted in the urine. Repletion of cell potassium requires correction of the magnesium deficit. Therefore, the metabolism of potassium and magnesium is closely linked. Isolated disturbances of potassium balance do not produce secondary abnormalities in magnesium homeostasis. In contrast, primary disturbances in magnesium balance, particularly magnesium depletion, produce secondary potassium depletion (Iezhitsa and Spasov, 2008). Furthermore, due to reduced function of plasma membrane Na^+/K^+ pump, Na^+ accumulates intracellularly and besides causing osmotic stress also causes release of mitochondrial Ca^{2+} by Na^+/Ca^{2+} exchange and at the same time there is reduction of Na^+/H^+ exchange across the cell membrane. In addition, as a result of magnesium deficiency there is reduced Mg^{2+}/

Ca^{2+} exchange at the cell membrane leading to increased intracellular Ca^{2+} (George and Heaton, 1975).

The Ca^{2+}ATPase is another important magnesium-dependent membrane associated transporter that regulates the intracellular ionic environment of the lens (Bara et al., 1993). It is expressed in four isoforms of which isoform1b is predominant in both the normal and UPL rat lenses (Nabekura et al., 2001). Each of the isoform is encoded by a distinct gene and additional alternate slicing of exons results in diversity (Strehler and Zacharias, 2001). As this enzyme uses ATP and maintains the lens calcium content by removing excess of calcium, magnesium deficiency and depletion of intracellular ATP leads to accumulation of calcium in the lens.

In the presence of magnesium deficiency the ATPase functions are lost due to depletion of cellular ATP (Alberty, 1968). ATP depletion results from interference with the synthesis of ATP which takes place in mitochondria by electron transport and oxidative phosphorylation, the reactions that utilize several enzymes which are magnesium-dependent. Moreover, as described above ATP depletion also results from increased NO release due to magnesium deficiency and adversely affects the function of plasma membrane ATPase (Bara et al., 1993). The reduced activity of plasma membrane Ca^{2+}-ATPase subsequent to increased iNOS expression, increased release of NO and consequent ATP depletion has been observed in UPL rats but treatment with disulfiram and aminoguanidine was shown to normalize the cellular ATP contents and therefore the enzyme function (Nabekura et al., 2004). Besides affecting the ATPase functions, NO can also cause ionic disturbances by altering the gap junctional proteins. NO has been shown to cause nitrosylation of cysteine residues at the C-terminal domain of connexin46, a gap junctional protein expressed in lens (Retamal et al., 2009).

In summary, magnesium deficiency results in increased cytoplasmic Na^{+} and Ca^{2+}, reduced K^{+} and reduced mitochondrial Ca^{+} in the lens fibers (Fig. 2).

3.6. Increased intracellular calcium leads to cataractogenesis

Increase in the intracellular calcium has been observed ahead of the development of lens opacity (Nabekura et al., 2003; Shearer et al., 1992). The increased cellular calcium thereafter causes activation of the enzyme calpain, which is a calcium-dependent intracellular cystein protease. Several isoforms of calpain are present in the lens, however calpain II appears to be the major form involved in cataractogenesis (Hightower et al., 1987; Azuma et al., 1990; Baruch et al., 2001). Activated calpain II causes proteolysis of the lens proteins, noticeably crystalline. Soluble crystalline is responsible for the lens optical properties and upon proteolysis it gets converted to an insoluble form leading to loss of lens optical homogeneity and development of cataract (Nabekura et al., 2003; Shearer et al., 1992; Dilsiz et al., 2000; Biswas et al., 2004). Nitrite ions have been shown to react directly with crystalline, resulting in its modification similar to that occurring in aging lens and cataract. This non-enzymatic nitration of crystalline may also be an important contributory mechanism in cataractogenesis (Paik and Dillon, 2000).

Increased calcium concentration has also been shown to cause noncompetitive inhibition of the enzyme acid phosphatase in a dose-dependent manner. This acid phosphatase is a magnesium-dependent enzyme and has been identified in the lenses of chicken, mice and rabbits. It is proposed to have significant role in maintaining the transparency of lens. It is a 55kD protein and has maximum activity at pH 5.5. *p*-Nitrophenyl phosphate was used as its substrate *in vitro*, however its *in vivo* substrate is not yet characterized. It is strongly activated by magnesium in a dose-dependent manner. The most effective concentration of magnesium required to activate the lens phosphatase in this study was 1–10 mM. Since the physiological concentration of magnesium in lens is 4–10 mM, it is likely that this phosphatase is activated by Mg. *In vitro*, this enzyme was also activated by cobalt and zinc but the physiological concentration of these metallic ions in lens is very low and therefore, their role does not appear to be of much significance (Umeda et al., 2003). Thus in addition to the calcium-induced crystalline proteolysis, inhibition of magnesium-dependent acid phosphatase may also be responsible for progression of lens opacification (Fig. 2).

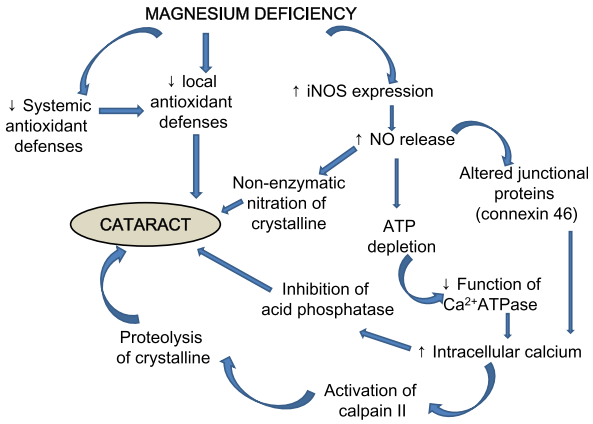

Fig. 2. Pathogenetic mechanisms of magnesium deficiency-induced cataractogenesis.

3.7. Magnesium deficiency-induced systemic oxidative stress also contributes to cataractogenesis

Magnesium deficiency has been shown to cause increased systemic oxidative stress. Increased systemic oxidative stress, generated outside the lens can be an important factor leading to cataract formation. Altered plasma antioxidant parameters such as lipid peroxidation products and GSH have shown increased oxidative stress in patients with cataract (Donma et al., 2002). The regulation of ocular antioxidants such as glutathione is dependent on their plasma levels (Stahl et al., 1996). Magnesium has been shown as an essential element in regulation of GSH metabolism in erythrocytes. Rats fed with low magnesium diet developed low erythrocyte GSH which reverted to normal value after magnesium supplementation (Hsu et al., 1982).

In human, magnesium deficiency is correlated with decreased total plasma antioxidant capacity and reduced blood glutathione levels (Keenoy et al., 2000). Hans et al. (2002) showed that rats receiving low magnesium diet (70 mg/kg) showed marked increase in plasma malondialdehyde, a lipid peroxidation product, with a corresponding decrease in plasma antioxidants as compared to those on control diet. Experimental magnesium deficiency in rats has been shown to significantly reduce the activity of the antioxidant enzymes, SOD and catalase (Kumar and Shivakumar, 1997). Rats fed with low magnesium diet have shown an increase in plasma nitrate plus nitrite level by 1.7 fold during first week further increasing up to 2.0–2.4 fold during 2nd and 3rd week. In addition RBC glutathione reduced by 50%. Administration of an NO synthesis inhibitor NG-nitro-L-arginine methyl ester (L-NAME) blunted the increase in nitrate plus nitrite level and restored RBC glutathione (Mak et al., 1996). These results indicate that magnesium deficiency reduces plasma antioxidant capacity subsequent to increased NO production as was the case within the lens.

Lowering of plasma antioxidant capacity reflects in the reduced ocular antioxidant capacity. Increased intraocular oxidative stress further sets in the sequence of events as discussed earlier, finally culminating into the cataract formation.

Excess of magnesium can cause postoperative IOL opacification. Treatment of cataract is done by phacoemulsification with implantation of intraocular lens (IOL). Late postoperative opacification of hydrogel IOL is widely reported. One of the recent studies compared the mineral element of explanted opacified hydrophilic acrylic lenses with the never implanted packed lenses. It was observed that magnesium was one of the prominent mineral present in the lens opacities in significantly higher quantities as compared to packed lenses. No correlation was found between the amount of mineral deposition and preexisting eye diseases such as glaucoma, uveitis, AMD (Fodor et al., 2011). It was suggested that the source of magnesium could be metal injectors, forceps and metallic components used intraoperatively (Mathys et al., 2008; Werner et al., 2006).

4. Conclusions

Magnesium is of critical importance in regulating cellular and molecular functions including those of ocular tissue. The pathogenetic role of magnesium deficiency in cataract has been studied widely. The association of magnesium deficiency with cataract may primarily be attributed to its highly important role as a cofactor for membrane associated ATPases. Magnesium deficiency also affects activity of several enzymes involved in ATP synthesis. Moreover, magnesium deficiency causes increased oxidative stress by increasing iNOS expression and release of excessive quantity of NO. Thus, magnesium deficiency causes increased lenticular oxidative stress and altered functions of membrane associated ATPases resulting into ionic imbalances that mainly consist of reduced intracellular potassium and increased intracellular sodium and calcium. Increased intracellular sodium causes cellular swelling by causing osmotic stress and increased calcium causes activation of calcium-dependent enzyme calpain that converts soluble cytoplasmic proteins into insoluble ones. All cellular changes in lens fibers resulting from magnesium deficiency finally culminate into development of lenticular opacities.

In spite of the minefield of data providing supportive evidence for the association of magnesium deficiency with cataract, currently, its role can only be emphasized as an associated factor with several other factors. Nevertheless, the review of currently available literature clearly supports the needs for further investigations to assess the role of magnesium as a supportive therapeutic approach in delaying the onset and progression of cataract.

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Competing interests

The authors declare that no competing interests exist.

Contributor

All authors have substantially contributed to conception, designing, drafting the article and in final approval of the manuscript version to be submitted. All authors have jointly decided to designate Assoc Prof Dr Igor Iezhitsa to be responsible for taking decision regarding the presence of authors and the order of their presence in the manuscript. Assoc Prof Dr Igor Iezhitsa has also been selected by all authors to be responsible for all future communication with the journal regarding this manuscript.

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