Metagenics

MAGNESIUM

RESEARCH LITERATURE REVIEW




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MAGNESIUM RESEARCH LITERATURE REVIEW

When You Want Effective Magnesium For Your Patients

Magnesium is an essential mineral, being the fourth most abundant cation in the body (after sodium, potassium and calcium) and the second most abundant intracellular cation after potassium. It is required in the biological function of at least 360 enzymes in the human body, and plays a fundamental role in many cell functions. These functions include: Energy transfer, storage, and use; protein, carbohydrate, and fat metabolism; maintenance of normal cell membrane function and the regulation of parathyroid hormone secretion. Systemically, magnesium lowers blood pressure and alters peripheral vascular resistance. Abnormalities of magnesium levels can result in disturbances in nearly every organ system, and can cause potentially fatal complications (e.g. ventricular arrhythmia, coronary artery vasospasm and sudden death from myocardial infarction).

MAGNESIUM ABSORPTION AND BIOAVAILABILITY: THE OPTIMAL FORM OF DELIVERY IS GLYCINE CHELATION

Ionically bound magnesium salts such as the chloride (MgCl), sulphate ($MgSO_4$) and oxide (MgO), and complexed forms like aspartate and orotate, all dissociate in solution to release magnesium ions and are known to induce bowel evacuation when taken in therapeutic doses.

A covalently bound magnesium-glycine chelate is not hydrolysed by digestive processes, nor does it dissociate in solution. This form of magnesium is readily absorbed as an amino acid complex, to provide rapid serum delivery while remaining intact. The intact chelate does not release magnesium, which would be bound to blood proteins and further reduce bioavailability. Rather, there is direct cellular uptake, again as an amino acid chelate, and release of the magnesium ion inside the cell due to lysosomal cleavage of the glycine residues.

The magnesium-glycine chelate (magnesium diglycinate) is a significant advance in magnesium supplementation technology, enabling the administration of therapeutic levels of oral magnesium supplementation which do not cause gastrointestinal upset and diarrhoea.[1]

In the 'Mauskop and Altura' study on migraine prophylaxis, it was found that magnesium diglycinate is "one of the better absorbed preparations". Their recommendation was based on a daily supplement of 600 mg of magnesium diglycinate. There is a large amount of experimental and clinical data that supports the use of this therapy and shows that 600 mg of magnesium has an excellent safety profile and a low cost profile.[133]

DEFICIENCY

Dietary magnesium deficiency is far more prevalent than is generally suspected. It can impact on many biochemical processes and be expressed via a diverse range of clinical symptoms and signs:

- Fatigue (insulin resistance) [p.8-9]
  - Diets high in fat, sugar, and salt
- Stress, anxiety, panic disorder, dementia, epilepsy [p.10]
- Pre-menstrual syndrome (PMS) [p.11-12], Infertility [p.12], Pregnancy [p.13], Pre-Eclampsia [p.13], Osteoporosis [p.14]
- Cardiovascular Diseases:
  - Hypertension [p.14]
  - Vasospasm [p.15]
  - Myocardial Infarction [p.16]
  - Elevated blood lipids [p.17]
  - Thrombosis [p.18]
  - Arrhythmia [p.15]
  - Angina [p.16]
  - Mitral Valve Prolapse [p.16]
  - Coronary Heart Disease [p.18]
- Neuromuscular conditions:
  - Muscle Cramping and Spasms [p.19]
  - Tension Headaches and Migraines [p.21]
  - Athletic Performance [p.19-20]
- Fibromyalgia [p.22]
- Chronic Fatigue Syndrome [p.22]
- Toxicity: Alcohol and Toxic Metals [p.23]

Dietary Sources of Magnesium

Magnesium is ubiquitous in nature and is especially plentiful in green vegetables, grain, nuts, legumes, and chocolate. Vegetables, fruits, meats, and fish have intermediate values. Food processing and cooking may deplete magnesium content, thus accounting for the apparently high percentage of the population whose magnesium intake is less than the recommended daily intake.

Prevalence of Magnesium Deficiency

A CSIRO study of Australian adults found the daily intake of magnesium was below the RDI for 50% of all males tested, and for 39% of all females.[8] In the United States deficiencies appear to be even more common. Approximately 80 to 85% of the adult females and 50 to 65% of the adult males had intakes below the USA recommended levels.[9]

Recommended Daily Intakes Rarely Achieved

The recommended daily intake (RDI) of magnesium in Australia is currently 320 mg per day for men and 270 mg per day for women. Pregnant and lactating women are considered to require an extra 30 and 70 mg per day respectively. The average Western diet is theoretically estimated to deliver about 360 mg of magnesium daily. It is questionable though, whether the RDI is actually achievable with a modern Australian diet, or if it is sufficient for a neutral magnesium balance.

Current research indicates that in most Western countries a sufficient magnesium supply is difficult to achieve, particularly in view of the increased demand for magnesium associated with common diets and lifestyles. Environmental factors such as soil quality, agricultural practices and air pollution also affect the magnesium content of the food supply.

Common Drugs and Alcohol Increase Magnesium Requirements

Alcohol consumption has a dramatic effect on magnesium levels, resulting in urinary excretion,[2] which induces magnesium deficiency.[3] This deficiency, in turn, contributes to many of the problems associated with chronic alcoholism.[4,5,6]

Many pharmaceutical medications increase magnesium requirements. Aminoglycosides (e.g. Gentamycin) may reduce magnesium absorption, as will loop and thiazide diuretics. Tetracycline antibiotics form insoluble complexes with magnesium, reducing the effectiveness of both the magnesium and the drug.

Magnesium may also interfere with some medications. It is possible that it could enhance the effect of calcium channel blockers (which may be desirable) and anti-arrythmic drugs.[7]

Magnesium Homeostasis: Distribution in the Body

The total body magnesium content of an average adult is around 25 g. Approximately 60% is present in bone, 20% in muscle, and 20% in soft tissue and the liver. Approximately 99% of the total body magnesium is intracellular, with only 1% in the extracellular space.

Magnesium Stores Slow to Mobilise

The plasma magnesium concentration is kept within narrow limits. Extracellular magnesium is in equilibrium with that in the bone, kidneys, intestine, and other soft tissues. In contrast to other ions, magnesium is treated differently in two major respects: (1) no hormonal modulation of urinary magnesium excretion occurs, and (2) bone, the principal reservoir of magnesium, does not readily exchange with circulating magnesium in the extracellular fluid space. This inability to mobilise magnesium stores means that in states of negative magnesium balance, initial losses come from the extracellular space; equilibrium with bone stores does not begin for several weeks. **Effectively, this means our day-to-day supply of magnesium is dependent on the diet, and/or magnesium supplementation.**

WHY IS MAGNESIUM SO IMPORTANT? IN A WORD: ENERGY

Fatigue is the most commonly reported complaint in clinic today. It is no coincidence that it is estimated that almost everyone is, to some degree, magnesium deficient.

Every cell in the body needs energy to function. Without sufficient energy the cell will not only fail to do its job, it will die. The major form of biological energy powering cellular metabolism is adenosine triphosphate (ATP). No matter how this energy is produced - whether via the immediate, non-oxidative or oxidative pathway – magnesium is absolutely essential.

The immediate energy system consists of:

1. Existing ATP, which can only sustain muscle contraction for less than a second
2. The formation of ATP from adenosine diphosphate (ADP) and inorganic phosphate, requiring the enzyme myokinase, which needs magnesium for its activity.
3. The production of ATP from ADP and creatine phosphate, which is mediated by creatine phosphokinase, an enzyme regulated by magnesium and hydrogen ions.

In the **non-oxidative**, **or glycolytic, energy system**, carbohydrates fuel anaerobic glycolytic reactions in the cytosol, converting glucose to pyruvate to produce ATP. Magnesium is a key component of many of the enzymes in this pathway.[10]

The Oxidative Energy System

In the presence of oxygen, the pyruvate from glycolysis is further converted to acetyl CoA, which powers the aerobic metabolism in the mitochondria – the citric acid, or Krebs cycle. magnesium is the key catalyst for the multi-enzyme regulatory switch between anaerobic and aerobic energy systems.

The citric acid cycle occurs within the mitochondrial matrix, and metabolises acetyl CoA to carbon dioxide. The first four reactions of this cycle are catalysed by isocitrate dehydrogenase, which requires magnesium for its activity. In the mitochondrial electron transport chain, ATP production is mediated by ATPase complexes, which also require magnesium to function.

All energy for muscle contraction comes from the hydrolysis of ATP, which is again mediated by magnesium-dependent ATPase.[11]

Insulin Resistance

A poor intracellular magnesium concentration, as found in non-insulin-dependent diabetes mellitus (NIDDM) and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance. A growing body of studies suggest that intracellular magnesium may play a key role in modulating insulin-mediated glucose uptake and vascular tone.[12] Insulin sensitivity can be improved by reduction of excessive body weight, regular physical activity and by correcting a subclinical magnesium deficiency.[13]

Nutritional Cofactors Involved in Improving Insulin Sensitivity

Insulin resistance appears to be a common feature and a possible contributing factor to several frequent health problems, including Type-2 diabetes mellitus, polycystic ovary disease, dyslipidemia, hypertension, cardiovascular disease, sleep apnoea, certain hormone-sensitive cancers, and obesity. Minerals such as magnesium, calcium, potassium, zinc, chromium, and vanadium appear to have associations with insulin resistance or its management. Amino acids, including L-carnitine, taurine, and L-arginine, might also play a role in the reversal of insulin resistance. Other nutrients, including glutathione, coenzyme Q10, and lipoic acid, also appear to have therapeutic potential.[14]

Calcium Regulation

Another vital action of magnesium is as a calcium channel regulator. The passage of calcium through a membrane is the physiological trigger or control for many functions: muscle contraction, nerve impulses, and many cellular secretions such as insulin, neurotransmitters, gastric acid and enzymes. Magnesium is the balancing ion, regulating and controlling the movement and activity of calcium, and is therefore a vital part of all these functions.

SPECIFIC STUDIES ON THE ACTIVITY OF MAGNESIUM AND ASSOCIATED COFACTORS

Stress

Any significant stressor has a dramatic effect on body magnesium homeostasis. Stress generates an increase in stress hormone (catecholamine) release, which initiates movement of cellular magnesium into the plasma with associated renal magnesium loss. Catecholamines also induce lipolysis, resulting in increased free fatty acid levels in blood. These fatty acids are able to bind magnesium, resulting in a further reduction in available magnesium and increased renal loss.

Complicating the magnesium depleting effect of stress, is the exaggerated release of stress hormones during magnesium deficiency. Thus, a vicious cycle can develop where stress increases cellular magnesium loss causing renal magnesium wastage, resulting in an exaggerated stress response.

A French study separated subjects into personality Types A and B. Exposure to stress of the Type-A personalities produced substantial decreases in intracellular magnesium in comparison to the Type-B subjects. The authors proposed that the dramatic magnesium depletion response to elevated stress hormones in the Type-A personalities, is a contributory factor in the higher incidence of stress-related disorders and cardiovascular disease observed in these people.[15]

Anxiety/Neurosis

Magnesium modulates neuronal excitability and decreases membrane fluidity by binding phospholipids and modulating calcium release. These effects are thought to be responsible for the psychological effects of magnesium deficiency, e.g. loss of concentration, disorientation, abstract thinking and memory loss.[16]

Magnesium levels were studied in a population of psychiatric in-patients who were admitted with a range of conditions including schizophrenia, mania with depression and neurosis. All patients showed substantially lower magnesium levels than normal. The deviation of magnesium levels from the mean also correlated significantly with the severity of symptoms.[17]

Supplementation with magnesium would be expected to improve the status of psychiatric patients.

Panic Disorder

Although the pathogenesis of panic disorder is unknown, magnesium therapy offers valuable assistance in panic attacks and neuronal hyperexcitability syndrome. Magnesium supplementation has demonstrated clinically significant responses in panic disorder.

According to diagnostic criteria (DSM-III-R and MKN-10), the symptoms of panic disorder are virtually identical with those of latent tetany. A group of 20 patients treated in a psychiatric out-patient unit for panic disorder had examinations necessary for diagnosing latent tetany, including clinical neurological examination, biochemical investigation with an emphasis on the levels of serum and red blood cell magnesium, and EMG. A concomitant incidence of latent tetany with known etiology - decreased levels of intracellular magnesium - and causal treatment with magnesium salts, was found in 18 patients (90%).[18]

Pre-menstrual Syndrome

Inadequate intake and deficiencies in magnesium are associated with the occurrence and severity of premenstrual syndrome (PMS).[19] The interaction of magnesium with oestrogen is likely to be a significant factor with respect to the pathogenesis of this common clinical problem, and prophylactic magnesium supplementation is expected to provide relief to a large proportion of these women. Magnesium supplementation has shown positive effects in women experiencing the condition.[20,21]

PMS Characterised by Cellular Magnesium Deficiency

When plasma and erythrocyte magnesium were measured in 105 patients with PMS it was found that the erythrocyte (cellular) magnesium concentration was significantly lower than that of a normal population. The plasma magnesium did not show this difference.[22] Supplementation therefore needs to target cellular uptake, which may be achieved with a diglycinate chelation of magnesium.

Magnesium Supplementation Relieves Premenstrual Mood Changes

Reduced magnesium levels have been reported in women affected by PMS. A double-blind, randomised study was used to evaluate the effects of an oral magnesium preparation on premenstrual symptoms in 32 women (24 to 39 years old) with PMS confirmed by the Moos Menstrual Distress Questionnaire. After two months of baseline recording, the subjects were randomly assigned to placebo or magnesium for two cycles. Magnesium supplementation (360 mg) or placebo was administered three times a day, from the 15th day of the menstrual cycle to the onset of menstrual flow. Magnesium treatment significantly affected both the total Menstrual Distress Questionnaire score and the cluster "negative affect." These data indicate that magnesium supplementation could represent an effective treatment of premenstrual symptoms related to mood changes. This study demonstrates the degree of intracellular magnesium deficiency in many of these patients, and the prolonged time necessary to correct cellular reserves with supplemental magnesium.[23]

Magnesium Reduces the Premenstrual Symptoms of Fluid Retention

The effect of magnesium on the severity of premenstrual symptoms was investigated in a randomised, double-blind, placebo-controlled, crossover study. A daily supplement of 200 mg of magnesium (as MgO) or placebo was administered for two menstrual cycles to each volunteer, who kept a daily record of her symptoms, using a 4-point scale in a menstrual diary of 22 items. Symptoms were grouped into six categories: PMS-A (anxiety), PMS-C (craving), PMS-D (depression), PMS-H (hydration), PMS-O (other), and PMS-T (total overall symptoms). Analysis of variance for 38 women showed no effect of magnesium supplementation compared with placebo in any category in the first month of supplementation. However, in the second month there was a greater reduction ($p = 0.009$) of symptoms of PMS-H (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with magnesium supplementation compared with placebo.[24]

The Combination of Magnesium and Vitamin B_6 Shows Best Results

A randomised, double-blind, placebo-controlled, crossover design was used to investigate the single and combined effects of daily dietary supplementation with 50 mg of vitamin B_6 and/or 200 mg magnesium (as MgO) for one cycle for the relief of mild premenstrual symptoms. Forty-four women (average age 32) were randomly assigned to take consecutively all four of the following treatments daily for one menstrual cycle: (1) 200 mg magnesium, (2) 50 mg vitamin B_6, (3) 200 mg magnesium + 50 mg vitamin B_6 and (4) placebo. Throughout the study, each volunteer kept a daily record of symptoms using a 5-point ordinal scale in a menstrual diary of 30 symptoms. Symptoms were grouped into six categories: anxiety, craving, depression, hydration, other, and total. Results showed a significant effect of the combination of 200 mg/day magnesium with 50 mg per day vitamin B_6 on reducing anxiety-related premenstrual symptoms (nervous tension, mood swings, irritability, or anxiety) ($p = 0.040$).[25]

Magnesium Beneficial in Dysmenorrhoea

Fifty patients suffering from primary dysmenorrhoea were treated with magnesium in a double-blind study. After six-months, 21 out of 25 women showed a decline of symptoms. For monitoring treatment results prostaglandin F_2 alpha (PGF_2 alpha) was measured every second month. Magnesium-therapy achieved a reduction of PGF_2 alpha in menstrual blood to 45% of initial values, compared with women receiving placebo whose PGF_2 levels were still 90% of the initial concentration. It is likely that the specific therapeutic effects of magnesium are based not only on inhibition of biosynthesis of PGF_2 alpha, but also on its direct muscle relaxant and vasodilatory actions. The use of magnesium is potentially a side-effect-free natural alternative to PG-synthesis and ovulation inhibitors in the treatment of primary dysmenorrhoea.[26]

Calcium Dysregulation Implicated in PMS

PMS afflicts millions of premenopausal women and has been described as one of the most common disorders in women. Research over the past few years suggests that a variety of nutrients may have an important role in the phase related mood and behavioral disturbances of PMS. There is scientific evidence, at least for a few of these micronutrients, specifically calcium and vitamin D, supporting cyclic fluctuations during the menstrual cycle that may help explain some features of PMS. Ovarian hormones influence calcium, magnesium and vitamin D metabolism. Estrogen regulates calcium metabolism, intestinal calcium absorption and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. Alterations in calcium homeostasis (hypocalcemia and hypercalcemia) have long been associated with many affective disturbances. PMS shares many features of depression, anxiety and the dysphoric states. The similarity between the symptoms of PMS and hypocalcaemia is remarkable. Clinical trials in women with PMS have found that calcium supplementation effectively alleviates the majority of mood and somatic symptoms. Evidence to date indicates that women with luteal phase symptomatology have an underlying calcium dysregulation with a secondary hyperparathyroidism and vitamin D deficiency. This strongly suggests that PMS represents the clinical manifestation of a calcium deficiency state that is unmasked following the rise of ovarian steroid hormone concentrations during the menstrual cycle.[27]

Infertility

Magnesium deficit is associated with a wide range of complications of female and male reproductive systems. Deficiency increases infertility, and the risk of miscarriage and pre-term birth[28,29,30] and low birthweight babies.[31,32,33]

The essential requirement of magnesium for sex hormone production and function underlies the importance of magnesium in infertility. It is known that oestrogen receptor binding is a magnesium-dependent process[34] and magnesium modulates FSH binding to receptors on the ovary.[35] It is also known that magnesium is important in governing the rate limiting steps in DNA synthesis and mitosis.[36]

Further, magnesium deficiency is associated with increased smooth muscle cell tone, which may reduce the patency of an otherwise normal fallopian tube.

In a study of the effects of magnesium supplementation on infertile women, all the women in the study demonstrated low red blood cell (RBC) magnesium levels, although not all subjects returned to normal even when given 600mg per day of magnesium for four months. Administration of selenium assisted the return of normal RBC magnesium levels, and all women subsequently fell pregnant within eight months of magnesium repletion.[37]

Approximately half of all infertility cases are thought to be wholly, or in part, due to suboptimal male fertility. Magnesium is an essential factor in many of the processes of sperm production and function.

Pregnancy

Magnesium Supplementation in Pregnancy is Essential

Pregnancy induces a significant (15%) decrease of magnesium levels in the serum and myometrium. A 25% increase of magnesium excretion in urine may be the most important reason. Magnesium supplementation during pregnancy seems necessary because it improves maternal health and foetal outcome. Magnesium supplementation reduces the incidence of pre-term labour and vaginal haemorrhage. Premature delivery is significantly reduced from 8.2 to 2.8%. Intravenous magnesium application in pharmacological doses is still the therapeutic basis in pre-eclampsia and eclampsia. In gynaecology, magnesium relieves premenstrual mood changes and alleviates dysmenorrhoea.[38]

Magnesium Reduces Pregnancy Complications

The multiplicity of actions of magnesium is clearly demonstrable in the complications of pregnancy. A double-blind study of magnesium supplementation during pregnancy found a significant reduction in complications over controls.[39] Another study, of over 4,000 women given magnesium during prenatal care, showed a significant decrease in intrauterine growth retardation, premature labour, premature rupture of membranes and hypertensive disorders.[40]

Leg Cramps

Leg cramps are common in pregnancy. Magnesium, because of its modulating effect on muscle cell reactivity, has demonstrated positive ameliorative effects. In a double-blind randomised placebo controlled trial to investigate leg cramps in pregnancy, it was found that otherwise healthy pregnant patients had a negative magnesium balance, which the researchers noted as typical. Oral magnesium supplementation effectively reduced leg cramps in comparison to controls, although the magnesium levels of the patients remained suboptimal after three weeks.[41]

Eclampsia and Pre-Eclampsia

Eclampsia remains one of the leading causes of maternal and perinatal mortality in many parts of the world. Management of eclampsia aims to stop the convulsions and prevent recurrence, control the blood pressure and correct fluid and electrolyte imbalance. Magnesium is a regulatory mineral in all of these processes, and the results of clinical trials demonstrate the potential of supplementation to avert the crisis.[42]

Several studies indicate a low magnesium intake or tissue store to be associated with a greater risk of developing pre-eclampsia.[43] Favourable results have been reported in 80% of 3,000 women given 200 mg per day magnesium for prophylaxis of pre-eclampsia while they were pregnant. The supplementation resulted in a marked reduction in pre-eclamptic episodes in patients taking prophylactic magnesium.[44]

Pre-Term Birth

The uterine antispasmodic property of magnesium and the prevalence of its deficiency underlies the importance of supplementation during pregnancy, especially in those women at risk of early delivery.[45] Magnesium is currently being used successfully either with tocolytic therapy, or alone, to prevent premature uterine contractions and pre-term births.[46] A study comparing the amount of fenoterol (a uterine antispasmodic) required either alone or in combination with magnesium in pre-term mothers, found that the dosage could be reduced by 50%.[47]

In a double-blind trial of 255 expectant mothers randomly selected to receive 300 mg per day prophylactic magnesium from diagnosis of pregnancy to delivery, pre-term delivery rate was significantly lower in the supplemental versus the control group.[48]

Osteoporosis

Bone tissue is acutely dependent on magnesium for normal metabolic growth and development. Under magnesium deficiency all phases of bone metabolism, including osteoblast activity, bone formation and fragility, as well as bone response to parathyroid hormone and vitamin D have been altered, and the risk of osteoporosis and/or osteomalacia is high.[49]

Research suggests that magnesium is at least as important as calcium in osteoporosis, because calcium absorption and utilisation require magnesium.[50,51,52,53,54,55,56,57]

In animal models, magnesium deficiency clearly results in osteoporosis,[58] whereas calcium deficiency generates osteomalacia.[59]

Several studies have also shown that a high magnesium/calcium ratio in the diet of normal women is associated with a greater mean bone density.[60,61,62] The only studies to show a positive effect of calcium alone on post-menopausal bone density were of women consuming less than 400 mg of calcium in their daily diet.[63]

Cardiovascular Disease

- **HYPERTENSION**

Clinical Hypotensive Effects of Magnesium Therapy

A large range of processes are affected by magnesium with respect to blood pressure regulation, so it is not surprising that magnesium supplementation has demonstrated substantial reductions in blood pressure in subjects with mild to severe hypertension.[64,65,66] Furthermore, low magnesium levels are associated with increased risk of hypertension.[67]

A double-blind placebo controlled crossover study found a dose dependent effect of magnesium on hypertension. The nine week study trialled 15 mmol magnesium per day for three weeks, followed by 30 mmol mg per day for another three weeks, and 40 mmol magnesium per day for the final three weeks. A significant decrease in the mean systolic blood pressure was recorded, from 154 mm Hg to 146 mm Hg and the mean diastolic blood pressure decreased from 110.2 mm Hg to 92 mm Hg.[68]

In a Dutch study, 91 elderly women with mild to moderate hypertension, and who were not on medication, were trialled with 20 mmol magnesium per day or placebo for six months. The magnesium was well tolerated and resulted in a 2.7 mm Hg mean reduction in systolic, and a 3.4 mm Hg drop in diastolic blood pressure over the placebo.[69]

A Japanese study found that magnesium lowered blood pressure in patients with mild to moderate essential hypertension. Subjects were given 600 mg elemental magnesium daily for two weeks. Supplementation elicited a significant fall in mean diastolic blood pressure from a baseline of 104.3mm Hg to 99.5mm Hg.[70]

Effects of Taurine and Glutamine

Taurine's role as a neurotransmitter may be the mechanism whereby it can influence blood pressure. A similar process may exist for glutamine - as a precursor to GABA. Both these were analysed in a trial with hypertensive rats. Taurine and GABA both resulted in blood pressure reduction in hypertensive rats.[71]

Effect of Antihypertensive Medication on Magnesium

Interestingly, antihypertensive therapy and diuretics often contribute to the common magnesium deficiency seen in hypertensive patients. Supplementation with oral magnesium appears to both reduce the high blood pressure and, subsequently, the requirement for these antihypertensive/ magnesium depleting treatments.[72]

• ARRYTHMIA

Low magnesium status is now well recognised as an electrolyte abnormality that relates to cardiac arrhythmia, ventricular tachyarrhythmia and sudden cardiac death.[73] Some reports have demonstrated significant anti-arrhythmic effects of magnesium which are not associated with low serum levels of magnesium.[74,75]

The effect of magnesium on supraventricular arrhythmias was evaluated and compared to a calcium antagonist (verapamil) in a randomised blind study. The efficacy of magnesium for conversion to sinus rhythm was at least as effective as verapamil, and its action more rapid. No side-effects were noted with magnesium, whereas six patients receiving verapamil had to be withdrawn from the study due to symptomatic side-effects (hypotension in three, cardiac failure in three).[76]

Magnesium and Potassium Regulation

Magnesium appears to be an important ionic regulator at the cellular membrane. In patients with low potassium, normal levels cannot be restored without magnesium repletion and often magnesium supplementation alone is effective in restoring potassium levels.[77,78] The effect of magnesium on potassium and calcium regulation is thought to mediate the anti-arrhythmic ability of magnesium.

• VASOSPASM

Coronary vasospasm appears to be a significant contributor to anginal symptoms and cardiac ischaemia. Considering the effect of magnesium deficiency on smooth muscle irritability, it is likely that magnesium deficiency predisposes to spasms of coronary vessels.

This was demonstrated in a study of 264 patients with mild coronary sclerosis who underwent detailed coronary angiography to determine the effect of magnesium on acute myocardial infarction and angina. Provocative testing for coronary vasospasm using acetylcholine demonstrated a protective effect of magnesium. Magnesium loading testing demonstrated that magnesium deficiency induces abnormal lipid metabolism, which is a promoter of coronary lesions and increases coronary vasospasm. The researchers commented on the possibility that vasospasm may promote coronary lesions by disrupting blood flow characteristics in the vessels.[79]

The authors concluded that the results of this study could be taken as the pathological relationship between coronary artery disease and magnesium.

Magnesium deficiency is an important and poorly recognised risk factor for heart disease which requires more clinical attention. A state of magnesium deficiency can be inferred in our society and is a strong contributor to the high mortality associated with cardiovascular pathology.

Type-A Behaviour and Coronary Vasospasm

Epidemiological evidence and animal studies have implicated dietary magnesium deficiency in ischaemic heart disease. It has been found that blood vessels, deficient with respect to extracellular magnesium, undergo sustained increases in basal tone, and exhibit increased constriction to circulating vasoactive agents, brought about by an augmented influx of ionised calcium. Other studies have shown that the coronary vasculature is especially sensitive to magnesium deficiency. Type-A behavior is by definition a personality characterised to be in a state of more or less constant self-induced stress. Plasma free fatty acid levels are known to be increased by all types of stress. This in turn has been recently demonstrated to reduce free ionised levels of magnesium in the blood. It is proposed that Type-A behavior is compatible with an intermittent virtual magnesium deficiency which could lead to coronary vasospasm, ischemia and eventually heart tissue necrosis.[80]

• ANGINA

The pain of angina is due to ischaemia in the cardiac muscle. The blood supply to the heart muscle through the coronary vessels is obviously inadequate and this may be due to atheroma, thrombosis or vasospasm, all of which are affected by magnesium status.

Clinical Trial of Magnesium Diglycinate and Angina

Research on magnesium diglycinate has demonstrated remarkable effects on angina pain. Sanvad, et al, studied patients with angina pectoralis to determine the effect of magnesium diglycinate on myocardial performance and requirement or nitroglycerine. Patients receiving 50 mg/day magnesium experienced a 25% increase in myocardial performance. Controls required an average of 29% more nitroglycerin to fend off anginal attacks through the trial.[81]

• MYOCARDIAL INFARCTION

Cardiac ischaemia and reperfusion are responsible for myocardial tissue damage during, and immediately after myocardial infarction (MI).

Magnesium Protects Against MI

Several trials have demonstrated a protective effect of magnesium against heart muscle injury due to myocardial infarct and they also show a reduction in subsequent mortality in those patients receiving magnesium.[82,83,84,85] Levels of magnesium and zinc are notably reduced in patients experiencing MI.[86]

The Leicester Intravenous Magnesium Trial ("LIMIT-2"), a double-blind, placebo controlled study, was undertaken by randomising 2,316 patients with suspect acute myocardial infarction. The 28 day mortality from all causes showed a 24 % reduction in the magnesium group. There was also a 25% reduction in the incidence of heart failure, a benefit conferred equally on thrombolysed and non-thrombolysed patients. The effects of magnesium sulphate therapy on early mortality is reported to be comparable to, but independent of, thrombolytic therapy.[87]

The effects on the myocardium of myocardial infarct patients receiving magnesium are multiple.[88,89] They include a reduction in afterload by decreasing vascular resistance, improving coronary blood flow, protection of mitochondria against calcium influx, and inhibition of postinfarctional dysrhythmias.

Infarct Size Reduced by Magnesium

The size of infarction also appears to be strongly influenced by magnesium supplementation. Two recent studies performed on porcine models demonstrated a significant reduction in infarct size.[90,91]

Prophylactic administration of magnesium in high risk individuals is expected to provide significant protection against myocardial infarction.

• MITRAL VALVE PROLAPSE

Several researchers have documented an association between magnesium deficiency and the incidence of mitral valve prolapse (MVP).[92,93]

In a prospective study of 94 patients with MVP, 59 (62.7%) were found to have low erythrocyte magnesium while only 35 (37.3%) had normal levels. The deficient patients were also noted to experience more muscle cramps and migraines. Forty-one of the 59 hypomagnesaemic patients were assigned to a randomised double-blind study of magnesium supplementation. Subjects were given between 250 and 1200 mg oral magnesium oxide or 128 to 256 mg magnesium chloride for up to four months. Four patients stopped because of diarrhoea. In the remaining subjects magnesium treatment resulted in marked symptomatic improvement.[94]

• BLOOD LIPIDS

Lowered magnesium levels have been associated with an increased risk of Cardiovascular Disease. The raised lipid profile in magnesium deficient subjects appears to be contributory to this process.

Clinical Trials on Magnesium and Blood Lipids

Triglyceride levels were examined in a controlled study of sixty-nine patients with hyperlipidaemia. Thirty-seven received 500 mg oral magnesium daily. A significant reduction in triglycerides was seen in the supplemented patients. Mean triglycerides fell from 198.17 to 163.2. Erythrocyte magnesium concentration increased in these patients although without significant changes in plasma concentration.[95]

In a study on the effects of various levels of magnesium intake on serum lipids and aortic cholesterol deposition in mice, the levels of both serum total cholesterol and lipid peroxides decreased relative to increases in the dose of magnesium. It was also found that adequate magnesium intake prevented cholesterol deposition in the arteries of the mice fed an atherogenic diet.[96]

The atherogenic potential of low density lipoproteins (LDL) and very low density lipoproteins (VLDL) appears to be dependent on oxidation of these particles. Several studies have shown considerable peroxidation of these lipoproteins under magnesium deficient conditions. Two recent studies demonstrate that magnesium deficiency in rats is significantly associated with increased peroxidation of triglycerides,[97] VLDL and high density lipoproteins (HDL).[98]

Magnesium deficiency further increases the atherogenic potential by increasing the uptake by the arterial endothelium of oxidised cholesterol and LDL. *In vitro* studies suggest that the uptake of LDL by the vascular wall and its subsequent oxidation is markedly enhanced in magnesium deficient states.[99] Rabbits fed a low magnesium diet were seen to accumulate oxidised cholesterol in their artery walls much more readily than those fed a magnesium sufficient diet.[100]

Benefits to Blood Pressure and the Blood Lipid Profile

In a double-blind, placebo-controlled study, thirty-three subjects were allocated to undergo either a four week treatment with oral magnesium supplementation ($Mg(OH)_2$; 411 to 548 mg magnesium per day) or a placebo.

- The systolic and diastolic blood pressure values decreased significantly in the magnesium group, but not in the placebo group.
- The urinary aldosterone excretion and packed cell volume increased significantly during the last two weeks of the experimental period compared with the run-in period and first two weeks of supplementation.
- There was a statistically significant positive correlation between the values for urinary noradrenaline excretion and diastolic blood pressure at the end of the supplementation period (both expressed as a percentage of the run-in value).
- Statistically significant increases in lecithin-cholesterol acyltransferase (LCAT), HDL-cholesterol and apolipoprotein AI were also observed after magnesium supplementation.
- A significant positive correlation was observed between the levels of LCAT and urinary magnesium excretion for the experimental period (expressed as a percentage of the run-in value).
- The total cholesterol:HDL-cholesterol ratio decreased significantly during the last two weeks of magnesium supplementation compared with the first two weeks and the run-in periods, but this did not occur in the placebo group.

These results suggest that magnesium supplementation may lower blood pressure through the suppression of the adrenergic activity and possible natriuresis, while also improving the serum lipids through the activation of LCAT in human subjects.[101]

• CORONARY HEART DISEASE/ATHEROSCLEROSIS

The physiological features of coronary artery disease strongly suggest influence of magnesium deficiency, and supplementation has shown significant effects in this serious pathology.

> "Magnesium deficiency alone has been shown to cause cardiac and arterial lesions in every species of animal in which it has been induced. High fat/low magnesium intakes appear to be conjoint pathogenic factors. The arterial lesions of high fat diets in several species are intensified by simultaneous magnesium deficiency and protected against by magnesium repletion."[102]

At the mitochondrial level, magnesium activates various enzymes and preserves both function and structure. The heart has a high mitochondrial density and enzyme activity which makes it particularly vulnerable to magnesium deficiency. Substantial evidence now suggests chronic magnesium deficiency causes functional cardiovascular abnormalities.[103]

Magnesium is an effective calcium channel blocker. Cellular calcium toxicity is known to be contributory to atherogenesis, and calcium channel blocking agents have demonstrated preventive effects in atherosclerosis.[104,105]

Antioxidant Activity

A magnesium deficient state is undeniably linked to exaggerated free radical tissue injury and several mechanisms are known to explain how magnesium deficiency leads to enhanced peroxidation and decreased oxidative defence processes.[106,107,108,109]

The role of magnesium as a cofactor in glutathione production[110] and the presence of high levels of copper and iron in magnesium deficient states support the role of magnesium to augment antioxidant defences against atherosclerosis.

• THROMBOSIS

An *in vivo* study of several potential antithrombotic agents, including heparin and aspirin, found poor efficacy, while magnesium demonstrated surprising capability without complications.[111] The researchers reported profound modification of thrombus formation with parenteral magnesium administration. Excessive bleeding was not associated with the thrombus preventing qualities of magnesium.

The effect of magnesium on blood homeostasis contributes toward our understanding of the capacity of magnesium to prevent myocardial infarct.[88,89] Platelet aggregation is a calcium dependent process, whereas magnesium is required for deaggregation and maintenance of platelet shape.[112] Further, release of serotonin by aggregated platelets is calcium dependent and inhibited by magnesium.[113] Thus, the net effect of a raised Calcium:Magnesium ratio is an elevated risk of thrombosis. The concern is that women may be consuming high levels of calcium without ensuring that the magnesium deficiencies, which are so prevalent, are addressed.

Muscular Aches, Pains, Cramps, Spasms and Stiffness

Magnesium deficiency is more common than is believed and should always be included in the differential diagnosis of patients who present with persistent or severe muscle pain.[114]

Magnesium Controls Tetanic Muscle Spasms

A prospective observational study was conducted to examine the efficacy and safety of magnesium sulphate for control of spasms and autonomic dysfunction in 40 patients with tetanus. Magnesium was infused intravenously, aiming to control spasms despite suppression of patellar reflex or respiratory insufficiency. Spasms were controlled in 38 of the 40 patients within a serum magnesium range of 2 to 4 mmol/L with only two patients needing additional neuromuscular blocking drugs. Seventeen of 24 patients (< 60 years) and six of 16 patients (> or = 60 years) did not require ventilatory support. Thirty-six patients were conscious and co-operative throughout their management. Sympathetic over-activity was controlled without supplementary sedation. Overall mortality was 12%; all five deaths were in patients greater than or equal to 60 years and no deaths were due to autonomic dysfunction. Magnesium is recommended as a possible first line therapy in the routine management of tetanus.[115]

Improvement of Spasticity in MS

The effects of magnesium glycerophosphate oral therapy on spasticity was studied in a 35-year-old woman with severe spastic paraplegia resulting from multiple sclerosis (MS). Significant improvement in the spasticity was seen after only one week from the onset of the treatment on the modified Ashworth scale, an improvement in the range of motion and in the measures of angles at resting position in lower limbs. No side-effects were reported and there was no weakness in the arms during the treatment.[116]

Athletics

Physical exertion and athletic performance are dependent on magnesium for ATP phosphorylation. Studies demonstrating a broad deficiency of magnesium in society point to athletes as being at high risk of developing magnesium deficiency because of their higher metabolic demands and increased losses through sweating.[117,118]

Hypomagnesaemia is associated with decreased physical performance and increased incidence of muscle cramps, which improve with magnesium supplementation.[119] A study of swimmers taking 65 mg elemental magnesium found an 86% reduction in muscle cramps. The reductions occurred after only three days of supplementation.[120]

Improves Athletic Performance

The prevalence of magnesium deficiency and the high risk of depletion for athletes indicates that supplementation may benefit these individuals. Several researchers have discovered improved performance with magnesium supplementation.[121] Female endurance athletes taking magnesium supplementation (15 mmol per day) found they could run at maximal intensity for longer, that sub-maximal oxygen uptake decreased by 10%, whereas maximal oxygen uptake (VO2) increased with a parallel change in work load. They also found sub-maximal respiratory minute volume and carbon dioxide formation decreased significantly, while maximal parameters increased. This data suggests an improvement in oxygen utilisation during magnesium supplementation, in female endurance athletes not exhibiting magnesium deficiency signs. The red blood cell magnesium content of the women taking magnesium increased significantly by 8%.[122]

Reduces the Effects of Exercise-Induced Physiological Stress in Triathletes

In a double-blind randomised study, 23 triathletes competing in an event consisting of a 500 m swim, a 20 km bicycle race, and a 5 km run were studied after four weeks of supplementation with placebo or 17 mmol per day magnesium orotate. The tests were carried out without a break. Blood was collected before and after the test, and between the different events for assaying energy stress and membrane metabolism.

Swimming, cycling, and running times decreased in the magnesium group compared with the controls. Serum glucose concentration increased 87% during the test in the control group and 118% in the magnesium group, while serum insulin increased 39% in the controls and decreased 65% in the magnesium group. Venous oxygen partial pressure increased 126% during the test in the controls and increased 208% in the magnesium group. Venous carbon dioxide partial pressure after the bicycle race decreased 66% (significantly) in the magnesium group compared with 74% in the controls. Blood proton concentration decreased to 90% in the magnesium group (significantly) compared with 98% in the controls. Blood leukocyte count increased from 5.92/nL to 11.0/nL in the controls and from 5.81/nL to 9.10/nL in the magnesium group, a significant difference indicating magnesium reduces the inflammatory impact of exercise. This is also shown by the serum cortisol being lower in the magnesium group before and after the test compared with the controls. CK catalytic concentration after the test was elevated 140% in the controls compared with 122% magnesium group.

The stress-induced modifications of energy and hormone metabolism described in this study indicate altered glucose utilisation after magnesium supplementation and a reduced stress response without affecting competitive potential.[123]

Improves Strength Gains from Weight Training

Magnesium plays an important role in protein synthesis, and this function may be most sensitive to magnesium insufficiency. DNA transcription, RNA aggregation and protein synthesis are all dependent on optimal magnesium concentration. During strength training, a suboptimal magnesium level would be likely to hinder gains from training.

A double-blind, placebo-controlled, seven week strength training program in 26 untrained subjects receiving magnesium found those being supplemented derived greater benefit from the training over controls. Dietary records of the patients were analysed and these athletes were supplemented with magnesium to bring them up to 8 mg/kg per day. This resulted in significant difference in strength gains in these athletes.[124]

Magnesium, zinc, and chromium are mineral elements required in modest amounts to maintain health and optimal physiologic function. For physically active persons, adequate amounts of these micronutrients are needed in the diet to ensure the capacity for increased energy expenditure and work performance. Most physically active individuals consume diets that provide amounts of magnesium and zinc sufficient to meet population standards. Women tend to consume less of these minerals than is recommended, in part because they eat less food than men. Inadequate intakes of magnesium and zinc have been reported for participants in activities requiring restriction of body weight. Acute, intense activity results in short-term increases in both urine and sweat losses of minerals that apparently diminish during recovery in the days after exercise. Supplemental magnesium and zinc apparently improve strength and muscle metabolism.[125]

Headaches

• TENSION HEADACHES

Although many theories and hypotheses have been offered for the etiology of tension headaches (TH), no one previous hypothesis seems to adequately explain them. In reviewing current and old hypotheses of TH, a new hypothesis becomes apparent, which is consistent with what is known about TH – it appears that magnesium metabolism may be pivotal in both the etiology and treatment of TH.

Since approximately 70% of patients who have a TH exhibit muscular tightness and tenderness, it is distinctly possible that problems in magnesium metabolism and dietary intake are the links to concomitant muscle tension and TH. The release of pain mediators, muscle cramps, muscle strains (and damage) and muscle tension are all associated with a magnesium-deficient state. It seems clear from the available data that TH's are more associated with muscle tension or scalp tension than any other headache type. From the data available, magnesium supplementation appears to be of great benefit in many of these situations.[126]

• MIGRAINES

The higher incidence of migraine amongst those prone to cellular magnesium depletion[127] and the influence of magnesium on prostanoids and thrombogenesis support the premise that magnesium deficiency is involved in the pathogenesis of migraine.[128,129]

Additional factors suggesting a role of magnesium deficiency in migraines include the role of magnesium in serotonin release and in vascular reactivity to serotonin. Migraine sufferers are known to release more serotonin from platelets than non-sufferers, which may contribute to vasospasm.[130] Calcium channel blockers have been effective in reducing migraines, and as magnesium is a natural calcium channel blocker, this may be a further mechanism to explain the clinical effectiveness of magnesium against migraines.[131]

Magnesium Reduces Frequency, Duration and Intensity of Migraines

In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18 to 65 years with migraine defined according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of four weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9 to 12 the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhoea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis.[132]

In vitro and *in vivo* studies indicate that magnesium deficiency could play a contributing role in the pathogenesis of migraine in up to 50% of patients. Chelated magnesium diglycinate appears to be one of the better absorbed preparations. Despite the absence of definitive large scale studies, we recommend magnesium supplementation (chelated magnesium diglycinate 600 mg per day) in patients who experience migraine. This recommendation is based on the excellent safety profile and low cost of the supplementation, and the large amount of experimental and clinical data that support the use of this therapy.[133]

Menstrual migraine is a problem for many women. The association between magnesium and both migraines and premenstrual syndrome suggests supplementation will benefit those sufferers. A double-blind placebo controlled study using 360 mg per day magnesium found a reduction in the number of migraines, as well as their duration and intensity. The beneficial effects of magnesium in this study were seen in all of the patients taking magnesium. The authors suggest low magnesium levels may lower the migraine threshold. A significant rise in magnesium status indices was found in those patients taking supplementation.[134]

Fibromyalgia

Fibromyalgia is a common clinical feature of chronic fatigue syndrome (CFS) and is associated with the presence of multiple tender points and depression. Chronic tissue hypoxia seems to be a contributing biochemical process in this condition and magnesium deficiency is a likely contributor.

Patients with fibromyalgia often suffer from myalgias, fatigue, sleep disturbances and anxiety.[135] These same symptoms are also found in patients with low magnesium levels.[136]

Clinical Trials of Magnesium in Fibromyalgia
Clinical studies have indeed found sufferers of fibromyalgia to be deficient in magnesium and to benefit from supplementation.[137]

Another more recent study on the treatment of subjects diagnosed with fibromyalgia show marked improvement with supplementation.[138] Patients took 1200 to 2400 mg of malic acid and 300 to 600 mg magnesium daily for eight weeks on the combination. Subjective improvement in pain score on ingestion of a magnesium/malic acid combination resulted within 48 hours. Their tender point index scores decreased from an average 19.6 to 8 and 6.5 after four and eight weeks respectively. On cessation of supplementation the fibromyalgia patients noted a subsequent subjective worsening of their condition.

A similar study using both malic acid and magnesium has confirmed the previous results.[139] The randomised placebo-controlled study found no clear treatment advantage when low dosage (1200 mg malic acid and 300 mg magnesium) was used for four weeks as a pilot trial. Doubling the dose for six months in the main trail showed significant reductions in primary pain and tenderness measures in the fibromyalgia patients. The researchers commented that the treatment appeared to be safe, although required to be taken for at least two months before positive effects began.

Chronic Fatigue Syndrome

Magnesium deficiency signs and symptoms are similar to those expressed by chronic fatigue syndrome (CFS) sufferers and these patients are known to be magnesium deficient.[140]

An examination of red blood cell magnesium in CFS patients found every subject to be lower than controls.[141] These same patients were treated with magnesium sulphate injections every week for six weeks. Those treated with magnesium had improved energy levels, better emotional state and less pain. Minimal changes were noted in the controls. All of those patients receiving magnesium supplementation achieved normal red blood cell magnesium before the end of the study, whereas only one of the magnesium deficient controls was found to have normal levels at trial termination.

In a case of CFS which was unresponsive to NSAIDs, minor tranquillisers and antidepressant drugs, weekly intravenous magnesium for six weeks resulted in reduced fatigue, and after seven months in hospital the patient was able to return home.[142]

It has been suggested that it is magnesium deficiencies in CFS patients that are responsible for the muscle pain they experience.[143] Muscle relaxation is a magnesium dependent process and in magnesium deficient states, myofibrillar relaxation may be impaired. The contraction of an antagonist against a partly contracted protagonist will result in myofibrillar damage, muscle pain and tenderness with easy fatigability of the muscles.

Folic acid is required for the maturation of many cell types, including most immune cells. Research has found chronic fatigue patients to be deficient in folic acid, suggesting supplementation may be of benefit to these patients.[144]

Alcohol Consumption

Magnesium Replacement Important for Alcohol Consumers

Forty-nine chronic alcoholics, moderate to heavy drinkers for at least 10 years, were randomised to receive oral magnesium or placebo treatment for six weeks according to a double-blind protocol. Effects on metabolic variables and muscle strength were analysed. Significant reduction of aspartate-aminotransferase (AST), alanine-aminotransferase (ALT) and gamma-glutamyl-transpeptidase (GGT) were seen after magnesium, whereas no change was observed with placebo. Bilirubin decreased in both groups. Serum sodium, calcium and phosphorous increased significantly during magnesium therapy compared with no statistically significant change in the placebo group. Serum potassium and magnesium increased slightly after magnesium supplementation and decreased in the placebo group, resulting in a significant difference between the two groups at the end of the study. Muscle strength increased significantly during magnesium treatment, contrasting to no change with placebo. Blood pressure, heart rate, haematological variables, serum lipids (cholesterol, HDL, TG), glucose tolerance, and creatinine were unchanged in the two groups after treatment. Alcohol consumption was similar before and during the trial and does not explain the differences between the two groups. The results show that short-term oral magnesium therapy may improve liver cell function, electrolyte status, and muscle strength in chronic alcoholics.[145]

Metal Toxicity

Protects Against DNA Damage and Carcinogenesis from Toxic Metals

Metals are emerging as very important carcinogens, with research increasingly demonstrating their toxicity and an increase in their distribution by industry.

The inhibitory effects of magnesium on tumour growth in animal systems has been known for several years. Part of this inhibitory activity is thought to be due to a chemopreventive effect against toxic metal carcinogenesis. Toxic (or “heavy”) metals have several unique characteristics. They have remarkable target site specificity, and, unlike organic carcinogens, they do not require metabolic activation.

Simultaneous administration of magnesium has been shown to eliminate the DNA methylation and carcinogenic potential of nickel.[146,147]

APPENDIX

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Review

Magnesium
An update on physiological, clinical and analytical aspects

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Abstract

There is an increased interest in the role of magnesium ions in clinical medicine, nutrition and physiology. The characteristics of the binding of magnesium and calcium ions to various components, macromolecules and biological membranes are described. Magnesium affects many cellular functions, including transport of potassium and calcium ions, and modulates signal transduction, energy metabolism and cell proliferation. The mechanism of cellular uptake and efflux of magnesium, its intracellular transport, intestinal absorption, renal excretion and the effect of hormones on these are reviewed. Magnesium deficiency is not uncommon among the general population: its intake has decreased over the years especially in the western world. The magnesium supplementation or intravenous infusion may be beneficial in various diseased states. Of special interest is the magnesium status in alcoholism, eclampsia, hypertension, atherosclerosis, cardiac diseases, diabetes, and asthma. The development of instrumentation for the assay of ionized magnesium is reviewed, as are the analytical procedures for total magnesium in blood and free magnesium in the cytosol. The improved procedures for the assay of different magnesium states are useful in understanding the role of magnesium in health and disease.

Abbreviations: Ca, calcium, calcium ion; Mg, magnesium, magnesium ion; P_i, inorganic phosphate; PTH, parathyroid hormone

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Magnesium and cardiac arrhythmias

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1. Possible arrythmogenic mechanism

There is a long history of the use of magnesium in the treatment of arrhythmias. Numerous studies have been carried out in an attempt to define the role of both intracellular and extracellular magnesium in the physiopathology and treatment of arrhythmias. Hypomagnesaemia has been suggested as a cause for arrhythmias of both sopraventricular and ventricular origin, but any relationship between hypomagnesaemia and the development of arrhythmias is extremely complex since patients with normal plasma levels of magnesium may in fact have a reduced body content of the ion which, as we know is located primarily inside the cells. Moreover, the close yet never fully explained relationship between the metabolism of magnesium and potassium, and the importance of the latter in the origin of arrhythmias has further complicated the development of our knowledge in this field.

Whereas the effects of magnesium on *surface* ECG and cardiac electrophysiology have been studied in depth in animals (Surawicz et al., 1961; Watanabe and Dreifus, 1972; Nishimura et al., 1985), studies on man are rather limited. Kulick et al. (1988) studied healthy subjects who were given magnesium intravenously and evaluated the main cardiac electrophysiological parameters together with the measurement of both plasma concentration and intracellular magnesium content in monocytes. The measurement of plasma and intracellular levels of magnesium is a particularly important aspect of this study since, despite the numerous reports of a positive or nul effect of magnesium on various forms of arrhythmia, intracellular levels of magnesium before and after treatment are often not mentioned. As a result, it is not clear whether patients who benefited from treatment with magnesium were characterized by a reduced body content of the ion or not. Kulick et al. (1988) found that treatment with magnesium produces a significant lengthening of the PR interval and this increase appears to be located at the level of the AV node. Magnesium also induces a

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Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis

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Abstract

Because (i) endothelial cells are important players in cardiovascular diseases and (ii) Mg deficiency promotes atherosclerosis, thrombosis and hypertension, we evaluated whether low concentrations of Mg could directly affect endothelial behavior. We found that low Mg concentrations reversibly inhibit endothelial proliferation, and this event correlates with a marked down-regulation of the levels of CDC25B. The inhibition of endothelial proliferation is due to an up-regulation of interleukin-1 (IL-1), since an antisense oligonucleotide against IL-1 could prevent the growth inhibition observed in cells exposed to low concentrations of the cation. We also report the up-regulation of Vascular Cell Adhesion Molecule-1 (VCAM) and Plasminogen Activator Inhibitor (PAI)-1 after Mg deficiency. VCAM is responsible, at least in part, of the increased adhesion of monocytoid U937 cells to the endothelial cells grown in low magnesium. In addition, endothelial migratory response is severely impaired. By cDNA array, we identified several transcripts modulated by exposure to low Mg, some of which—c-src, ezrin, CD9, cytohesin and zyxin—contribute to endothelial adhesion to substrates and migration.

In conclusion, our results demonstrate a direct role of low magnesium in promoting endothelial dysfunction by generating a pro-inflammatory, pro-thrombotic and pro-atherogenic environment that could play a role in the pathogenesis cardiovascular disease.

Keywords: Endothelial cell; Magnesium; Atherosclerosis; Gene expression; Inflammation

1. Introduction

Endothelial cells maintain the functional integrity of the vascular wall. Beyond their role in controlling permeability, they are involved in the maintenance of a non-thrombogenic blood–tissue interface, in the modulation of blood flow and vascular resistance, in the regulation of immune and inflammatory reactions [1]. It is well accepted that endothelial dysfunction plays an important pathogenic role in several diseases, among which atherosclerosis [2], hypertension [3], diabetes [1] and thrombosis [1]. In particular, a huge amount of experimental evidence supports the paradigm of endothelial dysfunction as the common link between risk factors and atherosclerotic burden [2]. Indeed, endothelial dysfunction actively participates in the process of lesion formation by promoting leukocyte adherence, increasing chemokine secretion and cell permeability to lipids, enhancing LDL oxidation, stimulating vascular smooth muscle cell proliferation and migration and platelet activation [2].

In addition, endothelial cells are protagonists in angiogenesis, i.e. the branching and sprouting of capillaries from preexisting blood vessels, which is a tightly controlled event crucial in development, in reproduction and wound healing [4].

Because of their strategical location at the interface between blood and vessels, endothelial cells are readily exposed to various signals (cytokines, metabolites, ions, free radicals, shear stress), some of which may promote maladaptative functional changes. Among others, low magnesium (Mg) status has been reported to be important in the pathogenesis of cardiovascular diseases [5]. Interestingly, low magnesium status, which is frequent in western countries, is a common denominator in hypertension [6], coronary artery disease [7], thrombosis [8] and diabetes [9]. During experimental Mg deficiency hyperlipemia, inflammation and early atherosclerotic lesions have been observed

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Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X

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Abstract

Magnesium (Mg) is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular Mg concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In vitro and in vivo studies have demonstrated that insulin may modulate the shift of Mg from extracellular to intracellular space. Intracellular Mg concentration has also been shown to be effective in modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation–contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli. A poor intracellular Mg concentration, as found in noninsulin-dependent diabetes mellitus (NIDDM) and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance in noninsulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily Mg administration, restoring a more appropriate intracellular Mg concentration, contributes to improve insulin-mediated glucose uptake. The benefits deriving- from daily Mg supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily Mg intake are predictive of a lower incidence of NIDDM. In conclusion, a growing body of studies suggest that intracellular Mg may play a key role in modulating insulin-mediated glucose uptake and vascular tone. We further suggest that a reduced intracellular Mg concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension.

Keywords: Magnesium; Glucose intolerance; Diabetes; Hypertension; Syndrome X; Calcium

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Magnesium and Exercise

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ABSTRACT: Magnesium is an essential element that regulates membrane stability and neuromuscular, cardiovascular, immune, and hormonal functions and is a critical cofactor in many metabolic reactions. The Dietary Reference Intake for magnesium for adults is 310 to 420 mg/day. However, the intake of magnesium in humans is often suboptimal. Magnesium deficiency may lead to changes in gastrointestinal, cardiovascular, and neuromuscular function. Physical exercise may deplete magnesium, which, together with a marginal dietary magnesium intake, may impair energy metabolism efficiency and the capacity for physical work. Magnesium assessment has been a challenge because of the absence of an accurate and convenient assessment method. Recently, magnesium has been touted as an agent for increasing athletic performance. This article reviews the various studies that have been conducted to investigate the relationship of magnesium and exercise.

I. INTRODUCTION

Magnesium is an essential mineral and a cofactor for over 325 enzymatic reactions involved in cellular energy production and storage, protein synthesis, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, cell growth and reproduction, adenylate cyclase synthesis, maintenance of cellular electrolyte composition, and stabilization of mitochondrial membranes.[1] Magnesium plays a central role in the control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vasomotor tone, and blood pressure.[1] Therefore, magnesium deficiency may lead to changes in gastrointestinal, cardiovascular, and neuromuscular function.[1] The magnesium intake of the general population may be suboptimal and, consequently, athletes may also be consuming inadequate amounts of magnesium.[2,3] Exercise is a potent stressor that appears to lead to magnesium depletion through alterations in blood magnesium levels as well as increased excretion through sweat and urine, and may compound a state of deficiency when magnesium intake is inadequate. Research has shown that magnesium deficiency may reduce physical performance and magnesium status may have an effect on exercise capacity. During the last decade there has been considerable interest in whether mineral supplementation can result in an improvement in athletic performance. Therefore, the aim of this review is to assess whether physical activity is a factor leading to a magnesium deficit, to determine the consequences of magnesium deficit in the pathophysiology of sport, and discuss the effects of magnesium supplementation on physical performance.[2,3] Prior to the discussion of magnesium and exercise, a comprehensive review of the chemistry, metabolism, and assessment of magnesium is given.

II. CHEMISTRY

Magnesium (Mg^{+2}) is a divalent metal ion. It is the fourth most abundant cation in the body after calcium (Ca^{+2}), potassium (K^{+}), and sodium (Na^{+}) and is the second most abundant intracellular cation after potassium (K^{+}).[4] Magnesium is usually bound to ligands, strictly octahedral in the

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NOTES

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