REVIEW ARTICLE

Magnesium deficiency and diabetes mellitus

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Magnesium, the second most common intracellular cation plays a fundamental role as a cofactor in various enzymatic reactions involving energy metabolism. Magnesium is a cofactor in the glucose-transporting mechanism of the cell membrane and various enzymes in carbohydrate oxidation. It is also involved at multiple levels in insulin secretion, binding and activity. The almost universal involvement of magnesium in a wide variety of cellular processes critical to glucose metabolism, insulin action and cardiovascular functions has been well appreciated. The incidence of subclinical magnesium deficiency is common in diabetes and cardiovascular disorders. However, limited attention has been drawn to the impact of magnesium deficiency on late diabetic complications, including cardiovascular disorders. Magnesium deficiency has recently been related with age-related diseases through free-radical mechanism. The existence of oxidative stress has been well documented in diabetes and late diabetic complications.

The present review discusses the functional role of magnesium in the pathogenesis of diabetes and introduces a relatively new concept on the implication of magnesium deficiency in diabetic complications.

MAGNESIUM is the fourth most common cation in the body and the second most common intracellular cation after potassium. The central role of magnesium within the chlorophyll molecule and as a cofactor for the enzymes in the 12-transphosphorylation reactions in photosynthesis makes it probably the most important inorganic element in the production of food and fossil fuel[1]. In addition, it has a fundamental role as a cofactor in more than 320 enzymatic reactions involving energy metabolism and nucleic acid synthesis[2].

Until recently, the function of magnesium in biological processes was largely ignored to the point where it was described as the 'forgotten' ion. In recent years, there has been an explosion of interest in the physiological and therapeutic properties of this essential element. It is involved in several processes, including hormone receptor binding and gating of calcium channels, transmembrane ion flux, regulation of adenylate cyclase, muscle contraction and neuronal activity, control of vascular tone, cardiac excitability and neurotransmitter release[3–5]. Magnesium increases the body's ability to utilize calcium, phosphorus, sodium, potassium, vitamins C, E and B complex[6].

From a physiological perspective, magnesium is primarily regarded as a calcium antagonist, as most of its actions are linked to calcium. Calcium is an ideal agent for fast signal transduction and cell activation as cytosolic free calcium is only 1/10,000 of the corresponding extracellular species, traditionally called ionized calcium[3]. Magnesium, on the other hand, having a slight gradient over the plasma, plays the complementary role of a more long-term regulatory element. Alterations of intracellular or extracellular magnesium concentration may affect cell function through its effect on calcium handling.

Most of the intracellular magnesium is located within the mitochondria apparently because magnesium binds strongly with ATP. In general, the more metabolically active the cell is, the higher is its magnesium content. Levels of magnesium in the plasma of healthy people are remarkably constant, being on an average of 1.7–2.4 mg/dl (0.7–1.0 mmol/l).

It has been estimated that refining and processing of food causes a substantial loss of magnesium. For example, the refining and processing of wheat to flour, rice to polished rice and corn to starch depletes magnesium by 82, 83 and 97% respectively[7]. Thus, modern food technology partially explains why a significant segment of the population has intake of magnesium below recommended dietary amounts and may be predisposed to chronic, latent magnesium deficiency. Drinking water, on the other hand, remains an important source of magnesium. There are several other factors which have reduced magnesium within the ecosystem as a whole. Acid rain causes exchange between magnesium and aluminium in the soil. This, coupled with intensive farming of the soil, has led to a reduction in magnesium within the food chain[8].

Absorption and regulation of magnesium

From recent studies, it has been observed that magnesium absorption in humans occurs uniformly throughout the small intestine[9]. Reports have shown an inverse curvilinear relationship between intake of magnesium and fractional absorption, which ranges from 65% absorption at low intake to 11% absorption at high intake[10]. Clinically,

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this suggests that treating magnesium deficiency with oral supplementation may require an extended period.

Plasma magnesium is carefully regulated within the narrow range of 1.7–2.4 mg/dl (0.7–1.0 mmol/l). In contrast to the tight hormonal control of concentrations of calcium in the blood, kidney is the primary regulator of magnesium balance. Normal intake of magnesium is approximately 300 mg per day, and about one-third of the intake is absorbed by the gastrointestinal tract. Renal magnesium handling is essentially a filtration–reabsorption process, even though magnesium secretion has been suggested[11]. Eighty percent of serum magnesium is ultra filterable out of which 70 to 80% is ionized. Over a 24 h period, 3500 mg of magnesium is filtered: in humans only 3–4% of this amount is excreted in the urine, or about 100 to 150 mg per day; an amount equal to that absorbed by the gastrointestinal tract each day[12].

About 20–30% of the filtered magnesium is reabsorbed along the proximal tubule, which is less than that of sodium, potassium or calcium. The thick ascending limb of the Henle's loop is now known to be the major site of magnesium reabsorption in the renal tubule (50–60%) and the principal locus of renal control of magnesium excretion[13]. The status of body magnesium balance is determined by the renal excretion of magnesium. The most striking change in renal magnesium handling occurs in response to alterations in plasma magnesium concentration. Recent evidences suggest that the cells within the distal tubule, and possibly the thick ascending limb of Henle, are capable of adapting to magnesium and calcium availability through receptors that sense the concentration of these cations[14]. Thus when the magnesium status is sub-optimal, these receptors sense the need for magnesium retention and cause more reabsorption.

Renal magnesium wasting may be either primary, due to renal defect or secondary, representing the response of the kidney in a normal manner to a variety of systemic and local factors that increase magnesium losses. Several drugs, particularly diuretics, thiazides, cisplatin, gentamycin and cyclosporin cause magnesium loss into urine by inhibiting magnesium reabsorption in the kidneys[15]. Lipid-lowering drug treatment in type-2 diabetic patients has recently been added to that list[16].

Hormonal modulation of magnesium

Despite early proposals for the existence of a specific hormonal control of magnesium homeostasis, no single endocrine factor that controls circulating or urinary magnesium has been identified. Among many extensive and excellent reviews dealing with magnesium homeostasis, one describes magnesium as the body's 'orphan ion', because of an apparent lack of a specific endocrine control similar to that existing for calcium, sodium and potassium[17]. A number of hormones, including parathyroid hormone and calcitonin, vitamin D, insulin, glucagon, antidiuretic hormone, aldosterone and sex steroids have been reported to influence magnesium balance, notwithstanding the possibility that these may not be primary regulators of magnesium homeostasis[18,19]. Recent observations suggest that these hormones act through a common second messenger, adenosine 3′,5′-cyclic mono-phosphate to enhance magnesium transport and modulate magnesium excretion at that nephron site[9].

Magnesium deficiency

Magnesium deficiency is common and multifactorial. Numerous research reports and clinical commentaries regarding magnesium deficiency have appeared in recent years. Magnesium deficit can be categorized into two types: magnesium deficiency and magnesium depletion. Dietary amounts of magnesium are marginal in the whole population and little alteration in magnesium intake may increase the prevalence of magnesium deficiency[20]. Magnesium depletion may be due to dysregulation of factors controlling magnesium status: intestinal hypo-absorption of magnesium, reduced uptake and mobilization of bone magnesium, sometimes urinary leakage, hyperadrenoglucocorticism by decreased adaptability to stress, insulin resistance and adrenergic hyporeceptivity. Magnesium deficiency in aging largely results from various pathologies and treatment to elderly persons, i.e. diabetes mellitus and use of hypermagnesuric diuretics. Osmotic diuresis caused by glucosuria (as in diabetes mellitus), mannitol and urea results in urinary magnesium wasting. It has been suggested that aging, stress and various disease states may increase magnesium requirement[21].

Magnesium deficiency has been demonstrated in 7–11% of hospitalized patients and is found to coexist in up to 40% of patients with other electrolyte abnormalities, particularly hypokalemia and to a lesser extent, hyponatremia or hypocalcemia[22]. The co-existence of secondary electrolyte abnormalities plays a key role in the clinical features of magnesium depletion. Among the endocrine and metabolic disorders associated with magnesium deficiency, diabetes mellitus is the most common[23]. Although hypomagnesemia reliably indicates magnesium deficiency, a normal plasma magnesium concentration does not exclude magnesium depletion. Alternative methods for the estimation of body magnesium store include direct measurement of intracellular magnesium using erythrocytes or tissue magnesium.

Deficiency of magnesium is closely linked to abnormalities in calcium and potassium metabolism. A fundamental interaction between magnesium and other ions seems to occur at the cellular level. Intracellular calcium concentrations are controlled within narrow limits, with transient increases rapidly returning to normal levels. The release of intracellular calcium plays a key role in many

cell functions, both basic (cell division and gene expression) and specialized (excitation, contraction and secretion)[24]. A common pathway for the release of intracellular calcium from many stimuli such as hormones, growth factors and neurotransmitters is phospholipase-C activation and hydrolysis of phosphatidylinositol 4,5-biphosphate into inositol 1,4,5-triphosphate (IP_3). IP_3 acts by binding to the transmembrane IP_3 receptor, causing opening of a calcium channel, which is part of the same molecule[25]. Magnesium acts as a non-competitive inhibitor of the IP_3-gated calcium channel and of IP_3 binding. Therefore, it may be considered as an intracellular calcium antagonist acting at IP_3-sensitive calcium-release channels.

It is well known that patients with moderate-to-severe magnesium deficiency commonly have accompanying hypocalcemia, which has been shown to be secondary to impaired secretion of parathyroid hormone as well as skeletal and renal resistance to the action of parathyroid hormone[26]. Altered serum calcium and magnesium concentrations result in increased neuromuscular hyperexcitability, which is responsive only to magnesium therapy. In addition to interactions with calcium, magnesium has a marked effect on the regulation of transmembrane sodium and potassium movement, as suggested by Bara *et al.*[27].

Experimental observations to date support the view that magnesium and potassium metabolism are closely linked[28]. Concentrations of magnesium and potassium have been inversely correlated. The mechanism behind this interrelationship may be the magnesium dependency of the activity of Na^+, K^+ ATPase, a physical influence per se by low magnesium concentration on the cellular membrane leading to leakage of potassium, and/or interaction between magnesium and the secretion of aldosterone.

Magnesium deficiency in diabetes

Magnesium ion has a fundamental role in carbohydrate metabolism in general, and in the action of insulin in particular[29]. Magnesium is a cofactor in the glucose-transporting mechanism of the cell membrane and various enzymes in carbohydrate oxidation. Cellular magnesium seems to play an important role in glucose metabolism as it is a critical cofactor for the activities of various enzymes involved in glucose oxidation and may play a role in the release of insulin. Magnesium is involved at multiple levels in insulin secretion, binding and activity[29]. It is also involved in many phosphorylation reactions and is a cofactor for ATPase and adenylate cyclase enzymes. Magnesium deficiency has recently been proposed as a novel factor implicated in the pathogenesis of diabetic complications. Hypomagnesemia can be both a consequence and a cause of diabetic complications. Linkage between magnesium deficiency and insulin resistance, carbohydrate intolerance, accelerated atherosclerosis, dyslipidemia, hypertension and adverse outcomes in pregnancies complicating diabetes have been observed or postulated[30]. Recognizing the signs of diabetes-associated magnesium deficiency is important because the deficiency can occur long before it is reflected by serum values.

Diabetes mellitus has been suggested to be the most common metabolic disorder associated with magnesium deficiency, having 25 to 39% prevalence[12]. Hypomagnesemia in diabetes represents secondary magnesium depletion which requires more or less specific correction of the different perturbations of the control mechanisms of magnesium deficit that are involved with diabetes. The mechanism responsible for magnesium deficiency in patients with diabetes is not completely known. Osmotic diuresis clearly accounts for a portion of the magnesium loss. It is believed that glycosuria which accompanies the diabetic state, impairs renal tubular reabsorption of magnesium from the glomerular filtrate. Magnesium is reabsorbed principally in the proximal tubule (30%) and thick ascending loop of Henle (65%), with minimal resorption (1–5%) in the distal convulated tubule. Hypomagnesemia results specifically from a reduction in tubular absorption of magnesium, as recently suggested by Garland[31]. Renal magnesium handling may be modulated by glucose and insulin even in non-diabetic individuals, where the administration of insulin with or without glucose increases urinary magnesium excretion rate[32]. A rise in the urinary magnesium excretion rates in diabetic patients with increasing insulin dosage has been reported despite maintenance of serum levels, suggesting the effect of insulin on renal magnesium handling[33]. Dietary magnesium intake may also be a factor in deficiency, as the individuals do not consume the fully-recommended daily allowance for magnesium. Glucose itself is a crucial part of cellular ion homeostasis, increasing intracellular calcium and decreasing intracellular magnesium[34]. Recent evidences suggest that insulin can increase free magnesium entry into the cell[35]. Furthermore, in the state of insulin resistance, insulin-induced entry of magnesium is also impaired. Glycemic control in patients with type-2 diabetes, however, may not correct low magnesium concentration, suggesting that other factors may regulate magnesium levels in diabetic patients[36].

The existence of a close relationship between metabolic control and impaired magnesium balance was confirmed by Fujii *et al.*[37] who observed that a marked depletion in plasma and erythrocyte magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor diabetic control. The relationship between magnesium and glucose metabolism is supported by a recent epidemiological study showing that deficient magnesium intake is a risk factor for the development of type-2 diabetes independent of age, body mass index, alcohol intake and family history of diabetes[38].

The influence of magnesium on cell membrane ATPase activity and consequently on intracellular Ca^{2+}, Na^{+} and K^{+} metabolism may also play a role in diabetic complications. The cellular abnormalities of diabetes mellitus may be related to altered transmembrane transport systems. Most Na^{+} extrusion and K^{+} influx are dependent upon the Na^{+}, K^{+} pump whose biochemical expression is the ouabain-sensitive Na^{+}, K^{+} ATPase (ref. 39). Na^{+}, K^{+} ATPase necessary for maintaining intracellular potassium concentration, is a magnesium-dependent enzyme. Na^{+}, K^{+} ATPase activity has been reported low in various tissues of animals with streptozotocin-induced diabetes and in the erythrocytes of type-I diabetic patients[40]. It has been reported that this impaired enzyme activity plays a role in the pathogenesis of diabetic polyneuropathy[41].

Clinical and experimental studies have documented decreased Ca^{2+} ATPase activity and intracellular Ca^{2+} accumulation in human and experimental diabetes mellitus[42,43]. The ATP-fuelled, Mg^{2+}-dependent Ca^{2+} pump in the plasma membrane is involved in maintaining low intracellular Ca^{2+} concentration in intact cells, by pumping Ca^{2+} from the cytosolic component to the extracellular space[44].

Hypomagnesemia and diabetes

Studies in experimental animals demonstrated that magnesium supplementation could retard or prevent the induction of insulin resistance and diabetes mellitus, while a magnesium deficit can predispose to hyperglycemia[45]. Moles and McMullen[46] have shown that low plasma magnesium concentrations may contribute to insulin resistance. The relationship between intracellular magnesium and insulin action is also supported by negative correlation between the integrated insulin response after glucose loading and erythrocyte-free magnesium concentration. The results of the prospective study of DeValk *et al.*[47] provided the support for an association between plasma concentration and development of progression of retinopathy in insulin using patients; but whether the plasma magnesium concentration is a causative factor or a marker remains to be determined. McNair *et al.*[48] reported that diabetes-induced damage to the eyes is more likely to occur in magnesium-deficient patients with insulin dependent diabetes mellitus (IDDM) and suggested hypomagnesemia as a possible risk factor in the development and progress of diabetic retinopathy. In pregnant women with IDDM who are magnesium deficient, lack of magnesium may even account for the high rate of spontaneous abortion and birth defects associated with IDDM[49].

Recent data indicate that hypomagnesemia may be linked to the development of diabetic complications via reduction in the rate of inositol transport and subsequent intracellular depletion. Grafton and Baxter[50] have suggested that hypomagnesemia leads to reduction of inositol transport and subsequent inositol depletion that might enhance the development of diabetic complications. Despite the evident role of hypomagnesemia in the outcome of diabetic morbidity, little clinical emphasis has been placed on the long-term treatment of hypomagnesemia in diabetics.

Magnesium has been reported to be mainly intracellular, and its intracellular uptake is stimulated by insulin, although the cellular physiology is not fully understood. In healthy subjects, insulin has been shown to stimulate erythrocyte magnesium uptake[51]. Studies have demonstrated that insulin regulates the intracellular magnesium concentration by stimulating the plasma membrane ATPase pump[52]. Intracellular magnesium deficiency may be the consequence of insulin resistance, but may also worsen this condition. The studies done by Rosolova *et al.*[53] indicated that insulin-mediated glucose disposal was decreased in non-diabetic subjects designated as having a low plasma magnesium concentration, than subjects with a high magnesium concentration. They also proposed that the association between a low plasma magnesium concentration and insulin resistance is not primary but is related to abnormalities of other cations, for example, a low plasma calcium concentration. A study to explore further the link between magnesium deficiency and insulin resistance, hypertension and cardiovascular disease looked at the effect of diet lacking in magnesium (< 0.5 mmol/day) on insulin resistance in non-diabetics[54]. The result showed that diet-induced magnesium deficiency leads to decreased insulin sensitivity in lean non-diabetics. In addition, urinary thromboxane concentration increased after magnesium deficiency, again pointing towards hypomagnesemia as a common factor in insulin resistance and vascular disease.

Humphries *et al.*[55] reported a clear association between the lowest consumption of dietary magnesium and the highest degree of insulin resistance among non-diabetic subjects. Dominguez *et al.*[56] confirmed this observation, finding that among both normotensive and hypertensive subjects, a higher magnesium level corresponded to a greater degree of sensitivity to insulin. Lefebvre and Scheen[57], in their evaluation of the role of magnesium in glucose metabolism, concluded that magnesium deficiency results in impaired insulin secretion, while magnesium replacement restores insulin secretion. Furthermore, experimental magnesium deficiency reduces tissue sensitivity to insulin.

Insulin resistance is a common finding in elderly people. Moreover, insulin resistance per se has also been associated with low extracellular plasma and intracellular erythrocyte magnesium content. At the same time, a close relationship between insulin, glucose homeostasis and intracellular magnesium has also been demonstrated to occur. Studies have shown that insulin induces opposite changes in plasma and erythrocyte magnesium concentration in normal men and that dietary magnesium supple-

ments can improve both insulin response and action in aged, non-insulin-dependent diabetic patients[58]. Aging is also associated with an impaired glucose handling and a low intracellular magnesium concentration, probably the consequence of an insulin-resistant state. There are more complex interrelationships between intracellular magnesium deficiency and insulin action. In particular, intracellular magnesium deficiency impairs the function of many rate-limiting, magnesium-dependent glycolytic enzymes utilizing high-energy phosphate bonds. As recently reviewed by Jackson[59], an age-related reduction in the activity of numerous enzymes such as hexokinase type-II and phosphofructokinase seems to occur in magnesium deficiency.

Diabetes patients tend to have low magnesium levels. Double-blind research indicates that supplementing with magnesium overcomes this problem[35]. Magnesium leads to improved insulin production in elderly people with NIDDM[60]. Elders without diabetes can also produce more insulin because of magnesium supplements, according to some[61], but not all studies[62]. Insulin requirements are lower in people with IDDM, who are supplemented with magnesium. In a study in type-1 diabetic patients oral replacement with magnesium hydroxide at a dosage of 250 mg twice daily resulted in increased levels of magnesium in the skeletal muscle[63]. This was associated with decreased insulin requirements but no reduction in glycosylated hemoglobin level in diabetic patients.

In a double-blind, randomized crossover study, Paolisso and colleagues[61] investigated the effect of magnesium supplementation in elderly subjects with insulin resistance on the handling of glucose following an intravenous glucose load and an euglycemic hyperinsulinemic clamp procedure. Magnesium pidolate at 4.5 g per day (15.8 mmol/day) for four weeks significantly improved insulin action, oxidative-glucose metabolism, increased erythrocyte magnesium concentration and decreased erythrocyte membrane microviscosity.

Magnesium deficiency and oxidative stress

Diabetes mellitus has been shown to be a state of increased free radical activity and is associated with higher prevalence of atherosclerotic disease and cardiovascular mortality[64,65]. Lipid peroxidation of cellular structures, a consequence of free radical activity, is thought to play an important role in aging, atherosclerosis and late diabetic complications. By-products of lipid peroxidation are increased in diabetes mellitus[66,67]. Mechanisms that contribute to the formation of free radicals in diabetes mellitus may include nonenzymatic and auto-oxidative glycosylation, the levels of inflammatory mediators and the status of antioxidant defence.

In recent years there has been a growing interest in magnesium and its correlation with the development of various age-related diseases, viz. hypertension, diabetes mellitus, cardiovascular diseases, atherosclerosis, myocardial damage and cardiac arrhythmias through free radical oxidation of cellular components. There is a large volume of literature suggesting that magnesium deficit contributes to the ageing process and vulnerability to age-related diseases[68]. Mammalian tissues contain numerous defences against oxidative stress, some of which have been shown to be compromised during magnesium deficiency. Weglicki *et al.*[69] have proposed that during magnesium deficiency, natural antioxidant defences present in mammalian tissues against oxidative stress may be compromised. Our recent studies have also demonstrated that magnesium deficiency is associated with increased oxidative stress through reduction in plasma antioxidants and increased lipid peroxidation[70]. Free radical oxidation of cellular components is a well-established mechanism of cellular injury in many of the above-mentioned age-related diseases.

Early studies by ul Hassan and Lehninger[71] established the requirement of magnesium for the biosynthesis of ascorbic acid *in vitro* by rat liver microsomes. Ascorbate may recycle tocopherol from the relatively stable tocopherol radical at the lipid interface and also function as a key aqueous-phase antioxidant in its own right.

Glutathione (GSH), a thiol containing tripeptide is present in the plasma and intracellularly in the reduced state. It has antioxidant properties to inhibit free radical formation, and functions more generally as a redox buffer. GSH is also a cofactor for many enzymes such as glutathione peroxidase, which catalyses detoxification of intracellular peroxides. Recent evidences suggest that GSH may also be important in blood pressure and glucose homeostasis, consistent with the involvement of free radicals in both essential hypertension and diabetes mellitus[72]. Magnesium is an obligatory cofactor in the enzyme reaction of GSH synthesis and in all biosynthetic enzyme reactions involving ATPase, and magnesium deficiency has been reported to inhibit biosynthesis of GSH[73]. Hsu *et al.*[74] investigated the concentration of GSH in erythrocytes and other target tissues of magnesium-deficient, magnesium-repleted, and their respective pair-fed control animals. Their data clearly showed decreased magnesium levels in plasma and a reduction of GSH concentration in erythrocytes. Studies by Barbagallo *et al.*[75] have demonstrated that GSH acts *in vivo* and *in vitro* to enhance intracellular magnesium content. They observed significant and independent positive relationship *in vivo* among intracellular magnesium content, GSH/GSSG ratios and insulin disposal, suggesting the role of magnesium in mediating the effects of glutathione on peripheral insulin action.

Vitamin E has been proposed to be the major lipid-soluble, chain-breaking antioxidant which protects the biological membrane from lipid peroxidation. It is one of the most effective scavengers of free radicals, and recent

studies indicate that vitamin E administration offers significant protection against the pro-oxidant influence of magnesium deficiency and prevents the occurrence of enhanced heart post-ischemic injury following magnesium deficiency[76]. Moreover, a decrease in tissue vitamin E content following long-term magnesium deficiency in rats has been reported[77].

Magnesium deficiency and cardiovascular diseases

Magnesium may have some relationship to the pathogenesis of hypertension and atherogenesis, diseases often concomitant with diabetes mellitus. Several epidemiological studies have suggested a relationship between the magnesium content in drinking water or urinary magnesium excretion and hypertension or IHD[78,79]. Several authors showed that in hypertensive animals, a reduction in serum magnesium occurs and an inverse relationship between intracellular, ionized magnesium and diastolic pressure has been shown[80]. Resnick[81] has recently formulated the 'ionic hypothesis' through which he tried to unify the pathogenesis of morbid conditions which apparently represent different pathologic entities, e.g. type-2 diabetes mellitus and arterial hypertension. The author has hypothesized that at the onset of these pathologies there may be an altered ionic metabolism, which causes a reduction in the intracellular magnesium and increase in the intracellular calcium. All that, through a modification in the intracellular pH and in the balance of sodium, would cause the onset of hyperinsulinemia, insulin resistance and the phenomenon of systemic and renal vasoconstriction. Depletion of intracellular free magnesium in diabetes and hypertension may explain the frequent clinical association between these two conditions especially because all kinases and other ATP-related enzymes and channels regulating insulin action and vascular tone are magnesium-dependent.

The mechanisms by which magnesium deficiency may increase the blood pressure level have not been clearly investigated. Although the cellular concentration of magnesium falls only slightly in most tissues, secondary effects on other cell constituents are well recognized. These include loss of potassium and accumulation of calcium and sodium[82]. Numerous experimental and clinical data indicate that magnesium deficiency can induce pathophysical disorders in the cardiovascular system, such as vasospasm, increased vasoconstrictor activity, elevation in smooth muscle and cardiac intracellular calcium concentration[26], formation of oxygen radicals, pro-inflammatory agents and growth factors and changes in membrane permeability and transport[69]. This entire phenomenon may contribute to the modification of blood pressure level during magnesium deficiency.

Studies by Corica *et al.*[83], to evaluate the concentration of magnesium in patients with type-2 diabetes mellitus, both normotensive and hypertensive, confirmed the reduction of magnesium concentration in diabetics compared to healthy controls at plasma, erythrocyte and platelet levels. However, no significant difference was found with regard to plasma and erythrocyte magnesium, whereas platelet magnesium was significantly lower in diabetic hypertensive vs diabetic normotensive group. The mechanism which determines a reduction in the magnesium concentration, in particular the intracellular ones, seems to be unclear, but may involve the cell membrane and the mechanism concerning the transmembrane flux of magnesium. The data of Corica *et al.* seem to support Resnick's hypothesis, confirming the existence of impairment in the ionic homeostasis in diabetic patients, which seems to be accentuated by the coexistence of a hypertensive state.

Pathophysiologically, magnesium depletion can directly cause vasoconstriction and frank hypertension which can predispose to cardiac arrhythmias and sudden death, can increase platelet aggregation and thus the potential for *in situ* thrombosis, and can produce the pathologic lesions of atherosclerosis, all the above occurring clinically to an increased extent in diabetes[84,85]. Hence it can be suggested that cardiovascular consequences of diabetes may be at least partly due to deficient magnesium.

The possible role of magnesium in the development of macro- and microangiopathy in diabetes has been the subject of several studies. Seeling and Heggtveit[86] and Mather *et al.*[87] have suggested that magnesium can prevent atherosclerotic disease by counteracting the adverse effect of excessive intracellular calcium, retaining intracellular potassium and contributing both to stabilizing the plasma membrane and maintaining the integrity of subcellular structures. VanRoelen *et al.*[88] also confirmed the negative correlation between poor erythrocyte magnesium content and the severity of microangiopathy. The possibility that magnesium may play a role in the prevention of atherosclerosis is further supported by the finding that chronic magnesium administration decreases collagen and ADP-induced platelet aggregability in type-2 diabetic subjects. This implication of magnesium as an important factor in glucose metabolism might at least partially explain its postulated role in diabetic retinopathy and large-vessel disease. The pathophysiological sequence of events leading to cardiovascular injury and formation of lesions in animal models of magnesium deficiency remains unclear. The observations that antioxidants such as vitamin E are able to block the cardiovascular lesions to a significant degree suggest a role of free radicals in these diseases[89].

Several studies provide evidence that magnesium deficiency affects lipid metabolism. Animal experiments have shown that magnesium deficiency causes elevation of total cholesterol[90] or triacylglycerol[91] concentration in serum. Several short-term studies showed that a diet high

in magnesium was associated with lower cholesterol and triglyceride levels in patients with IHD[92,93]. Magnesium deficiency in rats has been reported to induce hyperlipidemia and affect plasma lipoprotein distribution and composition[94]. The relationship between hypertriglyceridemia and atherosclerosis remains obscure, but data suggest that the mechanism responsible for atherogenicity of the hypertriglyceremic state may be related to increased susceptibility to peroxidation[95]. Magnesium repletion has also been shown to be associated with reduction of serum cholesterol, LDL and total cholesterol/HDL-cholesterol ratio in hypomagnesemic, renal-transplant recipients[96].

Magnesium has had a suggested role in nearly every physiological system. Although magnesium supplementation is used for treatment of some cardiovascular disorders, the beneficial effects of magnesium replacement in preventing diabetic complications have not yet been proven in long-term studies. Some observations have suggested that chronic magnesium supplementation may be useful in the treatment of patients with diabetes, improving the glycemic control and preventing the development of chronic complications[97,98].

The American Diabetes Association[98] admits that 'strong associations... between magnesium deficiency and insulin resistance', but does not admit that magnesium deficiency is a risk factor. Many doctors of natural medicine, however, recommend that diabetics with normal kidney function should be supplemented with 300–400 mg of magnesium per day.

Magnesium is a critically important nutrient and a useful therapeutic agent. Depletion of magnesium and hypomagnesemia are relatively common but difficult to diagnose and have been implicated in several disorders. In conclusion, it may be proposed that diabetes and other age-related disorders are prone to magnesium deficiency, which may further aggravate the disease through increased oxidative stress, dyslipidemia, ionic alterations and impaired ATPase activity. Further studies will continue to define the clinical scope of therapy with magnesium.

Conclusion

It may thus be proposed that magnesium deficiency may be a contributing factor to the clinical diseases associated with increased oxidative stress. The study indicates that the mechanism responsible for oxidative stress and ionic alterations in diabetes may partly be mediated through magnesium deficiency. The study also has a viewpoint that magnesium deficiency produces deleterious effect on glucose handling, which seems to be further aggravated by hyperglycemia. Whether the broader range of magnesium-related abnormalities such as oxidative stress, dyslipidemia, ionic imbalance and impaired ATPase activity can be reversed with repletion of magnesium requires a randomized clinical trial to determine.

In conclusion, it may be prudent to consider magnesium deficiency as a contributing factor in many diabetic complications and in the exacerbation of the disease itself. One of the most abundant of the earth's metallic elements and quantitatively the fourth most plentiful cation in human beings, magnesium may have wider metabolic implications than suspected hitherto.

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