

Magnesium and ischemic heart disease: a review of epidemiological, experimental, and clinical evidences

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Abstract. 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.

Key words: magnesium, ischemic heart disease, diabetes mellitus, hypertension, hyperlipidemia

Magnesium (Mg) is the second most abundant intracellular cation (next to potassium) and the fourth most abundant cation in the body. Mg is a co-factor for more than 300 cellular enzymes involved in cellular energy production and membrane functions. In addition, ionized magnesium (Mg^{2+}) has numerous structural functions, stabilizes cell membranes, regulates cell growth and reproduction and can function as a Ca^{2+} antagonist, thereby regulating muscle contraction, relaxation and neurotransmitter release. As a consequence of these biochemical activities, Mg plays a pivotal role in control of cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure, among other functions. Recently, improved methods for assessing Mg status, including ionized Mg, in the clinic have contributed to further understanding of Mg regulation in health and disease.

Mg deficiency is now considered to contribute to many diseases, and the role for Mg as a therapeutic

agent is being tested in numerous clinical trials. This review focuses on clinical conditions in which Mg deficiency has been implicated in a pathophysiological role in ischemic heart disease through its effect on diabetes mellitus, hypertension, and hyperlipidemia.

Magnesium and ischemic heart disease in epidemiology

Kobayashi [1] first noted that the nature of drinking water might influence death rates from cardiovascular disease; the incidence of strokes was high in areas with acid (soft) water. Schroeder surveyed the hardness of drinking water in each state of the United States, and correlated the death rates with state-wide water hardness or softness [2]. He also found that death rates from cardiovascular diseases were significantly higher in states with soft water than in states with hard water [3, 4]. In Finland, which has a

very high death rate from ischemic heart disease, there is a clear relationship with the amount of Mg in the soil [5]. Moreover, in Finland, which has the highest cardiovascular death rate in Europe, the dietary supply of Mg in 1963 had decreased to a third of the intake common in 1911 [6]. Karppanen depicted the steep rise in ischemic heart disease that coincides with increasing dietary Ca/Mg ratios [7]. The incidence of sudden cardiac death among the population of the Media Valle del Serchio area (Tuscany, Italy), composed of a population of 35,000, was found to be twice that of the European average. Research was carried out on the physical and chemical properties of drinking water in the same area, and this revealed a very low total hardness due to the paucity of Mg salts [8]. Rubenowitz examined the relationship between death from acute myocardial infarction and the level of Mg in drinking water using mortality registers and a case-control design. The odds ratios for death from acute myocardial infarction in the groups were inversely related to the amount of Mg in drinking water. For the group with the highest levels of Mg in drinking water, the odds ratio adjusted for age and Ca level was 0.65 [9]. According to the data on the hardness of drinking water collected from 27 municipalities in Sweden, where the drinking water quality had remained unchanged for more than 20 years, mortality caused by ischemic heart disease was inversely related to the Mg content [10]. Gartside reported that alcohol intake, dietary riboflavin, dietary iron, serum Mg, leisure time exercise, habitual physical activity, and female gender were independently, significantly, and inversely associated with coronary heart and vascular disease deaths and hospitalizations [11].

By contrast, in Japan, with its low cardiac death rate, the daily Mg intake was cited as 560 mg [12, 13]. We have described that low blood concentrations of Mg^{2+} are recognized as quite common in patients with AMI who were admitted to CCU in Japan [14]. However, as we failed to substantiate a relationship between blood Mg^{2+} level, water hardness and age-adjusted morbidity, we could not clarify whether this issue is a cause or a result of ischemic heart disease [14]. Miyake and Iki reported that water hardness is not preventive against mortality from coronary heart disease in Japan [15]. They described how such a preventive effect might not have been detected because of the lower levels and narrower range of water hardness in Japan, compared with those in Europe and the United States [15].

Those who had done or evaluated experimental work that showed Mg to be protective and excess Ca harmful in experimental cardiomyopathies or soft-

tissue calcification found their data suggested that the higher content of Mg might protect the myocardial cell against damage caused by ischemia and improve its ability to resist the effects of cardiotoxic agents [16-18]. Moreover, there are many experimental studies that showed Mg to be protective against myocardial ischemia. It has been shown to: a) reduce the intracellular calcium [19, 20] considered to be a central mechanism in ischemic myocardial damage [21]; b) dilate coronary arteries and have good hemodynamic effects [22, 23]; c) reduce total peripheral resistance [23, 24]; and d) inhibit platelet function, possibly by an effect on prostacyclin secretion [25, 26]. It is possible that increased intake of dietary Mg can offer protection against cardiovascular deaths.

In addition, 400 high risk individuals were asked to volunteer either for a Mg-rich diet or for a usual diet in a randomized fashion to study the effects of supplementation of Mg [27]. Total mortality and sudden deaths in the group with the Mg-rich diet were significantly less than in a group with the usual diet [27]. It is possible that an increased intake of dietary Mg in association with the general effects of a nutritious diet can offer protection against cardiovascular death.

Magnesium and diabetes mellitus

According to Durlach [28], diabetes mellitus is the most common pathological state in which secondary Mg deficiency occurs and Mg metabolism abnormalities vary according to the multiple clinical forms of diabetes. Plasma Mg levels are correlated mainly with the severity of the diabetic state, glucose disposal and endogenous insulin secretion. Various mechanisms are involved in the induction of Mg depletion in diabetes mellitus, i.e. insulin and epinephrine secretion, modifications of the vitamin D metabolism, decrease of blood pressure, vitamin B6 and taurine levels, increase of vitamin B5, C and glutathione turnover, treatment with high levels of insulin and biguanides. Furthermore, as potassium depletion in diabetes mellitus is well known, some of its mechanisms are concomitant to those of Mg depletion. Retinopathy and microangiopathy are correlated with the drop of plasma and red blood cell Mg [28].

Mg deficiency and diabetes mellitus

According to Takita and associates, contents of zinc and Mg in kidney, testis, and fatty tissue were lowered significantly in spontaneous type 2 diabetic (non-insulin-dependent) model rats (Goto-Kakizaki

rats) [29]. Zinc in liver and Mg in lung were also lowered [29]. In addition, Takaya referred to intracellular Mg and insulin resistance in patients with type 2 diabetes [30]. An inverse association was observed between the plasma Mg and insulin resistance due to intracellular changes. The suppressed intracellular Mg concentration may result in defective tyrosine-kinase activity and modify insulin sensitivity by influencing receptor activity after binding or by influencing intracellular signaling and processing. Intracellular Mg deficiency may affect the development of insulin resistance and alter the glucose entry into the cell [30].

Furthermore, many studies have shown that both mean plasma and intracellular free Mg levels are lower in patients with diabetes than in the general population. Resnick and associates suggest that extracellular and intracellular Mg deficiency is typical in chronic, stable, mild type 2 diabetes and may be a strong predisposing factor for the development of the excess cardiovascular morbidity associated with diabetes [31]. These investigators showed that the levels of serum Mg^{2+} and erythrocyte intracellular free Mg were significantly lower in untreated patients with type 2 diabetes and mild hyperglycemia than they were in healthy control subjects, while serum total Mg was not reduced. Mg 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 Mg accumulation. In diabetes mellitus, it is suggested that low intracellular Mg levels result from both increased urinary losses and insulin resistance. The extent to which such a low intracellular Mg content contributes to the development of macro- and microangiopathy remains to be established.

A reduced intracellular Mg content might contribute to the impaired insulin response and action which occurs in type 2 diabetes mellitus [32]. The plasma Mg concentrations of 582 unselected diabetic outpatients and 140 control subjects were measured by Mather and associates [33]. Plasma Mg correlated best with clinic blood glucose concentration and other significant associations were observed with glycosuria, age, sex, insulin therapy and biguanide therapy.

From the view point of epidemiology, Kao assessed the risk for type 2 diabetes associated with low serum Mg level and low dietary Mg intake in a cohort of non-diabetic middle-aged adults ($n = 12,128$) from the Atherosclerosis Risk in Communities Study, during 6 years of follow-up. Among white participants, low serum Mg level was a strong and independent predictor of incident type 2 diabe-

tes [34]. Moreover, all eligible deaths from diabetes (6,781 cases) of Taiwan residents from 1990 through 1994 were compared with deaths from other causes (6,781 controls), and the levels of Mg in the drinking water of these residents was determined by Yang and associates. There seemed to be a significant protective effect of Mg intake from drinking water on the risk of dying from diabetes mellitus [35]. Surprisingly, moderate but clinically obtainable improvement of metabolic control even in patients even with type 1 diabetes seemed to reduce the loss of Mg, increased serum HDL cholesterol, and decreased serum triglycerides [36].

Mg supplementation and diabetes mellitus

Soltani reported that oral Mg administration prevented vascular complications in STZ-diabetic rats [37]. Their study was designed to determine whether chronic Mg sulfate administration could prevent vascular complications of STZ-induced diabetes in rats. Mean arterial blood pressure in diabetics was significantly higher than control and Mg-treated rats. Baseline perfusion pressure of the diabetic group was significantly higher than control and Mg-treated groups with intact and denuded endothelium. Mg sulfate treatment decreased mean perfusion pressure of the mesenteric vascular bed in intact and denuded endothelium in comparison with non-treated diabetic rats. There was a significant increase in passive tension in the aorta of diabetic rats compared to control and Mg-treated rats. They concluded that Mg could control STZ-induced diabetes and prevent its vascular complications [37]. Rosolová evaluated the relationship between the plasma Mg concentration and steady-state plasma insulin and glucose concentrations at the end of a 3-hour infusion of octreotide, insulin, and glucose in healthy non-diabetic subjects. Variations in the plasma Mg concentration had a relatively modest but significant effect on insulin-mediated glucose disposal in healthy subjects, with lower plasma Mg concentrations associated with increased insulin resistance [38]. In addition, because insulin resistance may be associated with altered blood pressure, they also measured insulin sensitivity using an intravenous glucose tolerance test. They concluded that dietary-induced Mg deficiency 1) increases thromboxane urinary concentration and 2) enhances angiotensin-induced aldosterone synthesis. These effects are associated with a decrease in insulin action, suggesting that Mg deficiency may be a common factor associated with insulin resistance and

vascular disease [39]. Moreover, Mg supplements improve diabetic state. Eight elderly, moderately obese, type 2 diabetic subjects were treated with either Mg supplementation (3 g/day) to the diet or placebo. Dietary Mg supplementation vs placebo produced a slight but significant decrease in basal plasma glucose and an increase in acute insulin response after iv glucose [40]. Furthermore, insulin response and action were studied before and after chronic Mg supplementation (2 g/day) to diet in 8 aged non-insulin-dependent diabetes mellitus subjects. Net increase in acute insulin response, glucose disappearance rate after glucose pulse, and glucose infusion rate were significantly and positively correlated to the net increase in erythrocyte Mg content calculated after chronic Mg supplementation to diet [41]. Yokota referred to clinical efficacy of Mg supplementation in patients with type 2 diabetes. In 9 mild type 2 diabetic patients with stable glycemic control, water from a salt lake with a high natural Mg content (7.1%) (MAG21) was used for supplementation, after dilution with distilled water and was given for 30 days. Fasting serum immunoreactive insulin level decreased significantly, as did HOMA squareR. Furthermore, there was also a marked decrease of the mean triglyceride level after supplementation, and the patients with hypertension showed a significant reduction of their blood pressure [42]. Farvid reported that a combination of vitamin and mineral supplementation which included Mg and zinc had significant effects in decreasing blood pressure and serum malondialdehyde, and in increasing serum potassium in type 2 diabetic patients [43].

Diabetic treatment and Mg metabolism

Some diabetic treatments appear to improve Mg metabolism. Ewis showed a state of low levels of Mg and glutathione in both blood and liver of the diabetic male Wistar rats. Treatment with atenolol alone did not change these levels significantly, however administration of metformin or atenolol/metformin significantly increased the glutathione levels in both liver and blood, and returned the liver Mg content back to normal values [44]. Concentrations as low as 300 nM of pioglitazone, which is one of a new class of oral agents developed as antidiabetic agents which can increase insulin sensitivity, markedly increased the free Mg concentration in the adipocytes. Pioglitazone action was selective for Mg since intracellular free Ca concentration was not altered [45].

Magnesium and hypertension

Hypertension can lead to arterial damage. The mechanism of the morphological changes produced in the blood vessels by Mg deficiency is not clear. As Mg has a direct effect upon the relaxation capability of vascular smooth muscle cells [46], the changes almost certainly contribute to the increased arterial resistance by Mg deficiency. A contribution by vasoconstriction also seems likely, particularly since Mg deficiency (experimental) is usually associated with decreased serum concentrations of Mg and K, while in soft tissues there is a decreased content of Mg and K and increased content of Ca and Na. Increased plasma renin activity, blood serotonin level, and urinary aldosterone excretion have also been noted in Mg deficiency—all factors that also increase arterial resistance.

Mg, Na, K, Ca and blood pressure

Both cellular and whole body Na: K ratios are crucial to the maintenance of normal blood pressure. When sodium becomes too high and K too low, it causes hypertension. At the cellular level, proper function of the Na-K pump maintains K at a high intracellular concentration and Na at a high extracellular concentration. An additional requirement for balanced Na: K ratios is adequate Mg function. At the cellular level, Mg is required for the proper function of the Na-K pump which requires Mg-ATP as a source of energy and is responsible for maintaining the separation of Na and K across cellular membranes. In addition, Ca plays a central role in excitation-contraction coupling and this ion competes with Mg for binding sites on the membrane of the vascular smooth muscle cell. Like the saturation with K, a low Mg status also impairs proper Ca metabolism, affecting blood pressure [47].

Hypertension occurs when cellular Na: K ratios become too high, a consequence of a high sodium, low potassium diet or, indirectly, through a Mg deficient state which causes a pseudo K deficit. Likewise, Mg deficiency alters Ca metabolism and creates high intracellular Ca, low serum Ca, and low urinary Ca states even when Ca intake is adequate. High intracellular Ca and high cellular Na: K ratio both occur when cellular Mg becomes too low and the Mg-ATP driven Na-K pump and Ca pump become functionally impaired. High intracellular Ca also lead to hypertension, an indirect result of low Mg status [48].

In fact, aortic smooth muscle cells from SHR are characterized by markedly elevated intracellular Ca

and decreased intracellular Mg content compared with normotensive cells [49]. The increased Ca/Mg ratio in hypertensive cells may be a pathogenic factor for the development of arteriosclerosis and hypertension [50]. In addition, Pamnani reported that increased dietary K and Mg attenuate experimental volume dependent hypertension, possibly through endogenous Na-K pump inhibitor [51].

Mg, neurohumoral factors and blood pressure

Mg influences vasoconstriction via its influence on some neurohumoral factors [52]. Isolated coronary arteries from dogs were incubated in Krebs-Ringer bicarbonate isolation and exposed to normal, high, and low concentrations of Mg in the medium by Turlapaty and associates [53]. Sudden withdrawal of Mg from the medium increased, whereas high concentrations of Mg decreased, the basal tension of the arteries. The absence of magnesium in the medium significantly potentiated the contractile responses of both small and large coronary arteries to norepinephrine, acetylcholine, serotonin, angiotensin, and potassium [53].

Ca stimulates renin release and activity [54]. Low renin is usually associated with low intracellular Ca and high renin with high intracellular Ca [55, 56]. Mg deficiency promotes renin activity and low serum total Mg levels are associated with high renin hypertensives [54].

Mg modulates endothelium-dependent vasodilation in intact blood vessels as a change in the intracellular Mg concentration has an effect on NO release [51]. In addition, Maier reported that low Mg concentrations reversibly inhibit endothelial proliferation, and this event correlates with a marked down-regulation of the levels of CDC25B [57]. 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. They also reported 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, for the increased adhesion of monocytoid U937 cells to the endothelial cells grown in low Mg. Furthermore, endothelial migratory response is severely impaired. By cDNA array, they 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 [57]. They concluded that a direct role of low Mg in promoting endothelial dysfunction by gen-

erating a pro-inflammatory, pro-thrombotic and pro-atherogenic environment that could play a role in the pathogenesis cardiovascular disease [57].

Mg deficiency, Mg supplementation and hypertension

Analysis of the first National Health and Nutrition Examination Survey (NHANES) in 1984 revealed that a dietary pattern low in mineral intake, specifically Ca, K, and Mg, was associated with hypertension in American adults. Using more recent survey data from NHANES III and NHANES IV, Townsend re-examined the validity of this relationship. Blood pressure and nutrient intake data from 10,033 adult participants in NHANES III and 2311 adults in NHANES IV revealed findings similar to those of the earlier analysis, demonstrating that the association between inadequate mineral consumption and higher blood pressure was valid and persisted over two decades [58]. Prevalence of high blood pressure is greater for northern than southern Chinese. Relationships of north-south blood pressure differences with multiple dietary factors were investigated by International Study on Macronutrients and Blood Pressure (INTERMAP) [59]. Average systolic/diastolic pressure levels were 7.4/6.9 mmHg higher for northern than southern participants. Southern participants had lower body mass index, Na intake, Na/K ratio, and higher intake of Ca, Mg, phosphorus, and vitamins A and C.

According to Rylander [60], subjects with borderline hypertension were recruited and consumed 1) a water low in minerals, 2) Mg enriched water or 3) natural mineral water, in a random, double blind fashion during four weeks. Among persons with an initial low excretion of Mg or Ca in the urine, the urinary excretion of Mg was increased in the groups consuming the two waters containing magnesium after 4 weeks. A significant decrease in blood pressure was found in the group consuming mineral water at 2 and 4 weeks. They concluded that minerals taken in water are significant for the body burden and that an intake of mineral water among persons with a low urinary excretion of Mg or Ca may decrease the blood pressure [60]. Whang reported on the prevalence of hypomagnesemia (4.5%) and hypokalemia (17%) in 1,000 ambulatory hypertensive patients under treatment at the VA Medical Center, Oklahoma City [61]. The hypomagnesemic group required a greater number of antihypertensive medications than the nonhypomagnesemic patients to maintain their blood pressure in the acceptable range [61]. Salem reported that 1 g of Mg oxide for 1

month given to 21 hypertensive subjects resulted in significant decreases in mean arterial pressure [62]. Rosanoff also found that Mg supplements of 20 mmol per day or more will lower untreated hypertensive patients who are not Mg repleted [48].

Magnesium and hyperlipidemia

An important characteristic of hyperlipidemia associated with Mg deficiency is accumulation of triglyceride-rich lipoproteins and a decrease in the concentration of HDL [63]. The increase in triglyceride-rich lipoproteins is associated with a significant increase in the plasma apo B concentration, while the decrease in HDL is associated with a decrease in the plasma apo E and apo A1 concentrations. Moreover, triglyceride-rich lipoproteins isolated from Mg deficit rats were more susceptible to *ex vivo* oxidation with copper than lipoproteins isolated from control animals [64, 65]. As lipoprotein oxidation in the early stage of atherosclerosis, oxidative modifications of lipoproteins could play a significant role in the pathogenesis of vascular lesions following Mg deficiency [66, 67].

Mg, other electrolytes, and blood pressure

Regarding dietary fat and Mg balance, evidence was obtained early on that diets rich in fat interfere with Mg absorption. In 1918, Sawyer performed metabolic balance studies with 2 boys, 5 and 8 years of age, in which he explored the effects of fat intake on retention of Ca and Mg. Even though their Mg and Ca intakes were lower than in their normal diet, increasing the fat intake resulted in their excreting more of the divalent cations in both feces and urine.

Bersohn reported that the lower serum cholesterol and slightly higher Mg levels found in Bantus compared to white South Africans, correlated with the lower incidence of arteriosclerosis and the higher dietary intake of Mg of the Bantus [68, 69]. In an Australian study comparing serum cholesterol and Mg levels in several groups of aborigines and Europeans, Charnock confirmed the lower serum cholesterol levels of the aborigines (who have a low incidence of cardiovascular disease) than of the Europeans and found significant differences between serum Mg levels of the aborigines (1.7 mEq/L) and the Australians living in Adelaide (1.2 mEq/L) [70]. In addition, Nath reported that high serum cholesterol levels (288 mg/100 mL) and low serum Mg levels (1.5 mEq/L) were seen in patients with acute myocardial infarction, as compared with the average levels in controls and in old myocardial

infarction cases [71]. Rangam found that among 44 patients with hypercholesterolemia, 80% had hypomagnesemia [72].

Recently, Guerrero-Romero performed a cross-sectional population-based study to compare 192 individuals with metabolic syndrome and 384 disorder-free control subjects, matched by age and gender [73]. Low serum Mg levels were identified in 126 (65.6%) and 19 (4.9%) individuals with and without metabolic syndromes. The mean serum Mg level among subjects with metabolic syndromes was 1.8 ± 0.3 mg/dL, and among control subjects 2.2 ± 0.2 mg/dL. There was a strong independent relationship between low serum Mg levels and metabolic syndromes (odds ratio (OR) = 6.8, CI(95%) 4.2-10.9). Among the components of metabolic syndromes, dyslipidemia (OR 2.8, CI(95%) 1.3-2.9) and hypertension (OR 1.9, CI(95%) 1.4-2.8) were strongly related to low serum Mg levels [73].

Mg deficiency, Mg supplementation and hyperlipidemia

Some investigators have attempted to determine whether high serum cholesterol levels correlated with low Mg levels in patients with cardiovascular disease, following clinical reports that parenteral Mg administration was of value in treating patients with ischemic heart disease. Malkiel-Shapiro first reported lowering β -lipoproteins in patients with coronary insufficiency, with the use of intramuscular MgSO_4 begun at the time of an acute attack of coronary thrombosis or during acute coronary insufficiency [74]. They also found that patients with more advanced disease seemed to have the most striking improvement.

In addition, Bunce reported that increasing the Mg intake from 80 to 180 ppm, in dogs fed 20%-animal-fat diets, prevented the aortic lesions seen in dogs on the lower Mg intake, but allowed for a slight further rise in serum cholesterol [75, 76]. Nakamura also showed that the long-term feeding of 192 mg/100 g of Mg to rats on this atherogenic diet produced an early increase in serum lipids that fell only gradually within the year-long observation, but a significant decrease in arterial lipid deposition was evident within 2 months on the Mg-supplemented diet [77, 78]. Booyne demonstrated that supplementation of diets with maize meal, which has a high Mg content and interferes with fat absorption, raised serum Mg and lowered serum cholesterol levels of hyperlipemic whites [79].

A randomized double-blind, placebo-controlled, clinical trial, lasting 12 months was carried out by

Schuitemaker to assess the efficacy and clinical effectiveness of Mg-pyridoxal-5'-phosphate-glutamate (MPPG) in the treatment of clinical-chemical risk factors for cardiovascular disease [80]. No statistically significant differences in the total cholesterol was found between the MPPG group and the placebo group. The same was demonstrated for the other clinical-chemical values, except for LDL-cholesterol (effectiveness, $P = 0.04$). Evans examined the prophylactic and therapeutic effects of chelation liquid (CHL) using subcutaneous 300 mg EDTA + 500 mg Mg sulphate ($MgSO_4$) injections in rabbits which were fed a 1% cholesterol-supplemented diet [81]. Although the level of cholesterol and triglyceride were not significantly different in the two groups, the serum Ca concentration and the percentage of the area of aortic specimen occupied by atheroma were significantly lower in the CHL treated rabbits as compared to controls. Recently, Corica evaluated the effects of oral Mg supplementation on plasma lipid concentrations in patients with type 2 diabetes mellitus and clarified that chronic Mg supplementation produced a significant reduction of plasma cholesterol and LDL cholesterol, and an increase of HDL cholesterol [82].

Clinical trials using Mg in patients with acute myocardial infarction

Effects of Mg administration on the prognosis of patients with acute myocardial infarction (AMI) are controversial. Meta-analysis of previous relatively small clinical trials, which compared intravenous Mg with placebo in AMI patients, demonstrated that Mg reduced in-hospital mortality. This was mainly caused by reducing the incidence of serious arrhythmias and left ventricular heart failure [83, 84]. In contrast, when Shechter reported intravenous Mg administration reduced in-hospital mortality, the result was mostly due to hemodynamic factors [85].

However, the mortality within 1 month after the onset of AMI was significantly reduced by Mg administration in the LIMIT-2 [86], whereas ISIS-4 [87] and MAGIC [88] failed to corroborate that. Actually, in our previous study [89] we observed a significantly lower blood Mg^{2+} level in AMI patients and a significantly reduced MMP-1 and IL-6 release in the patients given $MgSO_4$. Mg administration may be beneficial in patients with really profound hypomagnesemia.

Conclusion

As described before, Mg plays an essential role in a wide range of fundamental cellular reactions in patients with ischemic heart disease. Hence, it is not surprising that deficiency in the organism or disturbances of Mg homeostasis may lead to serious biochemical or symptomatic changes. Especially, many epidemiological, experimental, and clinical studies support a pathological role for Mg in the etiology and development of diabetes mellitus, hypertension, and hyperlipidemia. Furthermore, the therapeutic value of Mg in the management of coronary risk factors and acute phase of myocardial infarction has been clarified. Experimental and clinical evidence support the importance of Mg deficiency in the development and maintenance of atherosclerosis. Dietary Mg supplementation should be considered as a preventive element in atherosclerosis.

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