

Role of Magnesium in Health and Disease

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Abstract

The list of conditions related to magnesium deficiency is quite high. The National Institute of Health information says that magnesium is a wonder drug but its use in clinical medicine is very scarce. Magnesium deficiency has been implicated in a wide range of clinical conditions such as insomnia, cramps, diarrhea, erectile dysfunction, headache, migraine, low blood pressure, loss of appetite, nausea, vomiting, weakness, numbness, tingling, seizures, personality change, abnormal heart rhythms, coronary spasms, cardiovascular disease, type 2 diabetes mellitus, depression, immune dysfunction, thyroid function alterations to name a few. Although supplementation is said to restore normalcy in a majority of cases, very few studies have been done in this direction. The role of magnesium in alleviating cancers of all types has been extensively studied, but treatment using magnesium is very limited. This review article aims to bring out research findings during the last 3 decades on the role of magnesium in health and disease and this will enable researchers to understand in detail and give awareness about further works to be carried out in this field, with an ultimate aim of using magnesium as a drug to cure a host of diseases.

Keywords: Magnesium, CVD, DM, lipid, MCI, renal failure, liver disease, reproductive, depression, cancer, thyroid, immune, alcohol.

INTRODUCTION

There is power and force in magnesium that cannot be equaled anywhere in the world of medicine. There is no substitute for magnesium in human physiology; nothing comes close to it in terms of its effect on overall physiology. Without sufficient magnesium, the body accumulates toxins and acid residues, degenerates rapidly and ages prematurely (1). It goes against a gale wind of medical science to ignore magnesium chloride used transdermally in the treatment of any acute or chronic disorder, especially cancer. Over 300 different enzyme systems rely upon magnesium to facilitate their catalytic action, including ATP metabolism, creatine kinase activation, adenylate cyclase, glutathione synthetase, Na-K-ATPase (2) and DNA & RNA transcription and repair (1).

Magnesium deficiency has been implicated in a host of clinical disorders but the medical establishment just cannot get through its thick skull that it is an important medicine. In this article, the host of organ functions and every known type of disease that are looked to the metal magnesium are being highlighted. It makes perfect medical sense to saturate the body with magnesium through transdermal means. Magnesium is the mineral of rejuvenation and prevents the calcification of our organs and tissues that is characteristic of the old age related degeneration of our body.

MAGNESIUM AND CARBOHYDRATE METABOLISM

The interrelationships between magnesium and carbohydrate

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metabolism have regained considerable interest over the last few years. Insulin secretion requires magnesium: magnesium deficiency results in impaired insulin secretion while magnesium replacement restores insulin secretion. Furthermore, experimental magnesium deficiency reduces the tissues sensitivity to insulin. Subclinical magnesium deficiency is common in diabetes. Some studies suggest that magnesium deficiency may play a role in spontaneous abortion of diabetic women, in fetal malformations and in the pathogenesis of neonatal hypocalcemia of the infants of diabetic mothers. Administration of magnesium salts to patients with type 2 diabetes tends to reduce insulin resistance (3).

Magnesium is an important ion in all living cells being a cofactor of many enzymes, especially those utilizing high energy phosphate bonds. The relationship between insulin and magnesium has been recently studied. In particular it has been shown that magnesium plays the role of a second messenger for insulin action; on the other hand, insulin itself has been demonstrated to be an important regulatory factor of intracellular magnesium accumulation. Conditions associated with insulin resistance, such as hypertension or aging, are also associated with low intracellular magnesium contents. Regular magnesium supplementation can contribute to an improvement in both islet Beta-cell response and insulin action in non-insulin-dependent diabetic subjects (4).

Enzymatic reactions involving the transfer of high-energy phosphate require a divalent metal ion as a participant. This is normally Mg^{2+} in biological situations, as its level within the cell is greater than other divalent metal ions. There is a growing body of evidence that its concentration is relatively low, approximately 0.5 mM. This low level permits control of important parts of carbohydrate metabolism, especially glycolysis, by Mg^{2+} (5).

Magnesium is an important coherent controller of glycolysis and the Krebs cycle. Many of the glycolytic enzymes are sensitive to Mg^{2+} . The most important effect is due to $MgATP^{2-}$ being a cofactor for a number of these enzymes while other chelation forms are

inactive or inhibitory (6).

A role for intracellular Mg deficiency in the development of insulin resistance and suggest that the effect occurs at a site(s) distal to glucose entry into the cell. The effect of Mg deficiency on insulin action appears to be reversible (7).

MAGNESIUM AND DIABETIS MELLITIS

A significant inverse association between magnesium intake and diabetes risk. This study supports the dietary recommendation to increase consumption of major food sources of magnesium, such as whole grains, nuts, and green leafy vegetables (8).

Oral magnesium replacement therapy corrects hypomagnesemia after a minimum treatment period of 3 months. These observations might be important for the prevention of diabetic late complications (9).

Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 diabetes compared with their counterparts without diabetes. Hypomagnesemia occurs at an incidence of 13.5 to 47.7% among patients with type 2 diabetes. Poor dietary intake, autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, osmotic diuresis, recurrent metabolic acidosis, hypophosphatemia, and hypokalemia may be contributory. The increased incidence of hypomagnesemia among patients with type 2 diabetes presumably is multifactorial. Because current data suggest adverse outcomes in association with hypomagnesemia, it is prudent to monitor magnesium routinely in this patient population and treat the condition whenever possible (10). Diabetes mellitus is the most common pathological state in which secondary magnesium deficiency occurs. Retinopathy and microangiopathy are correlated with the drop of plasma and red blood cell Mg. K deficiency increases the noxious cardiorenal effects of Mg deficiency. The treatment should primarily insure diabetic control (11).

Intracellular magnesium concentration is low in type 2 diabetes mellitus and in hypertensive patients. In patients with type 2 diabetes an inverse association exists between the plasma magnesium and insulin resistance due to intracellular changes. Magnesium is required for both proper glucose utilization and insulin signaling. Metabolic alterations in cellular magnesium, which may play the role of a second messenger for insulin action, contribute to insulin resistance (12).

Magnesium deficiency, both extracellular and intracellular, is a characteristic of chronic stable mild Type 2 diabetes, and as such, may predispose to the excess cardiovascular morbidity of the diabetic state. Mg-io measurements may provide a more readily available tool than has heretofore been available to analyse magnesium metabolism in a variety of diseases (13).

In all diabetics plasma magnesium concentrations were inversely related to plasma glucose values ($r_s = -0.33$; p less than 0.01) and in non-insulin-treated patients to plasma insulin concentrations ($r_s = -0.28$; p less than 0.05), the former confirming previous observations. Direct relation of plasma magnesium concentration with glucose disposal was unexplained by its influence on insulin secretion but was related to insulin sensitivity; hence magnesium may be an important determinant of insulin sensitivity in maturity onset diabetes (14).

Experimental studies in animals and cross-sectional studies in humans have suggested that low serum magnesium levels might

lead to type 2 diabetes; however, this association has not been examined prospectively. A graded inverse relationship between serum magnesium levels and incident type 2 diabetes was observed. From the highest to the lowest serum magnesium levels, there was an approximate 2-fold increase in incidence rate (11.1, 12.2, 13.6, 12.8, 15.8, and 22.8 per 1000 person-years; $P = .001$). No association was detected between dietary magnesium intake and the risk for incident type 2 diabetes in black or white participants. Low serum magnesium level is a strong, independent predictor of incident type 2 diabetes. That low dietary magnesium intake does not confer risk for type 2 diabetes implies that compartmentalization and renal handling of magnesium may be important in the relationship between low serum magnesium levels and the risk for type 2 diabetes (15).

The magnesium deficiency has been associated with chronic diseases, amongst them, diabetes mellitus. Epidemiological studies had shown low levels of magnesium ingestion in the general population, as well as a relation between the ingestion of food rich in magnesium and the reduction of diabetes installation and its complications. Hypomagnesemia is frequently present in diabetic patients, however there is not an exact elucidation of the mechanism of magnesium deficiency in diabetes mellitus. The supplementation with magnesium has been suggested in patients with diabetes mellitus who have proven hypomagnesemia and the presence of its complications (16).

MAGNESIUM AND PROTEIN METABOLISM

Magnesium is an essential cofactor for the synthesis and salvage of purine and pyrimidine nucleotides. It plays important roles in the structure of nucleic acids and affects their interaction with proteins and other ligands. Magnesium is required for DNA replication, transcription into RNA and translation into protein. In spite of the diverse roles of magnesium in these fundamental processes, metabolic regulation by magnesium has not been observed. Its role in the regulation of cell growth, division and differentiation remains uncertain (17).

MAGNESIUM AND LIPID METABOLISM

In plasma, magnesium deficiency increased triglyceride and free cholesterol levels and decreased esterified cholesterol levels. Rats fed a magnesium-deficient diet containing sucrose showed particularly high triglyceride plasma levels. In liver, magnesium-deficient rats fed sucrose showed a significant increase in triglycerides, lactate and α -glycerophosphate and a significant decrease in glycogen. With magnesium deficiency, triglycerides were significantly increased in the very low density lipoprotein (VLDL) and low density lipoprotein (LDL) fractions and cholesterol levels were increased in the VLDL and LDL and significantly lower in the high density lipoprotein (HDL) fractions. The detrimental effect of severe magnesium deficiency associated particularly with a high carbohydrate diet content and more especially with a sucrose diet is discussed (18).

Mg(2+) deficit and the lower blood concentration of Mg(2+) was a frequent in patients with the main risk factors, hyperlipidemia, hypertension, diabetes, and obesity. Magnesium is necessary the activity of lecithin cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL), which lowers triglyceride levels and raises HDL-cholesterol levels (19).

One of the factors involved in accelerated atherosclerosis in

hemodialysis patients is dyslipidemia. Magnesium does not appear to increase lipoprotein synthesis. It may be involved in the regulation of some enzymes responsible for lipoprotein synthesis. The correlation of serum magnesium and triglyceride that was found could be due to changes in hepatic triglyceride metabolism, as lipoprotein (a) is a factor involved in accelerated atherosclerosis. Its association with serum magnesium could be important in hemodialysis patients (20).

Epidemiological and experimental studies have shown that magnesium is closely related to regulation of lipid metabolism, membrane structure and permeability, ion migration through cellular membranes, endocrine hormone and platelet function. Plasma from cardiac catheterized patients suffering from chest pains contained higher levels of oxysterols than age and sex matched patients free of chest pain. Studies with cultured arterial cells in media deficient in magnesium or containing oxysterols indicated that both magnesium and oxysterols have an important role in lipid metabolism in patients with coronary heart disease (21).

MAGNESIUM AND MYOCARDIAL INFARCTION

Mechanisms underlying cardiac fibrogenesis in magnesium deficiency are unclear. It was reported earlier from this laboratory that serum from magnesium-deficient rats has a more pronounced stimulatory effect on cell proliferation, net collagen production, and superoxide generation in adult rat cardiac fibroblasts than serum from rats on the control diet. Circulating and cardiac tissue levels of angiotensin II were significantly elevated in magnesium-deficient animals (67.6% and 93.1%, respectively, vs. control). Plasma renin activity was 61.9% higher in magnesium-deficient rats, but serum angiotensin-converting enzyme activity was comparable in the two groups. Furthermore, preliminary experiments *in vivo* using enalapril supported a role for angiotensin II in magnesium deficiency. There was no significant difference between the groups in serum aldosterone levels. The findings suggest that circulating angiotensin II and aldosterone may stimulate fibroblast activity and contribute to a fibrogenic response in the heart in magnesium deficiency (22).

The higher the lymphocyte potassium concentration, the greater the reduction in the incidence of arrhythmias. Serum magnesium levels increased by 16.5% and lymphocyte magnesium concentrations by 72% in the magnesium treated group. Intravenous magnesium reduces the incidence of serious arrhythmias after acute myocardial infarction. Serum magnesium levels increased by 16.5% and lymphocyte magnesium concentrations by 72% in the magnesium treated group. Intravenous magnesium reduces the incidence of serious arrhythmias after acute myocardial infarction (23).

Intracellular magnesium ([Mg]_i) plays an important role in the regulation of myocardial metabolism. Sublingual epithelial cell [Mg]_i correlates well with atrial [Mg]_i but not with serum magnesium. [Mg]_i levels are low in patients undergoing cardiac surgery and those with AMI. Intravenous magnesium sulfate corrects low [Mg]_i levels in AMI patients. Energy-dispersive x-ray analysis determination of sublingual cell [Mg]_i may expedite the investigation of the role of magnesium deficiency in heart disease (24).

Lower than normal dietary intake of Mg can be a strong risk factor for hypertension, cardiac arrhythmias, ischemic heart disease, atherogenesis and sudden cardiac death. Deficits in serum Mg appear often to be associated with arrhythmias, coronary vasospasm and high blood pressure. Evidence is accumulating for a role of Mg²⁺ in the modulation of serum lipids and lipid uptake in

macrophages, smooth muscle cells and the arterial wall. Shortfalls in the dietary intake of Mg clearly exist in Western World populations, and men over the age of 65 years, who are at greatest risk for development and death from ischemic heart disease, have the greatest shortfalls in dietary Mg. It is becoming clear that Mg exerts multiple cellular and molecular effects on cardiac and vascular smooth muscle cells which explain its protective actions (25).

Short-term (S-T) dietary deficiency of magnesium (Mg) (21 days) in rats would: 1) result in reduction in serum(s) sphingomyelin (SM) and changes in several blood lipids, HDL-cholesterol (HDL-C) and phosphatidylcholine (PC) concomitant with elevations in s cholesterol (chol), s LDL+VLDL and triglycerides (TG), as well as reduction in the PC/cholesterol ratio; 2) lead to oxidative stress, characterized by reductions in glutathione (glut) content in the various chambers of the heart and activation of e-NOS and n-NOS in the atria, ventricles and aortic smooth muscle (ASM); 3) produce early cardiac damage characterized by leakage of creatine kinase (CK) and lactic dehydrogenase (LDH); and 4) demonstrate that these pathophysiological changes are a result of profound reductions in s ionized Mg (Mg²⁺) and activation of the SM-ceramide pathway (26).

Magnesium may be important in the pathogenesis of coronary heart disease and sudden death. Magnesium dilates both the epicardial and resistance coronary arteries in humans. Furthermore, the coronary arterial response to magnesium is dose dependent and independent of EDNO (27).

The significance of magnesium has been debated because of difficulty in accurate measurement and other associated factors, including other electrolyte abnormalities. The serum magnesium level represents < 1% of total body stores and does not reflect total-body magnesium concentration, a clinical situation very similar to that of serum potassium. Magnesium is important as a cofactor in several enzymatic reactions contributing to stable cardiovascular hemodynamics and electrophysiologic functioning. Its deficiency is common and can be associated with risk factors and complications of heart failure. Typical therapy for heart failure (digoxin, diuretic agents, and ACE inhibitors) are influenced by or associated with significant alteration in magnesium balance. The intricate role of magnesium on a biochemical and cellular level in cardiac cells is crucial in maintaining stable cardiovascular hemodynamics and electrophysiologic function. In patients with congestive heart failure, the presence of adequate total-body magnesium stores serve as an important prognostic indicator because of an amelioration of arrhythmias, digitalis toxicity, and hemodynamic abnormalities (28).

Magnesium (Mg) plays an essential role in a wide range of fundamental cellular reactions in patients with ischemic heart disease. It has been well known that Mg plays a pivotal role in control of cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure, among other functions. Especially, many epidemiological, experimental, and clinical studies support a pathological role for Mg in the etiology and development of major coronary risk factors as diabetes mellitus, hypertension, and hyperlipidemia as well as ischemic heart disease. Furthermore, the therapeutic value of Mg in the management of coronary risk factors and ischemic heart disease has been clarified. Dietary Mg supplementation should be considered as a preventive element in atherosclerosis and ischemic heart disease (29).

1.0 and 2.0 mM Mg²⁺ inhibits the tonic contraction and that 8.0 mM Mg²⁺ inhibits the periodic as well as the tonic contraction of isolated human coronary arteries. Diltiazem inhibits the periodic

contraction, whereas nitroglycerin suppresses tonic contraction without affecting the periodic contraction (30).

The use of high dose magnesium as first line drug therapy for OHCA was not associated with a significantly improved survival. Early defibrillation remains the single most important treatment for ventricular fibrillation (VF). Further studies are required to evaluate the role of magnesium in cardiac and cerebral resuscitation (31).

Deficiency and efficiency of some essential micronutrients may play a role in the development of heart disease. The micronutrient supplements containing K⁺ and Mg²⁺ may be beneficial, but because of potential risks, use should be carefully monitored and restricted to men taking potassium-losing diuretics (32).

Intravenous administration of magnesium has proved to have beneficial effect in acute myocardial infarction. Magnesium seems to act at different levels of the cardiovascular system. Of the greatest importance is the direct influence of Mg²⁺ on the cardiomyocyte which includes: reduction of cytoplasmic calcium overload, protection of mitochondria against calcium influx, and diminution of cellular potassium, magnesium and ATP depletion. By means of these effects, or by its direct action on myocardium, Mg²⁺ inhibits the origin of postinfarctional dysrhythmias. Further more, magnesium reduces afterload by decrease in vascular resistance, and improves coronary flow (33).

Intravenous magnesium therapy may reduce mortality in patients with acute myocardial infarction. Further large scale trials to confirm (or refute) these findings are desirable (34).

Magnesium infusion during a coronary occlusion has a significant benefit in reducing the IS in this model. Magnesium may have a beneficial clinical role in AMI, especially if administered before reperfusion as a bolus followed by a constant infusion (35).

Magnesium administration has an infarct size limiting effect independent of its effects on myocardial oxygen consumption and incidence of arrhythmia in rabbits. The infarct size limiting effect of magnesium is attributable, at least in part, to augmentation of adenosine mechanism (36).

The cardiovascular actions of the magnesium ion at pharmacological concentrations include coronary and systemic vasodilatation, platelet inhibition, and antiarrhythmic effects. Magnesium has also been reported to protect myocardial tissue in experimental models of ischaemia and reperfusion. The side-effects of magnesium treatment were transient flushing, related to speed of injection of the loading dose, and an increased incidence of sinus bradycardia (2p=0.02). Exploratory subgroup analyses of 28-day mortality did not indicate any effect modification by thrombolysis or aspirin, or by previous treatment with beta blockers, calcium antagonists, or diuretics. Intravenous magnesium sulphate is a simple, safe, and widely applicable treatment. Its efficacy in reducing early mortality of myocardial infarction is comparable to, but independent of, that of thrombolytic or antiplatelet therapy (37).

It has recently been suggested that intravenous infusion of magnesium may reduce mortality and the incidence of serious arrhythmias in patients with ischaemic heart disease and acute myocardial infarction. Magnesium infusion was accompanied by a significantly increased incidence of atrioventricular conduction disturbances. The results suggest that patients suffering from acute ischaemic heart syndromes do not benefit from intravenous magnesium supplementation (38).

MAGNESIUM IN RENAL FAILURE

Renal excretion is the major route of magnesium elimination from the body and a positive magnesium balance would be expected under conditions of renal insufficiency. While magnesium intoxication is a real hazard when magnesium-containing drugs are given, magnesium balance may be normal or even decreased in uraemic patients. This is usually due to decreased dietary intake combined with the impaired intestinal magnesium absorption which characterizes chronic renal failure. Impairment of magnesium absorption seems to be related to deficient synthesis of the active metabolite of vitamin D by the non-functioning kidney. Following the institution of chronic haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) treatment, the major determinant of magnesium balance is the concentration of magnesium in the dialysate. Changes in the dialysate magnesium have been used to reduce the incidence of renal osteodystrophy, to alleviate uraemic pruritus, or to retard the development of arterial calcification in chronic renal disease. However, uncertainty about magnesium, calcium and parathyroid hormone relationships in renal failure makes a reasoned approach to such manipulations extremely difficult (39).

Chronic metabolic acidosis decreased renal TRPM6 expression, increased Mg²⁺ excretion, and decreased serum Mg²⁺ concentration, whereas chronic metabolic alkalosis resulted in the exact opposite effects. In conclusion, these data suggest that regulation of Ca²⁺ and Mg²⁺ transport proteins contributes importantly to the effects of acid-base status on renal divalent handling (40).

The kidney has a vital role in magnesium homeostasis and, although the renal handling of magnesium is highly adaptable, this ability deteriorates when renal function declines significantly. In moderate chronic kidney disease (CKD), increases in the fractional excretion of magnesium largely compensate for the loss of glomerular filtration rate to maintain normal serum magnesium levels. However, in more advanced CKD (as creatinine clearance falls <30 mL/min), this compensatory mechanism becomes inadequate such that overt hypermagnesaemia develops frequently in patients with creatinine clearances <10 mL/min. Dietary calcium and magnesium may affect the intestinal uptake of each other, though results are conflicting, and likewise the role of vitamin D on intestinal magnesium absorption is somewhat uncertain. Although various studies have shown that patients with higher serum magnesium tend to have lower PTH levels, many of these suffer from methodological limitations. Finally, we examine the complex and often conflicting results concerning the interplay between magnesium and bone in uraemic patients. Although the exact role of magnesium in bone metabolism is unclear, it may have both positive and negative effects, and it is uncertain what the optimal magnesium levels are in uraemic patients (41).

A number of factors affect the concentration and distribution of magnesium in patients with chronic renal failure (CRF). Poor nutritional intake, impaired absorption from the intestine, vomiting, diarrhea, the use of diuretics and acidosis may result in a negative balance. More commonly, accumulation of magnesium may be the consequence of reduced renal excretion (42).

Magnesium is predominantly an intracellular cation that plays a critical role in cellular physiology. Serum levels are often slightly elevated in patients on chronic hemodialysis and older reports suggests that total body stores may also be increased, based on

bone biopsies in patients treated with higher dialysate magnesium levels than are currently in use today. Several studies have shown that magnesium, particularly in the form of magnesium carbonate, is an effective phosphate binder and can decrease patients' exposure to calcium. While short-term or adjuvant use of magnesium carbonate appears safe and effective as a phosphate binder, more studies are needed to evaluate the long-term effects on vascular calcification, bone histology, and mortality (43).

The continued use of molecular techniques to probe the constitutive and congenital disturbances of magnesium metabolism will increase the understanding of cellular magnesium transport and provide new insights into the way these diseases are diagnosed and managed (44).

MAGNESIUM IN LIVER DISEASE

Six weeks of Mg supplementation did not increase muscle Mg, although Mg supplementation and spironolactone treatment were independent predictors of muscle Mg. The intervention had no effect on muscle strength and mass, but both increased during the study, probably owing to the general care (45).

Magnesium deficiency can cause dyslipidemia and insulin hypersecretion, which may facilitate gallstone formation. However, the effect of long-term consumption of magnesium on the risk of gallstone disease is unknown, a protective role of magnesium consumption in the prevention of symptomatic gallstone disease among men (46).

Cellular magnesium content is a better parameter when determining alterations in magnesium status in alcohol-induced diseases of the liver than plasma magnesium concentrations, which can still remain in the normal range even in severe forms of cirrhosis (47).

Chronic terminal cirrhotics are magnesium depleted which should be taken into account in case of liver transplantation and also in other interventions. Spot sampled serum ionized magnesium revealed magnesium depletion poorly (48).

The plasma levels of Zn and Mg were found to be reduced, as were the urine levels of Mg. Urine Zn, on the other hand, was higher than normal. Plasma Zn correlated inversely, and urine Zn directly, with the severity of the disease, rather than with alcohol consumption or treatment with diuretics (49).

MAGNESIUM AND BOWEL DISEASE

Mg deficiency is a frequent complication of inflammatory bowel disease (IBD) demonstrated in 13-88% of patients. Decreased oral intake, malabsorption and increased intestinal losses are the major causes of Mg deficiency. Twenty-four-hour urinary excretion of Mg is a sensitive index and should be monitored periodically. Parenteral Mg requirements in patients with IBD are at least 120 mg/day or more depending upon fecal or stomal losses. Oral requirements may be as great as 700 mg/day depending on the severity of malabsorption (50).

Serum Mg levels were significantly lower in the Crohn's group than in a group of hospital controls; 5-10 mmol of IV Mg were required daily to prevent Mg depletion during IV nutrition and some patients required higher intakes. Three patients with particularly severe malabsorption required oral Mg supplements in the long-term. The rationale for using our method of assessing Mg status, and the

importance of recognizing and treating chronic Mg deficiency are presented (51).

Magnesium (Mg) deficiency increases genomic instability and Mg intake has been reported to be inversely associated with a risk of colorectal cancer (CRC). That organo-Mg inhibits inflammation-related mouse colon carcinogenesis by modulating the proliferative activities and chromosomal instability of CRC and suppressing colonic inflammation may suggest potential use of organo-Mg for clinical chemoprevention trials of CRC in the inflamed colon (52).

MAGNESIUM AND REPRODUCTIVE SYSTEM

It has been revealed that low serum magnesium (Mg) is often associated with insulin resistance (IR), cardiovascular problems, diabetes mellitus, and hypertension. Patients with polycystic ovary syndrome (PCOS) are known to have a high incidence of insulin resistance. This study was designed to determine whether women with PCOS exhibit serum magnesium deficiency and its potential association with IR. The risk of PCOS for subjects with Mg deficiency was 19 times greater than those who had normal serum Mg concentrations ($p \leq 0.0001$). No correlation was found between Mg and insulin sensitivity or secretion, FPG, dyslipidemias, and also androgen concentrations. After adjustment for calcium concentration the role of magnesium to predict PCOS attenuated and became non-significant ($\beta: -1.9, p: 0.7$) (53).

Further studies are needed to clarify the actual role of magnesium in the physiology of the male reproductive tract, especially its association with premature ejaculation (54).

Decreased levels of magnesium gives rise to vasoconstriction from increased thromboxane level, increased endothelial intracellular Ca^{2+} , and decreased nitric oxide. This may lead to premature emission and ejaculation processes. Magnesium is probably involved in semen transport. More research into the role of magnesium in the male physiology of reproductive tract, especially its association with premature ejaculation, is advocated (55).

Contraction of smooth muscles of the vas deferens plays an important role in the propulsion of sperm into the pelvic urethra. Reactivity of the vas deferens to electrical stimulation is modulated by extracellular Mg^{2+} concentration. The possible relevance of these data to sperm transport through the vas deferens is discussed (56).

No significant changes in sperm characteristics, blood ionized or total Mg, or ejaculate total Mg levels were detected. However, ejaculate ionized Mg levels increased in Group M from 0.18 ± 0.05 to 0.30 ± 0.05 (mmol/l; mean \pm SD, $p < 0.05$). Within the observation period of 3 months, one pregnancy occurred in the partner of a male from Group M. In conclusion, magnesium orotate treatment at a dose of 3000 mg/day leads neither to a significant improvement of sperm variables nor does it increase the pregnancy rates of female partners of treated males as compared to those of controls. Thus, magnesium orotate treatment was not shown to be effective therapy for idiopathic male infertility (57).

MAGNESIUM AND DEPRESSION

The female subjects who were diagnosed with clinical depression and premenstrual dysphoric disorder were treated with daily dose of 360 mg. of magnesium. Depression was evaluated for three months. Nearly all the female patients responded positively to the magnesium therapy with elevation of mood, relaxation and sleep duration (58).

The incidence of depression is increasing worldwide. Much is still unknown about the possible role of magnesium in depression prevention and treatment. Magnesium has an effect on biological and transduction pathways implicated in the pathophysiology of depression. The possible role of magnesium in depression prevention and treatment remains unclear. Magnesium seems to be effective in the treatment of depression but data are scarce and incongruous. Disturbance in magnesium metabolism might be related to depression. Oral magnesium supplementation may prevent depression and might be used as an adjunctive therapy. However, more interventional and prospective studies are needed in order to further evaluate the benefits of magnesium intake and supplementation for depression (59).

Depressive symptoms are frequent in students and may lead to countless problems. Several hypotheses associate magnesium with depression because of the presence of this mineral in several enzymes, hormones, and neurotransmitters, which may play a key role in the pathological pathways of depression. The aim of this study was to assess whether magnesium intake could modulate depressive symptoms (60).

That hypomagnesaemia could be an epiphenomenic biochemical trait in less drug-responsive depressed patients. It is also plausible that lower Mg levels and hyperactive traits identify a biological subtype of patients with increased catecholaminergic functioning and a poorer response to aminergic drugs. Moreover, Mg depletion could partly account for the correlation between low Mg levels and poor outcome and this raises the question of Mg's possible therapeutic role in depression (61).

Numerous studies have been performed on magnesium (Mg) metabolism in patients with mood disorders but consistent results have not been obtained. A relationship between catecholamines and Mg metabolism has been described and our results support the hypothesis that hypermagnesaemia might lead to hypoactivity and psychomotor retardation which is so often observed in depressed patients (62).

A higher magnesium intake has been related to lower depressive symptoms. However, epidemiological evidence on this issue is scarce (63).

There is more than sufficient evidence to implicate inadequate dietary magnesium as the main cause of TRD, and that physicians should prescribe magnesium for TRD. Since inadequate brain magnesium appears to reduce serotonin levels, and since antidepressants have been shown to have the action of raising brain magnesium, we further hypothesize that magnesium treatment will be found beneficial for nearly all depressives, not only TRD (64).

MAGNESIUM AND CANCER

The relationship between magnesium and cancer is not as simple as could be assumed from the well-established requirement of magnesium for cell proliferation. Basic and pre-clinical studies indicate that magnesium deficiency can have both anti- and pro-tumour effects. The role of magnesium in cancer is also critically examined with regard to mitochondrial function, apoptosis and resistance to treatment. Finally, we bring together the latest experimental evidence indicating that alteration in the expression and/or activity of magnesium channels is a frequent finding in cancer cells and human tumour tissues examined to date, and we discuss the potential implications for developing novel diagnostic and therapeutic strategies (65).

A complex relationship links magnesium and cancer. Impaired magnesium homeostasis is reported in cancer patients, and frequently complicates therapy with some anti-cancer drugs. More studies should be undertaken in order to disclose whether a simple and inexpensive intervention to optimize magnesium intake might be helpful in the prevention and treatment of cancer (66).

Relationship between magnesium and cancer is complex. In mice inoculated with LLC cells and receiving low-magnesium diet, a higher metastatic potential was observed as compared to control mice. In conclusion, our results demonstrate a direct role of magnesium in tumor growth and also point at deleterious effect of lowmagnesium status on tumor metastasis (67).

Magnesium is involved in a wide range of biochemical reactions that are crucial to cell proliferation, differentiation, angiogenesis, and apoptosis. Changes in magnesium availability have been shown to influence biological responses of immuno-inflammatory cells. Equally plausible seems to be an involvement of magnesium in the multistep and interconnected processes that lead to tumor formation and development; however, the "how" and "when" of such an involvement remain to be defined. Here, we reviewed in vitro and in vivo data that indicated a role for magnesium in many biological and clinical aspects of cancer (68).

Low Magnesium (Mg)-containing diet reversibly inhibits the growth of primary tumors that develop after the injection of Lewis lung carcinoma (LLC) cells in mice. The inhibition of LLC tumor growth in Mg-deficient mice is due to a direct effect of low Mg on LLC cell proliferation and to an impairment of the angiogenic switch. We also observed an increase of nitric oxide synthesis and oxidative DNA damage. Complementary DNA arrays reveal that Mg deficiency modulates tumor expression of genes involved in the control of cell cycle, stress response, proteolysis, and adhesion. Our results suggest that Mg has multiple and complex roles in tumor development (69).

Many studies have investigated the relation between magnesium and iron intake and diabetes and, separately, between diabetes and pancreatic cancer. A statistically significant inverse relation was noted between magnesium and pancreatic cancer for subjects with a body mass index of ≥ 25 kg/m² (RR $\frac{1}{4}$ 0.67, 95% CI: 0.46, 0.99; P-trend $\frac{1}{4}$ 0.04). Although, overall, no relation between magnesium or iron intake and pancreatic cancer was observed in this cohort of men, an inverse association with magnesium was suggested among overweight individuals, which should be examined in other studies (70).

Mg deficiency increases susceptibility to chemical oncogens. The abnormal metabolism of tryptophan (yielding a carcinogenic metabolite) that indicates functional or absolute pyridoxine deficiency is an indirect clue to Mg deficiency. Vitamin B₈-activated enzymes require Mg as a cofactor. However, the early warnings against the use of Mg as part of an antineoplastic program against established cancer were justified, since rapidly metabolizing cells (such as cancers) are dependent on Mg. There are similarities between experiences with Mg and with Se and Zn. All three are required for normal metabolism; Se also protects against free radicals in the environment. Mg and Zn have increased established tumor growth, and their depletion has been applied to antineoplastic programs, with risks comparable to those of using anti-metabolic agents (71).

The main target in the relationship between Mg and metals in carcinogenesis is either membrane as regards Pb and Cd, or nucleus as regards Pt, Ga, Co and Ni. The ideal treatment of Mg disturbances in carcinogenesis should control the factors which

regulate cellular and subcellular Mg distribution in neoplastic tissues as well as those which avoid Mg depletion in extra malignant tissues (72).

The possible association between the risk of ovarian cancer and the levels of calcium and magnesium in drinking water from municipal supplies was investigated in a matched case-control study in Taiwan. There may be a significant protective effect of magnesium intake from drinking water on the risk of ovarian cancer death (73).

MAGNESIUM , BONE DISEASE & OSTEOPOROSIS

Dietary Mg intake has been linked to osteoporosis. Previous studies have demonstrated that severe Mg deficiency [0.04% of nutrient requirement (NR)] results in osteoporosis in rodent models. Mg intake of 10% of NR in rats causes bone loss that may be secondary to the increased release of substance P and TNF- α (74).

MAGNESIUM AND THYROID

Training until exhaustion causes reduction in thyroid hormone activity in sedentary and sportsperson. It has been established that Mg supplementation however, prevents reduction in thyroid hormone activity in sedentary and sportsperson (75).

Plasma and RBC Mg concentrations were low in half of the hyperthyroid subjects, but mean values were not significantly different from controls. Urinary excretion and clearance of Mg were lower in hypothyroid subjects, but differences were removed when expressed relative to Cr excretion and clearance (76).

Magnesium supplementation decreased the elevated total cholesterol and triglyceride concentrations of the diabetic rats to the control level. It was concluded that oral magnesium supplementation might decrease the diabetes-induced disturbances of lipid metabolism (77).

Serum T4 response to TRH challenge was significantly reduced in Mg-deficient as compared to Mg-adequate rats at all time intervals. The reduction of T4 level could be due to an impaired T4 synthesis or release in Mg-deficient rats (78)

Plasma magnesium concentration was elevated by acute MgCl₂ infusions to determine the reabsorptive capacity of magnesium. Thyroid deficient rats reabsorbed 15-30% more of the filtered magnesium at any given plasma concentration. Thyroid hormone has a direct effect on the tubule which if chronically absent results in subtle sodium and calcium wasting and renal retention of magnesium. Administration of thyroid hormone to euthyroid or thyroid deficient rats twenty-four hours prior to experimentation had no effect on calcium and magnesium handling (79).

MAGNESIUM AND ADRENAL GLAND

Magnesium ion (Mg) directly inhibits aldosterone production in rat adrenal glomerulosa cells, while potassium ion directly stimulates aldosterone production. It is reported that Mg shows antihypertensive effect in patients with essential hypertension. Secondary hyperaldosteronism induced by diuretic treatment in patients with congestive heart failure accelerates potassium and magnesium ions' excretion in urine. Aldosterone antagonists, such as spironolactone and eplerenone, correct not only potassium deficiency but also magnesium deficiency induced by diuretics. Mg

supplementation also may be useful procedure to correct potassium and magnesium deficiency, because Mg itself inhibits aldosterone release from the adrenal glands (80).

MgSO₄ showed an inhibitory effect on aldosterone production stimulated by angiotensin II (10pM to 10nM), whereas it had no significant effect on aldosterone production due to ACTH stimulation (10pM to 10nM). These data suggest that magnesium has an inhibitory action on aldosterone production in vitro and may be a physiological regulator of aldosterone production (81).

MAGNESIUM AND IMMUNE FUNCTION

Epidemiological and experimental studies underline the role of magnesium in inflammation. Several data indicate an enhanced response of phagocytes (granulocytes, macrophages) derived from magnesium-deficient animals or cultured under low magnesium conditions to the inflammatory mediators' stimulation. Magnesium status is an important modulator of the phagocyte response to immune stimuli and consequently could be implicated in a wide range of pathophysiological issues, e.g. those related to the production of radical oxygen species (ROS). It is likely that magnesium directly modulates phagocyte priming by its calcium antagonism and indirectly by its effect on the immunoinflammatory processes, the source of the priming mediators (82).

Experimental magnesium deficiency in the rat induces after a few days a clinical inflammatory syndrome characterized by leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins, excessive production of free radicals. Increase in extracellular magnesium concentration, decreases inflammatory response while reduction in the extracellular magnesium results in cell activation. Magnesium deficiency contributes to an exaggerated response to immune stress and oxidative stress is the consequence of the inflammatory response. Inflammation is the missing link to explain the role of magnesium in many pathological conditions (83).

Magnesium status is a well-known modulator of the immune system. Magnesium is an important modulator of immune cell function under in vitro conditions. However, a magnesium supplementation seems to be unable to prevent any exercise-associated alterations in immune cell function in athletes with balanced magnesium status (84).

Recent findings regarding roles for magnesium in immune competence confirm and extend previous knowledge of its participation in natural and adaptive immunity. The detrimental effects of severe magnesium deficiency have been confirmed. There is better comprehension of how magnesium relates to mechanisms that control cellular activities and regulate interactions among cells that affect immune functions (85).

Physical exercise may deplete magnesium, which together with a marginal dietary magnesium intake may impair energy metabolism, muscle function, oxygen uptake and electrolyte balance. Magnesium deficiency leads to immunopathological changes that are related to the initiation of a sequential inflammatory response. Although in athletes magnesium deficiency has not been investigated regarding alterations in the immune system, the possibility exists that magnesium deficiency could contribute to the immunological changes observed after strenuous exercise (86).

In athletes, exercise leads to the exhaustion of magnesium and

consequently to the decline of immune function (87).

MAGNESIUM AND ALCOHOL CONSUMPTION

Clinical and experimental evidence indicates alcohol consumption as one of the major causes of magnesium loss from several tissues. As a result of this loss, serum magnesium tends to decrease while urinary magnesium excretion increases 2-3 fold. Experimental data confirm that chronic consumption of 6% ethanol in the Lieber De-Carli diet for 3 weeks results in a marked decrease in total tissue magnesium content in rats. This decrease affects brain, liver and all skeletal muscle, including heart, to a varying extent. Ethanol impairs magnesium transport and homeostasis in brain, brain vasculature, skeletal muscle, heart and liver cells, as a first step towards more mechanistic studies aimed at relating magnesium loss with the incurrance of short- and long-term ethanol-induced complications in these organs (88).

Acute and chronic ethanol administration results in a decrease in cellular Mg²⁺ content and an alteration of Mg²⁺ transport in liver cells. The defect in hormone-activated Mg(2+) transport observed in the chronic EtOH model [Young, A., Cefaratti, C., & Romani, A. (2003). Chronic EtOH administration alters liver Mg²⁺ homeostasis. *Am J Physiol* 284, G57-G67] depends not only on a reduced cellular Mg²⁺ content but also on the impaired Mg²⁺ transport mechanisms present in the hepatocyte plasma membrane, in particular the Mg²⁺-entry pathway, which prevents the liver cell from restoring cellular Mg²⁺ homeostasis (89).

A significantly higher, alcohol dose-related excretion of Mg and Ca (calcium) in the urine after the oral Mg load among consumers of alcohol. Although the study is based on a small number of subjects with differences in smoking habits, it is suggested that alcohol consumption even in moderate amounts could contribute to Mg deficiency (90).

Moderate consumption of ethanol lowers mortality from coronary artery disease, and one of the possible mechanisms is an antiarrhythmic action. In the group consuming beer, whose plasma magnesium rose from 0.89 (SD 0.01) to 0.98 (SD 0.02) mmol/L (P < 0.0025). This level of beer consumption did no obvious harm to liver function and its possibly beneficial effect on plasma magnesium deserves further investigation (91).

Alcohol-induced cellular loss of [Mg²⁺] is associated with cellular Ca²⁺ overload and generation of oxygen-derived free radicals; chronic pretreatment with vitamin E prevents alcohol-induced vascular injury and pathology in the brain (92).

A comprehensive and critical review of the evidence relating magnesium (Mg) deficiency to alcohol consumption reveals several important types of interactions. A number of aspects of the clinical syndrome of alcoholism contribute to and intensify that already existing reduction in body Mg stores. Relatively little attention has been paid to the possible value of Mg administration as a preventive measure to forestall or minimize the deleterious effects of chronic use of alcohol or to prevent the development of cancer than can occur in this setting (93).

Increased intracellular calcium, which was partly due to magnesium depletion and suppressed sodium pump activity, and expanded body fluid volume, had a possible role in the development of alcohol-induced hypertension. It is also suggested that oral magnesium supplementation had a hypotensive effect on alcohol-induced hypertension possibly through decreased

intracellular sodium concentration caused by an activation of sodium pump and decreased sympathetic nervous activity (94).

Alcohol has been shown to reduce serum calcium concentrations in several animal studies. There was an inversely related diminution of serum calcium and magnesium concentrations with increasing serum alcohol. These effects of alcohol may play a role in the metabolic and clinical disorders observed in severely intoxicated people (95).

Although alcohol has long been known to induce cardiac depression and cardiomyopathy, it is not known whether drug therapy or pharmacologic manipulation can be used to prevent or reverse these toxicities. High [Mg²⁺] (15 mM) given either before or during ethanol-induced cardiotoxicity is effective in attenuating both functional and metabolic damage caused by high ethanol perfusion in the rat heart (96).

MAGNESIUM AND GENETIC DISORDERS

The continued use of molecular techniques to probe the constitutive and congenital disturbances of magnesium metabolism will increase the understanding of cellular magnesium transport and provide new insights into the way these diseases are diagnosed and managed (97).

Ionic magnesium (Mg²⁺) depletion has long been known to cause hyperexcitability with convulsive seizures in rodents, effects that have been reversed by treatment with magnesium (Mg). Hyperexcitable children have low ERC-Mg with normal serum Mg²⁺ values, and that Mg²⁺/vitamin B6 supplementation can restore normal ERC-Mg levels and improve their abnormal behavior (98).

CONCLUSION

This paper has covered a wide range of research findings in the areas of magnesium linking its significance in the restoration of various health and clinical symptoms. Most of the research findings compiled in this paper refers to studies carried out on humans with very few on animals. Taking into account the enormous role of magnesium in the regulating nearly 300 enzyme activities, this review article may have missed certain findings and therefore the authors recommend further up gradation of the role of magnesium in human health and disease.

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