CARDIOVASCULAR RISK FACTORS AND MAGNESIUM : RELATIONSHIPS TO ATHEROSCLEROSIS, HYPERTENSION AND ISCHAEMIC HEART DISEASE

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Gazi Medical Journal 6 : 95-103, 1995

SUMMARY : *A great deal of interest has recently been focused upon the biochemical and physiological roles of magnesium in cellular and cardiovascular systems of the body. Magnesium in coronary artery disease is reviewed with regard to its role in the pathogenesis of arteriosclerosis, coronary spasm, myocardial function, acute myocardial infarction, platelet aggregation, and ventricular arrhythmias. The role of magnesium is also discussed in endothelium-dependent responses and in the pathogenesis of hypertension.*

Key Words : *Magnesium, Hypertension, Atherosclerosis, Endothelium-Dependent Relaxing Factor, Ischaemic Heart Disease, Arrhythmia, Vascular Smooth Muscle.*

Basic Biochemistry and Physiology of Magnesium

Approximately 21-28 g of magnesium, 60 % of which is a relatively nonexchangeable component of bone, is found in the adult body of man. Cells contain about 38 % of the total Mg in the body: 1-2 % resides in the extracellular component. Approximately 30-35 % of the Mg in plasma is thought to be bound nonspecifically to proteins (22). With a normal diet, 30-40 % of the ingested magnesium is absorbed via the jejunum and ileum. Under normal circumstances, the kidney is the prime regulator of Mg balance in the body (44).

Roles of Mg in Cell Metabolism

Mg catalyzes or activates more than 325 enzymes in the body and is pivotal in the transfer, storage, and utilization of energy (6). It activates phosphate groups and reactions that involve ATP. Mg can cause a conformational change during catalytic process (e.g. Na-K ATPase), by promoting aggregation of multienzyme complexes (e.g. aldehyde dehydrogenase) or by a mixture of mechanism (e.g. F1-ATPase) (25). Within the cell nucleus, Mg regulates DNA and RNA synthesis and plays a vital role in regulating cell growth, reproduction and membrane structure (1,57). The role of Mg in regulating cell membrane permeability, transmembrane electrolyte flux and cell adhesion is becoming widely accepted (10,29).

Recent studies reveal that the magnesium concentration in many mammalian cell types ranges between 0.1 and 1.0 mM (6,29).

Physiological Roles of Mg

As a consequence of its numerous biochemical cellular activities, Mg plays a pivotal role in control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vasomotor tone, blood pressure and/or

peripheral blood flow (1,3,4).

It has been realised that intracellular free Mg+2 ([Mg+2]ı) is lower than previously suspected and that several systems have Km values for Mg within this range. This opens the possibility that [Mg+2]ı may vary physiologically and might be a physiological modulator. This suggestion has been strengthened by the discovery of specific Mg transport systems in cells, several of which are regulated hormonally. Because Mg is an essential component in the coupling of cell surface receptors (e.g.ß-adrenoceptors) to G proteins, second messenger systems are attractive candidates for sites of Mg action (61).

Mg can modulate Ca action in several ways: Mg blocks entry of Ca via the receptor operated channels of vascular smooth muscle cells; Mg modulates Ca binding and release from the sarcoplasmic reticulum; Mg competes with Ca over nonspecific binding sites on the plasma membrane; Mg can block the slow Ca channels; Mg can act to maintain low resting levels of Ca and trigger muscle contraction and relaxation (55).

At cell membranes, internal Mg can regulate ion flux through voltage-gated, acetylcholine-activated, Ca-activated and ATP-activated K channels (60).

Epidemiology Of Ischaemic Heart Disease

Evidence has accumulated to indicate that electrolyte disturbances may induce fatal arrhythmias, elevate blood pressure and possibly blood lipid levels, and even produce coronary spasms. Therefore, electrolyte disturbances may have important implications in the present high prevalence of ischaemic heart disease (IHD). The negative correlation between IHD and the content of magnesium in the water is especially consistent (30). Residents of soft water areas with high death rates from IHD have lower concentrations of magnesium in the heart and in the coronary arteries than residents of hard water areas (20). Moreover, a diminished level of myocardial magnesium has been found after sudden death from IHD (31). So far, of the minerals that are deficient in soft water, magnesium is the only element that has found to be lowered in the cardiac muscle of victims of sudden death from IHD (56). The ratio of calcium to magnesium in the diet might be important in determining deaths rates due to IHD (30). Later epidemiological studies indicate that magnesium in hard water primarily protects against sudden deaths but not necessarily against deaths due to chronic forms of ischaemic heart disease (2).

Haemodynamic Effects of Mg

When magnesium is given intravenously as a slow bolus or short infusion in sufficient amount to raise serum [Mg+2] about twofold, flushing and a sensation of cutaneous warmth occur. Peripheral resistance falls by 20-35 % with a compensatory rise of around 25 % in cardiac index. A slight fall in blood pressure and rise in heart rate may be seen. The haemodynamic response is similar in normal subjects and untreated hypertensives and in men with coronary artery disease (40,63).

When $MgSO_4$ was infused to normal subjects a 60 % increase in urinary excretion of 6-keto-$PGF_{1\alpha}$, the stable metabolite of prostacyclin, has been found. Pre-treatment with either ibuprofen or indomethacine abolished both the rise in 6-keto-$PGF_{1\alpha}$ output and the blood pressure changes in response to infused magnesium (19). It was shown that infusion of prostacyclin and of magnesium elicit closely similar responses (14). In addition, concentrations of magnesium producing a haemodynamic effect in vivo stimulate the release of prostacyclin from human endothelial cells in vitro (58).

Other mechanisms regulating vascular tone may also be modified by magnesium, however, it has been shown that magnesium competes with calcium to inhibit both the production of endothelium-derived relaxing factor (EDRF) and the contraction of vascular smooth muscle in bovine pulmonary artery and vein (26). Similar findings were also shown in canine coronary and feline middle cerebral arteries (34,52). Recent evidences identify that EDRF requires calcium for its synthesis in (or perhaps release by) vascular endothelium (43). External magnesium is also required for endothelium dependent relaxation to occur in canine coronary arteries (8).

Altura et al. have shown that magnesium inhibits basal, myogenic, and hormone-induced contraction in vascular smooth muscle. Antagonism by magnesium of vascular calcium flux is seen at leak, voltage-operated and receptor-operated calcium channels and appears to occur in

all vascular beds, in contrast to the organic calcium channel blockers such as the dihydropyridines and verapamil which show some vascular selectivity (9). The vasodilator action of magnesium has been shown to be competitively inhibited by calcium in man by forearm plethysmography (24).

Effects of Mg on Coronary and Peripheral Circulation

Segmental coronary artery spasm can frequently be demonstrated angiographically in patients with recent myocardial infarction and may be a trigger to acute thrombotic occlusion (37,63). Magnesium competes with calcium to inhibit contractility of coronary arteries, as with other vascular smooth muscle (9). Extracellular magnesium is necessary for endothelium-dependent relaxation in coronary arteries (8) and in vitro withdrawal of magnesium both increases coronary artery tone and potentiates the contractile response to angiotensin, 5-HT, noradrenaline, acetylcholine and potassium (56).

Kimura et al. indicated that pharmacological concentrations of magnesium can relieve spasm in human coronary arteries in vitro (32). Although serum [Mg+2] is normal, Goto et al. have reported that magnesium depletion can be demonstrated in patients with variant angina, in whom myocardial ischaemia occurs episodically at rest or on exercise as a result of coronary spasm, by a significantly increased magnesium retention relative to controls following an intravenous magnesium load (28). In a separate placebo-controlled study intravenous magnesium sulphate suppressed exercise-induced vasospastic angina in patients with the variant form but was without therapeutic effect in patients with stable effort angina due to fixed coronary stenoses (35). Patients with a history of angina on autopsy exhibit severe cardiac deficits in Mg, whereas patients without a history of angina appear to exhibit a near-normal myocardial Mg content (31).

Chadda et al. reported the effects of low magnesium diet in dogs. After 100 days, the dogs developed ECG changes of coronary artery spasm when they were given ergonovine and several dogs died suddenly, apparently from an ischaemic episode with ventricular fibrillation (19). A possible association between cerebral spinal fluid Mg and brain Mg and the aetiology of strokes has been reported (5).

Hypomagnesaemia has been shown to induce sharp increases in tension development in a variety of mammalian blood vessels, including coronary blood vessels. Peripheral vessels which do not have spontaneous or basal tension (i.e. vessels which do not have spontaneous action potentials arising in the vascular smooth muscle cells) such as intrapulmonary arteries and veins, renal arteries and veins, carotid and femoral arteries, or splanchnic arteries, do not undergo vasospasm when Mg is lowered unless a vasoconstrictor agent is present. However, vessels which develop spontaneous mechanical activity (e.g. cerebral and coronary arteries, rat aortae and mesenteric arterioles, piglet mesenteric arteries, human umbilical vessels, and anterior-mesenteric portal veins) undergo spasm or enhanced potential spike frequency and amplitude as the Mg in their environment is reduced. Elevation in Mg induces relaxation in these vessels. In this context, it is interesting to note that syndromes which are currently thought to involve vasospasm in their aetiology (e.g. transient ischaemic attacks, sudden death IHD, angina, migraine attacks, and possibly Raynaud's phenomenon) all center around organ regions which contain arteries and arterioles whose tone has been shown, at least experimentally, to be very susceptible to change in the extracellular Mg concentration (4, 6, 27, 34, 39, 56).

The release of prostacyclin stimulated by magnesium infusion (40) is likely to have qualitatively similar effects to those described in patients with coronary artery disease when prostacyclin was infused (14). These included a reduction in coronary vascular resistance, an increase in coronary blood flow at rest, and reduced myocardial lactate production.

Protection of Ischaemic Myocardium

It has been demonstrated that asphyxia can result in rapid (within 30 seconds) and progressive loss of myocardial Mg. Later it has been clearly demonstrated that asphyxia, anoxia, coronary ligation or cardiac surgery can result rapid loss of myocardial Mg and K followed by elevations in myocardial Na and Ca (36).

Loss of cellular Mg is one of the earliest signs of myocardial injury, with a 2-fold increase in Mg efflux occurring during hypoxia and, furthermore, in 675 clinical cases of sudden death due to ischaemic heart disease, myocardial magnesium content was reduced by 12-38 %, with a

concomitant increase in calcium content (7). Likewise, a significant drop in the magnesium content of cardiac tissue is noted after periods of ischaemic injury in humans and dogs and the loss of cellular Mg is associated with an increased efflux of K and depletion of tissue K (50).

When myocardial cells become ischaemic, a cascade of adverse metabolic changes is triggered. During ischaemia and hypoxia, ATP production decreases and total tissue [ATP] declines. Associated with the reduction in [ATP] is an initial increase free $[Mg+2]_i$ due to a reduction in the amount of Mg bound to ATP. This increase in $[Mg+2]_i$ may be compensated by an increased efflux, which eventually results in depletion of intracellular Mg (Fig. 1). As aerobic metabolism declines, cellular ATP is depleted to the detriment of active membrane ionic transport and other energy-dependent processes. Anaerobic metabolism generate lactate, resulting in intracellular acidosis. If Mg efflux occurs by a Na+-Mg+2 counter-transport, the increased efflux of Mg would be coupled to an increase in Na influx. If $[Na+]_i$ rises significantly, this could be a contributing factor in producing calcium overload, which is a major contributing factor in myocardial injury due to reversal of the Na+-Ca+2 exchanger $[Na+]_i$ and $[Ca+2]_i$ increase and cell swelling occurs. Increased calcium uptake into mitochondria further inhibits ATP synthesis while the contracture caused by elevated $[Ca+2]_i$ accelerates ATP hydrolysis (16, 53, 54).

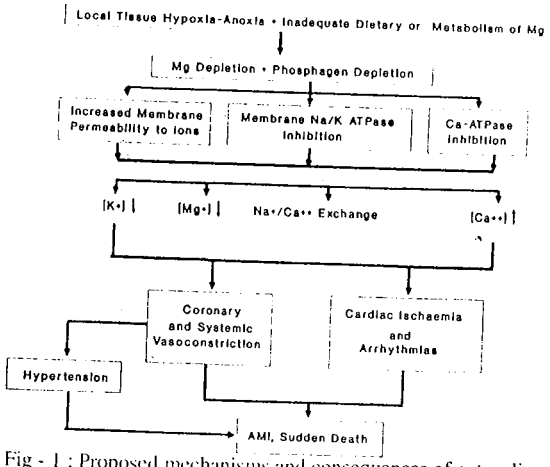

Fig - 1 : Proposed mechanisms and consequences of cytosolic calcium overload in ischaemic myocardium (From Woods KL, 1991).

Ca overload may result from a decreased ability of the sarcoplasmic reticulum to accumulate Ca because of the changes in Mg. The lowering of cellular ATP levels results in the opening of ATP-depleted K channels. Outward movement of K through these and other types of K channels reduces internal K and subsequently depolarizes the cell. Outward movement of K through these channels could be increased by depletion of internal $[Mg+2]_i$ that normally renders these channels inwardly rectifying. Efflux of Mg is aggravated by stimulation of ş-adrenoceptors, which increase utilization of ATP. Under these conditions, calcium overload might be worsened by increased influx of Ca through voltage-gated Ca channels (26, 36, 60).

There are several known mechanisms whereby magnesium might provide cellular protection during ischaemia. These include the inhibition of cellular calcium influx across the sarcolemma, reduction of mitochondrial calcium overload and conservation of intracellular ATP as Mg-ATP (23). There is also direct experimental evidence that some protection of myocardium can be achieved by raising extracellular Mg to supraphysiological levels during ischaemic arrest (61, 63).

Borchgrevink et al. confirmed a protective effect of increased extra cellular Mg during reperfusion of the post-ischaemic rat heart, as assessed by rate of recovery of ATP and creatine phosphate levels, correction of intracellular pH and recovery of pump function (17).

Effects of Mg on Arrhythmias

Interest in the possible role of magnesium as a factor in the pathogenesis of arrhythmias comes from a number of different sources. Epidemiological evidence suggest the incidence of ischaemic heart disease correlates with the quantity of magnesium in water and in soil (30).

Although myocardial cells are protected against Mg loss if the Mg concentration outside the cell is lowered, some reduction of intracellular free [Mg+2] can be expected in patients with hypomagnesaemia. The fall of the free [Mg+2] concentration can be great enough to shift the Ca binding to troponin and exert a slight, positive inotropic action. However, another effect of lowering free [Mg+2] on intracellular Ca binding will be more important. Lowering of the free [Mg+2] concentration leads to increase Ca uptake

in the cell, to reduce the capacity and the rate of Ca binding by the sarcoplasmic reticulum, and to increase the frequency of spontaneous cyclic contractions in skinned preparations induced by Ca-triggered release of Ca from the sarcoplasmic reticulum. It was demonstrated that Mg is an important stabilizer of intracellular Ca turnover. If intracellular free [Mg+2] drops to sufficiently low levels, hypomagnesaemia may therefore induce Ca-triggered Ca release following normal contractions. Since intracellular Ca is exchanged for Na at the sarcolemma (a process that depolarizes the membrane), Ca-triggered Ca release is accompanied by after-potentials, which may induce arrhythmias (48). It could be suggested that an interrelationship between magnesium, calcium and potassium exists (Fig. 2), and that the antiarrhythmic activity of magnesium is observed in hearts perfused with supraphysiologic calcium concentration, provided that the potassium concentration is reduced and the basic role of magnesium in maintaining cardiac rhythmicity is related to its role in maintaining potassium and calcium homeostasis (49).

Magnesium has been shown to be effective in the clinical treatment of various types of

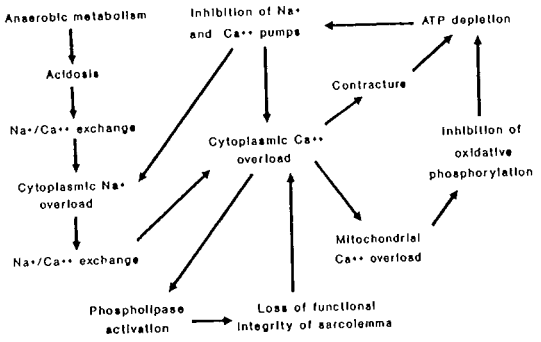

Fig - 2 : Hypothetical ischema for the dysfunction of normal cardiovascular tone by deficits in dietary Mg intake and inadequate metabolism of Mg (From Altura and Altura, 1984).

dysrhythmias. Ventricular arrhythmias related to digitalis intoxication, drug-induced torsade de pointes, or arrhythmias related to electrolyte deficiency reduced by magnesium infusion and magnesium has been shown to be a useful component of cardioplegic solutions (18). The model of hearts perfused with Krebs-Henseleit solution containing high [Ca+2] and low [K+] consistently exhibits sustained ventricular tachycardia and ventricular fibrillation soon after the release of the coronary artery ligation. It has been shown that, in isolated rat hearts perfused with a low [K+] and high [Ca+2], increasing magnesium concentrations progressively decreased the incidence of reperfusion-induced arrhythmias and that, a parallelism between the bradycardic effect of magnesium and its antiarrhythmic activity, are in agreement with the protective effect of slow heart rate towards ischaemia- and reperfusion-induced arrhythmias (18). Similar beneficial effects of increasing magnesium concentrations has been found after global and regional ischaemia, furthermore, magnesium has been shown to exert an antifibrillatory effect in anaesthetized dogs subjected to coronary artery ligation (15). It is well established that catecholamines play a major role in the development of severe rhythm disturbances in the ischaemic and reperfused heart. After an accumulation in the extracellular compartment during ischaemia, there is a sudden release of catecholamines during reperfusion and arrhythmia. The liberation of catecholamines by the heart muscle was reduced by magnesium (18). Post-ischaemic administration of Mg attenuates the metabolic damage after ischaemia in the isolated rabbit and rat heart (17).

Effects of Mg on Hypertension

There is some evidence suggesting that lowered magnesium levels may induce an increase in arterial blood pressure and cause the development of resistance to antihypertensive drug therapy (Fig. 2). It is also noteworthy that magnesium deficiency predisposes to potassium deficiency, and may induce refractoriness to potassium repletion (21,31). In-vitro studies suggest that magnesium may play a direct role in intracellular potassium homeostasis. Isolated rat diaphragms exhibit accelerated losses of muscle potassium when bathed in magnesium free Krebs-Ringer bicarbonate solution (6). Isolated rat septa labeled with 42K demonstrated significant efflux of cell potassium when bathed in low magnesium perfusate, and reversal of potassium efflux with high magnesium perfusate (6). It has been shown that magnesium-depleted patients demonstrated hypomagnesaemia, hypokalaemia and hypocalcemia accompanied by muscle potassium

depletion and kaliuresis. Magnesium repletion reversed all serum abnormalities and corrected the muscle potassium depletion without any additional potassium intake (59). Recent studies have shown that increased intakes of potassium exert antihypertensive effects (31). Mg is essential for stabilising the intracellular potassium and its transport across cell membranes and regulate the cellular and subcellular distribution and intracellular concentration of K (6).

It has been suggested that some forms of hypertension could be due to the direct effects of a hypomagnesaemic state on arteriolar and venular tone. The hypomagnesaemia could produce progressive vasoconstriction of arterioles, precapillary sphincters, and venulas in the microcirculation, and thus would eventually increase overall systemic vascular resistance, curtail capillary blood flow, and result in hypertensive disease (4,6). It has been confirmed that magnesium supplementation does clinically affect blood pressure in 18 hypertensive patients (21).

A number of studies in spontaneously hypertensive rats clearly demonstrate (except for one study) that the serum content of total Mg is significantly reduced in hypertensive animals (11,41). An examination of most of the clinical studies on hypertensive patients, so far studied, who received diuretics, where blood pressure often continued to rise, demonstrated that serum Mg is clearly reduced by about 15-20 % (11).

Resnick et al. examined red blood cells from hypertensive subjects and found that the ionized Mg determined by 31P nuclear magnetic resonance (NMR) spectroscopy was inversely related to the diastolic blood pressure. That is, the greater the elevation in diastolic blood pressure, the lower the ionized red blood cell Mg content (47).

In a study, uninephrectomised male wistar rats, given weekly implants of deoxycorticosterone acetate in order to produce malignant salt-induced hypertension, were used. The groups which received Mg supplements with drinking water exhibited significant lowering of blood pressure. There was a deficit in serum [Mg+2] in salt-induced hypertensive rats and serum [Mg+2] are restored to normal in rats allowed to drink Mg supplement. Interestingly, serum phosphate levels are also reduced in animals with malignant hypertension, whereas rats given Mg exhibit a restoration of phosphate to normal levels. Hypophosphataemia itself is known to produce high blood pressure (12).

Monocrotaline, a plant extract, is known to produce specific pulmonary hypertension in all mammals so far investigated. Rats which received monocrotaline exhibited significant elevation in pulmonary blood pressure. Controls and control animals which received oral Mg exhibited no alterations in pulmonary pressure. However, monocrotaline-treated animals which received oral Mg for 21 days exhibited a significant amelioration of pulmonary hypertension (38). Arteriolar and arterial walls clearly underwent significant hyperplasia, after monocrotaline, with encroachment of the lumens. Mg therapy reversed the monocrotaline-induced hyperplasia. Obviously, elevated levels of Mg must exert significant attenuating effects on collagen and elastin synthesis and smooth muscle cell hyperplasia (38).

It has been suggested that male children of parents with a genetic history of familial hypertension exhibit significant deficits in red blood cell Mg content (51).

Anti-platelet Effects of Magnesium

Calcium plays an important role in platelet activation and under certain experimental conditions magnesium can be shown to inhibit platelet function (13). The calcium antagonists have little inhibitory action on platelets, however, it is unlikely that magnesium will have a direct anti-platelet effect at clinically attainable concentrations (63). Rats which were fed with magnesium deficient diet developed hypomagnesaemia, hypertriglyceridemia and increased susceptibility of platelets to thrombin-induced aggregation (46).

One of the properties of EDRF is its ability to inhibit platelet aggregation (43) and external magnesium is also required for endothelium-dependent relaxation to occur in canine coronary arteries (8).

A potentially important indirect effect is suggested by the evidence that magnesium stimulates the release of prostacyclin from human vascular endothelium in-vitro and, potentiates the inhibitory action of human endothelial cells on platelet aggregation (58) and increase the

production of prostacyclin in human volunteers infused with intravenous magnesium (40).

Effects of Magnesium on Atherosclerosis

Atherosclerosis is an irregular thickening of the inner arterial wall, which reduces the size of the lumen. The thickening is caused by the accumulation of plaque consisting of smooth muscle cell, connective tissue, deposition of lipid and calcification. The sequence of events appears to be an initial damage to the vessel wall, development of plaque and finally occlusion of the vessel, frequently by formation of a thrombus. According to the histopathological studies on animals who died from hypomagnesaemic gross tetany, hemorrhagic lesions which were probably induced by vascular contractions resulting from spasm were observed. Inflammatory and degenerative lesions of the wall with calcium deposition were also observed. The same observations as those naturally occurring cases of hypomagnesaemia have been reported under experimental conditions. Mg deficiency causes arterial damage, thickening of the wall, thinning and fragmentation of elastic membranes calcification and collagen accumulation (45).

Divalent cations possess the properties of increasing fecal excretion of fatty acids by forming insoluble soaps or complexes. Mg supplementation reduces vascular lipid infiltration in various species fed a diet rich in saturated fat. If the ingested saturated fatty acids are not absorbed or absorbed very poorly, they should not be atherogenic to the same extent. This explanation of the decrease in lipid absorption seems to be very unlikely, since the dietary content of Ca is much higher than that of Mg. An increase in Mg intake cannot exert such a great modification in lipid absorption (45).

Mg deficiency is associated with an increase in triglycerides, an increase in free cholesterol and a decrease in esterified cholesterol. Triglycerides were significantly increased in the VLDL and LDL fraction. Cholesterol levels significantly increased in the VLDL and LDL fractions but were significantly lower in the HDL fraction (46). It was shown that hyperlipidemia induced by Mg deficiency was not due to an excessive production of lipids by the liver and induction of hypertriglyceridemia was due to a reduced uptake of circulating triglycerides (46).

Sudden death victims in hard water areas have less atheromas than those in soft water areas (20). Excessive intake of vitamin D which causes renal retention of calcium and renal loss of magnesium, may accelerate the development of atherosclerosis (59).

Ouchi et al. declared that moderate Mg deficiency could promote atherosclerotic lesions, such as intimal fibrosis and calcium deposits, by combining with some atherogenic diet which causes damage to arterial smooth muscle cells (42).

It has been demonstrated that dietary Mg suppresses the development of atherosclerotic plaque in the intimal surface of the aortas of rabbits on high cholesterol diets and dietary Mg significantly decreased cholesterol content in the aorta without reducing total cholesterol concentration in plasma. Moreover, Mg supplements did not further affect plasma HDL cholesterol concentration (42).

The calcium entry-blocking actions of Mg may contribute to the suppression of the development of atherosclerotic lesions; calcium antagonists have reportedly suppressed the development of atherosclerosis in cholesterol-fed rabbits (62). Interestingly, lanthanum, a trivalent cation, has suppressed the development of atherosclerosis in cholesterol-fed rabbits. Lanthanum has been shown to block Ca entry by occupying Ca binding sites in various types of cell membranes, and the action of lanthanum is similar to that of Mg (33).

In conclusion; dietary intake of Mg seems to be an important and may be critical factor in the prevention of atherosclerosis, hypertension, cardiac disease, stroke and sudden cardiac death. In addition, such a hypothesis would suggest that a suboptimal dietary intake of Mg should put human being at risk for the development of cardiovascular disease.

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