



## The Israel Society for Research on Magnesium in Biology and Medicine: Proceedings of the First Meeting

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The first meeting of the Israel Society for Magnesium Research in Biology and Medicine was held at Tel Aviv University on 6 June 2000. The goal of the Society is not only to encourage magnesium research but also to increase awareness of the importance of prevention, early diagnosis and adequate treatment of Mg deficiency states. It hopes to create a consensus on the national laboratory reference interval for Mg, the optimal daily food Mg requirement, and the choice of the optimal Mg vehicles to be used in therapeutics.

In a brief review, Dr. Stendig-Lindberg highlighted some salient points on the role of magnesium in biology and medicine. On removal of Mg from its central position in the chlorophyll molecule, photosynthesis ceases, which illustrates the importance of this element to life on earth. The basic biological functions of Mg are twofold: a) it binds to substrates, enzymes and cell constituents, serving as a biological glue [1]; and b) it activates enzymes by combining with the enzyme, the substrate, or both, by affecting a conformational change of the enzyme protein, or by changing the concentration of the substrate in an enzymatic reaction. The fundamental intracellular processes regulated by magnesium are listed on Table 1. In Mg-deficient states, the intracellular changes include a decrease of  $Mg^{++}$ ,  $K^+$ , inorganic phosphate and the energy-rich phosphagenes ATP, ADP and PC. At the same time there is an increase in intracellular  $Na^+$ ,  $Cl^-$ ,  $Ca^{++}$

and cAMP activity, as well as an increase in the interstitial  $H_2O$  content [2]. Magnesium deficiency, which is detrimental to health and in its severe form is incompatible with life, is highly prevalent in Israel, among others, because of the high level of stress (increase in catecholamines induces Mg diuresis) and the high ambient temperature (causing profuse loss of Mg in sweat). Mg deficiency is especially common in susceptible population groups that have an increased Mg requirement, such as adolescents, pregnant and lactating women, and workers and soldiers exposed to strenuous effort and/or high ambient temperature [3,4]. Unfortunately, the Mg daily food content in Israel of 200-300 mg, similar to that of other western diets, is inadequate and does not meet even the "normal" Mg requirement. It falls short of the United States Recommended Daily Allowance of 350-420 mg per day, which in addition allows a daily magnesium supplement of 350 mg,

giving a total of 700-770 mg daily. Balance studies, however, indicate an even higher requirement, e.g., adolescents require 1,050 mg magnesium per day [5]. The Mg deficiency may be manifest, i.e., the serum Mg concentration lies below the lower border of the reference interval of 0.82-1.06 mmol/L found in a steady state (i.e., in a state of saturation of metabolism when all the body compartments are filled with Mg). Alternatively, the Mg deficiency may be manifest, characterized by fluctuating S-Mg values signifying the presence of intracellular Mg deficit. The degree of intracellular Mg deficit can be gauged by means of the Mg retention test: the greater the amount of the i.v. administered Mg retained, the greater the intracellular deficiency. However, since the procedure is cumbersome, it is advisable to estimate the 24 hour urinary Mg content instead. Since the 24 hour

S-Mg = serum magnesium concentration

**Table 1.** Intracellular processes regulated by magnesium

- Intermediary (fat and carbohydrate) metabolism, protein and nucleic acid metabolism
- Energy production (oxidative phosphorylation, glycolysis) and energy consumption (active transport, muscle contraction)
- The voluntary contraction force of the skeletal muscle
- The basic tone of smooth muscle including the smooth muscle of the arteries (including those of the coronary arteries)
- The contraction force of the cardiac muscle
- The influx and efflux of electrolytes, including that of calcium
- Receptor binding
- Bone turnover
- Neuromuscular transmission
- The stability/permeability of cell membrane
- The correct replication of the genetic code

Mg = magnesium

U-Mg value is significantly correlated to intracellular Mg content [6,7], it shows, in Mg deficiency, a progressive decrease due to Mg conservation by the kidney. Consequently, two estimates of S-Mg at an interval of 7–10 days and one estimate of 24 hour U-Mg will aid in diagnosing Mg deficiency, which is often missed – masked by a seemingly “normal” S-Mg.

### Mg in Cell Physiology

Magnesium ions in the function of excitable tissue was the subject of Dr. Rahamimoff's presentation. Mg ions have a profound effect on almost every excitable tissue in the body. Among the various effects of Mg ions, Prof. Rahamimoff focused on two aspects of synaptic transmission: the effects of Mg ions on transmitter release and the effect of Mg ions on post-synaptic function. Quantal release of transmitter from pre-synaptic nerve endings is of paramount importance in synaptic communication among nerve cells. The key element in the quantal liberation of transmitter is the fusion of the synaptic vesicle with the surface membrane. This fusion process is triggered by the entry of calcium ions into the surface membrane of the pre-synaptic vesicle. Mg ions compete with Ca in this process of transmitter release and thus play an important role in the regulation of transmitter liberation. Since transmitter liberation is of importance also in synaptic plasticity, Mg ion is one of the major participants in this complicated activity of neuronal communication. Glutamate ions are the main excitatory transmitter in the nervous system. Glutamate is released from pre-synaptic nerve terminals and affects different post-synaptic receptors. Some of these receptors are directly activated by glutamate, but other receptors (NMDA receptors) are partially blocked by magnesium ions; thus a depolarization is necessary to relieve this magnesium block of the post-synaptic receptors. Thus, magnesium ions are part of a comprehensive orchestra of ion channels regulating

post-synaptic excitability and transmission properties of excitatory synapses in the brain. It is noteworthy that the blockage of ion channels by Mg ions plays a pivotal role in the function of the heart. One of the important ion channels that stabilizes the function of the heart is the inward rectifier. While directing the potential of heart cells, this inward rectifier is wide open and stabilizes the membrane, preventing the generation of extra-systole and arrhythmia. Upon depolarization this channel closes and thus facilitates the generation of the action potential and heart contraction. The closure of this channel is achieved in part by Mg ions. Thus, Mg deficiency can cause life-threatening cardiac arrhythmias by the lack of the blockade of this inward rectifier potassium channel in the heart.

### Mechanical properties of human erythrocytes regulated by intracellular Mg

Reporting on his experimental work, Dr. Korenstein discussed the central role played by the mechanical properties of circulating blood cells in microcirculation. However, exploring the regulation of its mechanical characteristics by physiological effectors, such as hormones, has been very limited. Moreover, in view of the fact that the main function of oxygenated RBCs is to deliver oxygen to respiring cells of the body, the possibility that deoxygenation of normal human RBCs alters their mechanical properties has scarcely been addressed. Initial support for the possible regulatory effect of oxygen on the mechanical properties of normal human RBCs emerges from the previous study where RBCs subjected to cyclic oxygenation and deoxygenation revealed a reversible decrease in the amplitude of submicron mechanical fluctuations of the cell membrane. These fluctuations, which reflect the bending deformability of the membrane-skeleton, were monitored by time-dependent light scattering from a small area ( $\sim 0.25 \mu\text{m}^2$ ) of the cell surface

by a method based on “point dark field microscopy.” Since one of the main changes accompanying deoxygenation is the elevation of intracellular free  $\text{Mg}^{++}$ , they examined the dependence of cell membrane fluctuations on intracellular free  $\text{Mg}^{++}$ . Elevation of intracellular  $\text{Mg}^{++}$  in the high concentration range (0.8 mM) rigidified the red blood cell. Analysis of one aspect of the transduction mechanism shows that deoxygenation increases the level of tyrosine phosphorylation of band 3. When the rise in intracellular free  $\text{Mg}^{++}$  concentration in deoxygenated RBCs is simulated via clamping, the intracellular Mg of oxygenated RBCs by ionomycin, band 3 phosphorylation, is elevated by up to tenfold. These findings suggest that the visco-elastic properties of human erythrocytes may be regulated by Mg-induced band 3 tyrosine phosphorylation [9].

### Mg and the cardiovascular system

Dr. Shechter with his Israeli and U.S. colleagues studied 50 patients with stable coronary artery disease who participated in a supervised cardiac exercise program. They were randomized into two groups: 25 patients received MgO tablets, 30 mmol/day, and 25 received placebo for 6 months. Thereafter, in order to distinguish between the flow-mediated endothelium-dependent and the endothelium-independent vasoreactivity of the brachial artery, the former was measured using 10 MHz ultrasonography 1 hour and 30 min after occlusion of 3 min duration of the brachial artery by means of a blood pressure cuff, and the latter after administration of sublingual nitroglycerin. The flow-mediated endothelium-dependent vasoreactivity was significantly increased in the Mg-treated group ( $P < 0.02$ ). The intracellular  $\text{Mg}^{++}$  was measured using X-ray dispersion analysis of sublingual cells. The results suggested that Mg administration could benefit patients with stable coronary artery disease. In another study, a group of 49 patients with stable coronary artery disease was examined with the same methodology used in the previous experiment in order to deter-

U-Mg = 24 hour urinary magnesium concentration

RBCs = red blood cells

mine whether increased intracellular  $Mg^{++}$  level enhances brachial artery reactivity. The flow-mediated percentage change in the diameter of the brachial artery was highly significantly associated with intracellular  $Mg^{++}$  content ( $P < 0.001$ ), suggesting a role for Mg in the treatment of stable coronary artery disease [10].

Dr. Scherer and colleagues who previously showed that a Mg-supplemented diet modulated blood lipid levels and atherogenesis in the rabbit now used low density lipid receptor-deficient mice and Mg-enriched drinking water. The experimental animals received either distilled or Mg-enriched water and a low cholesterol diet for 12 weeks followed by 6 weeks on a high cholesterol diet. Mg, Ca and lipids were measured after 12 and 18 weeks and the extent of the atherosclerotic changes at the aortic sinus level was noted. The experimental animals given Mg-fortified water were found to have a higher plasma Mg concentration – the Ca content did not differ – and the extent of atherosclerotic changes was decreased by two-thirds. A decrease occurred even in the animals that were fed a high cholesterol diet [11].

### Mg in therapeutics

Dr. Attias and his colleagues from Humboldt University, Berlin, and the German Federal Environmental Agency, reported on the effect of Mg in prevention and treatment of environmentally induced hearing loss. Exposure to high level noise affects about 30% of industrial workers, excluding soldiers. Since mechanical hearing protection does not prove sufficiently efficient, the effect of Mg in prophylaxis of high level noise-induced reduction of hearing was tested in a double-blind placebo-controlled study. A daily drink containing 167 mg magnesium proved to reduce the incidence of hearing loss, and a negative correlation between the intensity of high level noise and the Mg content of erythrocytes and mononuclear cells was observed. In another double-blind placebo-controlled study, the temporary threshold shifts and the oto-acoustic cochlear emissions were studied in hu-

mans. Mg was found to correlate with the oto-acoustic cochlear emissions and to offer protection against TTS. Lower TTS and better cochlear status were also obtained in Mg-supplemented experimental animals, compared with controls. Moreover, histopathologic examination established that the damage to cochlear outer hair cells was less in the Mg-supplemented animals. Finally, ongoing studies suggest that Mg may also have a therapeutic effect once a reduction of hearing loss occurs [12].

Dr. Onn and colleagues investigated the effect of Mg on asthma. A group of 26 asthmatics (6 males and 5 females) including 16 severe and 10 mild cases, 6 non-atopic and 20 atopic cases, and 11 apparently healthy controls were investigated for S-Mg, U-Mg, erythrocyte and mononuclear cell Mg content, and serum immunoglobulin E level. Spirometry and skin prick test were carried out before and after a 4 hour Mg retention test. The test, consisting of infusion of 0.2 mg/kg of  $MgSO_4$ , showed the presence of Mg deficiency in 50% of the patients and in 72% of the apparently healthy controls. In all asthmatic patients the FEV1/ FVC ratio increased after the infusion. U-Mg and erythrocyte Mg content were significantly increased in non-atopic compared with atopic patients, and in severe asthmatics compared with those with only mild asthma ( $P < 0.05$ ). In conclusion, all patients responded to the brief Mg infusion with bronchodilation. The severely ill asthmatics were more Mg deficient than the milder cases, suggesting that Mg deficiency causes aggravation of the disease. The non-atopic cases were more deficient than the atopic ones, suggesting that Mg deficiency may play a role in pathogenesis of non-atopic asthma [13].

Dr. Bahar and Dr. Berman and colleagues demonstrated how intrathecally injected  $MgSO_4$  produces stable spinal anesthesia. In the first study, the intracellular concentrations of  $Ca^{++}$ ,  $Mg^{++}$ ,  $Na^+$  and  $K^+$  of the thoracic and lumbar spinal segments were measured after

$MgSO_4$  anesthesia and after 4% lidocaine injection.  $Na^+$  and  $K^+$  concentrations decreased significantly 1 hour after lidocaine injection and 24 hours after  $MgSO_4$ , whereas  $Mg^{++}$  concentration rose only slightly after both injections.  $Ca^{++}$  concentration rose significantly 30 and 60 min after  $MgSO_4$  injection and remained elevated 24 hours later. Intracellular  $Ca^{++}$  concentration was significantly increased after 4% lidocaine injection as well. A possible association of these changes with the action of  $Ca^{++}$  channels was discussed [14]. In the second study, the  $Mg^{++}$ ,  $Ca^{++}$ ,  $Na^+$  and  $K^+$  content of blood mononuclear cells of experimental rats were measured after intrathecal injection of 6.3%  $MgSO_4$  or 4% lidocaine solution.  $Na^+$  and  $K^+$  concentrations increased 15 min after lidocaine and 30 min after  $MgSO_4$  injection, remaining elevated throughout a 24 hour period. Intracellular  $Mg^{++}$  was slightly elevated 1 hour after lidocaine and 2 hours after  $MgSO_4$  injection. There were no significant changes in  $Ca^{++}$  concentration. The mononuclear cells of the circulating blood appeared to be protected from the changes in the spinal cord cells that occurred as a result of the intrathecal anesthesia induced by  $MgSO_4$  and lidocaine solutions respectively [15].

Dr. Mayan and colleagues presented two cases of women with eclampsia and premature labor who received Mg tocolytic therapy. During hypermagnesemia resulting from the treatment, the patients developed prolonged symptomatic hypocalcemia and undetectable parathyroid hormone concentration. He reviewed the few similar cases reported previously in the literature and discussed the possible cause. He proposed that since Mg was an agonist for the calcium sensor receptor, the latter was involved in the development of the hypermagnesemia-induced hypocalcemia [16].

Dr. Stendig-Lindberg reported on the continuation of an earlier 2 year controlled trial of oral Mg treatment in 31 postmenopausal osteoporotic women who received tablets of  $Mg(OH)_2$ , 250–750 mg magnesium per day, for 6

TTS = temporary threshold shifts

months followed by 250 mg daily for 18 months. Increase in bone density of 1–8% occurred in 71% of cases and arrest of the disease in another 16% (*Magnes Res* 1993;6:155–63). Thus 89% (27 patients) responded and only 13% (4 patients) showed a decrease in bone density. Two consenting patients agreed to continue the therapeutic trial beyond the 2 years, one a responder and the other a non-responder. They received 250 mg magnesium as Mg(OH)<sub>2</sub> tablets daily. Bone density scan and laboratory screening were carried out periodically and their compliance was checked. The bone density of one patient, aged 53, increased by 3% by the end of the 2 year trial. After 8 years of follow-up treatment her bone density increased by 20%, reaching 108% of that in age-matched and 93% in young female controls – a total increase of 23%. The second patient, aged 56, showed no response after the controlled 2 year trial, but a 14% increase after 2 years follow-up treatment when her bone density reached 109% of that in age-matched and 92% in young female controls. The value remained virtually stationary during another 8 years, rising by a further 2% two years later when the patient reached the age of 70 – a total increase of 16%. These findings illustrate that adequate Mg intake leading to a steady state of magnesium abolished menopausal osteoporosis and prevented the onset of senile osteoporosis [17].

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## Capsule

### Connecting plaques and tangles in Alzheimer's disease

Controversy still rages over which of the two hallmark pathologies of Alzheimer's disease, amyloid plaques and tau tangles, is the primary cause of neurodegeneration in the brain. Two reports, by Lewis et al. and Gotz et al., now show that the two pathologies are not unconnected. Working with

transgenic mice, the two groups independently demonstrated that beta-amyloid deposits in the brain influence the formation of tau tangles in areas of the brain known to be affected in Alzheimer's disease.

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