Magnesium deficiency and sudden death

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Over the past three decades, a variety of epidemiologic, autopsy, clinical, and animal studies have suggested an association between magnesium (Mg) deficiency and sudden death. This association may have far-reaching implications, because sudden death continues to be a major cause of cardiovascular mortality in the United States and accounts for over 300,000 deaths per year.[1, 2] Early studies showed an inverse relationship between drinking water content and cardiovascular disease incidence,[3, 4] but much of this relationship was subsequently shown to be the result of an association between water hardness and sudden death.[5] A number of water-borne minerals were examined as potential cardiotoxic or cardioprotective factors, and over the past few decades a consensus has emerged that low Mg content in drinking water is associated with high rates of sudden death.

Magnesium metabolism

Distribution and measurement. After potassium, Mg is the most common intracellular cation. It is an important component in a variety of biologic processes, and it is critical for the actions of many enzymes. Mg is distributed throughout the body as follows: approximately two thirds is located in bone, close to one third is intracellular, and the rest is extracellular.[6, 7] A 70 kg adult contains about 2000 mEq of Mg (1 mEq = 0.5 mmol = 12 mg), and normal serum values vary between 1.5 and 2.5 mEq/L.[8]

Because the blood contains less than 1% of total body Mg stores, serum Mg is poorly reflective of whole body levels. However, although normal serum levels may be seen in the setting of Mg deficiency, if serum levels are low, Mg deficiency is usually present.[7-9] Sophisticated means have been developed to assess total body Mg stores,[7, 10] but these techniques are not commonly available, and they have been used in very few studies.

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Nutritional sources. The body's Mg requirements have been estimated to range from 18 to 33 mEq/day, while average intake in the United States has been estimated to range from 20 to 30 mEq/day.[6-7, 11] Because average intake is so close to requirement levels, nutrition surveys suggest that dietary Mg is often barely adequate to meet daily requirements.[11, 12] Foods rich in Mg include nuts, cereals, seafoods, and green leafy vegetables.[8, 13] Boiling these foods in Mg-deficient soft water may leach out Mg, while boiling in Mg-rich hard water may prevent its loss.[14] In addition, gut absorption of water-borne Mg may be more efficient than that of food-borne Mg. Consequently, Mg bioavailability may be greater from water than from food sources.[15] Because of the marginal intake and absorption of Mg from food sources, it has been estimated that in hard water areas, 20% to 40% of a person's daily Mg requirements may be provided by the Mg contained in drinking water.[16]

Water hardness. Magnesium and calcium (Ca) are the principal minerals that determine water hardness, but the proportions of these minerals may vary substantially.[17] In North America, Mg:Ca ratios generally range from 1:1 to 1:5, but in certain areas of Western Europe, they may be two orders of magnitude lower.[18] Knowledge of Mg and Ca contributions to water hardness is important when assessing studies relating Mg deficiency and sudden death. In many of the early epidemiologic studies, exact mineral content was not reported, and this presents a problem when trying to evaluate these studies.

Magnesium deficiency and sudden death

Epidemiologic studies. In the late 1950s and early 1960s, evidence began to accumulate documenting striking geographic differences in the incidence of cardiovascular disease. Cardiovascular disease was shown to be more common in areas with increased mineral content in drinking water. The relationship was first described by Kobayashi[3] in Japan, and shortly thereafter by Schroeder[4] in the United States. Kobayashi's findings related stroke incidence and the acidity of river water. Schroeder subsequently analyzed regional incidences of cardiovascular disease and found an inverse relationship with water hardness.

In the 1960s and early 1970s, Anderson et al.[5, 19] conducted a series of studies in Ontario, Canada. Since there is a gradient of water hardness across Ontario, these investigators examined the incidence of acute and nonacute ischemic heart disease in hard and soft water areas. Little relationship was found with nonacute heart disease, but an inverse relationship was found between water hardness and sudden death. In hard water areas (water hardness >200 ppm), the standardized death rate from ischemic heart disease was 365 in 100,000, and 120 in 100,000 of these deaths were sudden. In soft water areas (water hardness <100 ppm), the death rate was 416 in 100,000, and 195 deaths in 100,000 were sudden. Among deaths ascribed to heart disease, the proportion of sudden deaths was 20% to 30% higher in soft water areas compared with death rates in hard water areas.

Following these early reports, epidemiologic studies in a number of countries confirmed the inverse relationship between drinking water hardness and sudden death, while a few reports found no correlation.[20-27] (The lack of correlation between water hardness and sudden death in several reports was later explained by the inclusion of hard water areas with unusually low Mg concentrations.) Although analytical techniques were different among the studies, several found similar correlation coefficients between water hardness and cardiovascular disease (−0.59 to −0.70), and others found that cardiovascular mortality or sudden death was at least 10% more common in soft water areas than in hard water areas.

Once a relationship between water hardness and sudden death was established, investigators examined whether it was the result of a cardiotoxic factor in soft water or a cardioprotective factor in hard water. Initially, a cardiotoxic factor was suspected, because it was known that soft water can leach out undesirable minerals from pipes and geologic layers.[28] No strong correlations were found when a variety of minerals was examined, however, and a cardioprotective factor began to be suspected. Many elements were investigated, with attention focusing on Mg and Ca because of their importance in determining water hardness. Mg was found to correlate most closely (in an inverse fashion) with sudden death rates.[29, 30]

Autopsy studies. Autopsy data were next examined in an effort to link intracellular Mg levels with drinking water intake and sudden death. Investigators were particularly interested in myocardial Mg content. Anderson et al.[31] examined myocardial tissue from people dying of trauma in hard and soft water areas. Myocardial Mg content was significantly lower in people living in soft water areas compared with levels in people living in hard water areas (207 versus 222 μg/gm wet weight, respectively). These differences in Mg content were only found in myocardial tissue samples; they were not present in serum samples or in tissue samples from diaphragm or pectoralis muscle.[16]

Table I. Selected reports examining myocardial magnesium content and cause of death*

Reference	*Year*	*Myocardial Mg content (μg/gm)* (n)	
		Controls†	*Sudden deaths*
Chipperfield and Chipperfield[32]	1973	205 (14)	172 (19)
Anderson et al.[33]‡	1975		
Soft water region		918 (54)	697 (27)
Hard water region		982 (29)	744 (12)
Chipperfield and Chipperfield[34]	1978	186 (158)	154 (59)
Johnson et al.[35]	1979	221 (7)	194 (14)
Chipperfield and Chipperfield[36]§	1979	186 (158)	179 (7)
Elwood et al.[37]	1980	181 (305)	159 (489)

n, Number of patients.
*Mg content is in micrograms/gram for wet weights of myocardial tissue.
†Controls were individuals who died because of trauma, accidents, or suicide.
‡Mg content is reported for dry weights of myocardial tissue. Deaths are ischemic versus nonischemic.
§Sudden infant deaths versus adult controls.

A series of studies also examined myocardial Mg content in people dying of sudden death and in controls who died of trauma (Table I).[32-37] These studies consistently showed depressed levels of myocardial Mg in people who died suddenly. Although it is clear that myocardial Mg content is decreased after sudden death, it is still unclear whether this is a cause or an effect.

Animal and clinical studies. In conjunction with epidemiologic and autopsy studies, animal and clinical studies were also conducted. These studies suggest two possible mechanisms for the association between Mg deficiency and sudden death: arrhythmogenesis and coronary artery vasospasm. According to the arrhythmogenesis theory, Mg deficiency increases cardiac irritability and facilitates cardiac arrhythmias.[38] Experimental studies[39] show that Mg is an essential cofactor for Na-K adenosine triphosphatase (ATPase), an enzyme that influences cardiac irritability by regulating ion fluxes across myocardial cell membranes. Clinical reports[40-42] suggest that Mg deficiency is linked with cardiac rhythm disturbances including premature ventricular beats, ventricular

quently lead to a decreased plasma HDL cholesterol level.

The reduction in plasma HDL cholesterol concentrations during long-term β-receptor blockade are thus the result of a change in lipoprotein metabolism. Indeed, particularly because of blockade of β_2-adrenergic receptors,[14] the activity of the two enzymes lipoprotein lipase and LCAT is reduced with the result that increased numbers of VLDLs are metabolized and thus catabolized to HDL to a lesser extent.

On the other hand, this process can be accelerated by stimulation of β_2-adrenergic receptors,[14] resulting in an increase in the HDL fraction (Fig. 5). It is therefore easy to understand why β-receptor blockers with ISA have only a slight effect on plasma lipoproteins, inasmuch as ISA counteracts the described mechanism that leads to changes in lipoprotein concentrations. During treatment with celiprolol even a nonsignificant increase in plasma LCAT activity is observed,[15] which could be attributed to its β_2-partial agonist activity. The observed increase in plasma HDL cholesterol levels during treatment with celiprolol can probably be attributed to its β_2-receptor agonistic activity.

In general, decreases in serum HDL cholesterol levels occur with nonselective (mixed) β-receptor blockers with no ISA, whereas there are only slight or no such changes observed with predominantly β_1-selective receptor blockers or with nonselective β-receptor blockers with ISA. On the contrary, increases in plasma HDL cholesterol levels are even found after β_1-selective receptor blockers with partial β_2-agonist activity. The favorable lipoprotein profiles after treatment with celiprolol (Fig. 1) are primarily caused by its partial β_2-agonist activity because, for example, the β_2-agonist terbutaline has also been found to produce an increase in plasma HDL cholesterol concentrations similar to that observed with celiprolol.[8, 24]

Catabolism of HDL occurs as a result of hepatic lipase activity at the surface of hepatocytes (Fig. 5). The data on the effect of adrenergic agents on hepatic lipase activity are confusing, however. Propranolol reduced the hepatic lipase activity in liver homogenates of rats fed a cholesterol-enriched diet.[25, 26] Dzau and Sacks,[5] however, found no effect of propranolol on the hepatic lipase activity in vivo or in cultured hepatic cells. The activity of hepatic lipase is increased with the α_1-receptor blocker doxazosin.[25] These data do not support a role for hepatic lipase in mediating the decrease in plasma HDL levels with β-blockers or the increase in HDL levels with α_1-blockers. Further studies, including testing of β_1-blockers with partial agonist activity, are required to clarify the influence of adrenergic agents on hepatic lipase and HDL catabolism.

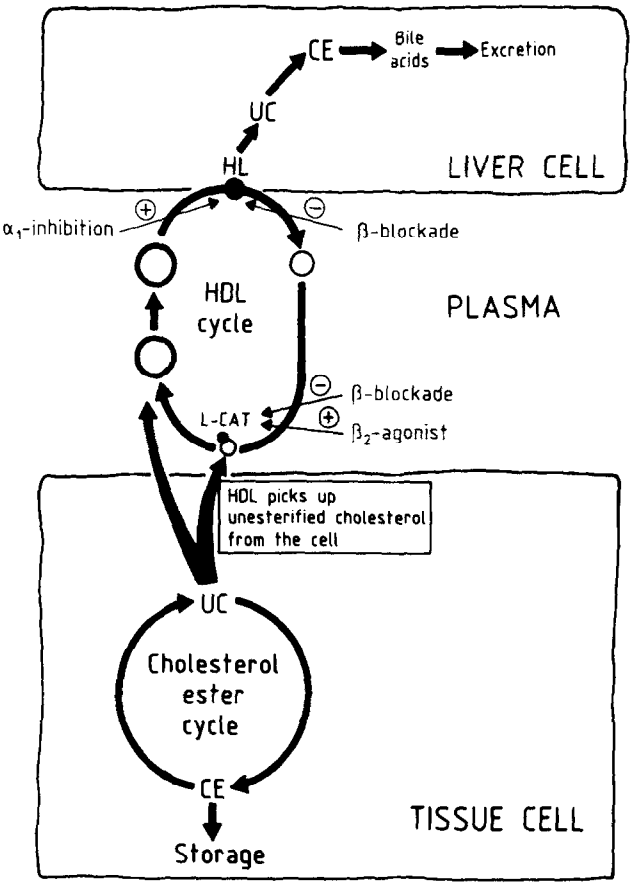

Fig. 5. Effect of α- and β-blockade on lecithin cholesterol acyltransferase *(L-CAT)* and hepatic lipase *(HL)*. ⊖, Inhibition; ⊕, stimulation. HDL is primarily responsible for removal of excess cholesterol from tissues and its transport to liver. HDL picks up unesterified cholesterol from cell. L-CAT converts this unesterified cholesterol in the outer layer of the HDL particle in cholesterol esters, which migrate to the core of the HDL particle, allowing additional cholesterol to be taken up. Final hepatic uptake of HDL particles is regulated by hepatic endothelial hepase.

Possible direct effects of β-receptor blockers on intracellular cholesterol metabolism. It is possible that β-receptor blockers interfere directly with cholesterol metabolism at three distinct steps in the pathway: (1) cholesterol esterification through acyl coenzyme A cholesterol acyltransferase (ACAT), (2) hydrolysis of cholesterol esters by cholesteryl hydrolase, and (3) cholesterol synthesis from acetate (Fig. 6).

ACAT inhibition. It has been shown that ACAT inhibitors will reduce the esterification of cellular cholesterol (Fig. 6) and lead to an increase in free cholesterol and HDL binding activity and enhanced efflux of cholesterol.[27] Thus if we assume that inhibition of cellular ACAT by β-blockers occurs, this will

then supplementation might be able to reverse the situation rather quickly. If sudden death is related to pathologic changes caused by chronic Mg deficiency, then supplementation may have to be given for many years before a change in death rates is observed. One study[59] addressed this question tangentially by observing changes in death rates following a change in the source of community water supplies and coincidental increases in drinking water hardness. Within a few years of drinking water changes, reductions in death rates were evident. This study did not quantify the Mg content of the drinking water, however, and overall cardiovascular mortality was assessed rather than sudden death. No interventional trials have yet addressed this issue.

Methodology. What is the best method of increasing Mg intake? One method is public health education to increase the use of Mg-rich hard water for drinking and cooking. Health education could be used to discourage the use of water softeners to treat water used for drinking and cooking. (Conventional water softeners remove natural Mg.) At the same time, the consumption of Mg-rich food and water could be encouraged.

A second method of supplementation is the addition of Mg to community water supplies, similar to fluoridation. If Mg content in soft water areas could be raised to levels found in hard water areas, a drop in sudden death rates would be strong evidence that supplementation makes a difference.

A third method of increasing Mg intake involves the fortification of foods. In Finland, substitution of Mg for part of the sodium in table salt was shown to be a safe way of increasing Mg intake, and this substitution was associated with an increase in serum Mg.[60] Sudden death rates could not be examined in this study because of the small number of patients investigated.

Finally, oral Mg supplementation has been suggested for people at high risk of sudden death. This type of supplementation would be similar to potassium supplementation for cardiac patients who are receiving diuretics. The advantages of oral supplementation over other methods are that it is cheap and that it can be easily targeted at high-risk groups. In addition, oral Mg has long been prescribed by clinicians who were influenced by the early epidemiologic studies. With the exception of hypermagnesemia in patients with renal failure, few adverse effects have been reported. Although large-scale clinical trials have not yet been attempted, the long history of oral Mg supplementation testifies to its safety.

Feasibility. Is Mg supplementation feasible? Public health education to increase Mg intake is unlikely to be controversial, but the questions of how to supplement Mg and in whom remain unanswered. Large-scale Mg supplementation of community water supplies is impractical because of technologic and political obstacles.[18, 61] Fortification of foods is technically feasible and would be less controversial, since many foods are now fortified with vitamins and minerals. To date, however, oral Mg is the best studied of the alternatives and might well be the most feasible initial intervention. Patient acceptability, low cost, and the possibility of targeting high-risk groups make this an easy method to implement and monitor.

Conclusions. Substantial evidence suggests that Mg deficiency is associated with sudden death, but most data come from observational rather than interventional studies. Proof that Mg supplementation reduces the risk of sudden death is needed before efforts to increase Mg intake are undertaken. Sufficient data have accumulated to justify a large, randomized, placebo-controlled trial for the primary prevention of sudden death. If such a study demonstrates that Mg supplementation reduces both sudden death and overall mortality rates, then large-scale efforts may be warranted.

Summary. A link between Mg deficiency and sudden death is suggested by a substantial number of studies published over the past three decades. Data come from epidemiologic, autopsy, clinical, and animal studies. They suggest that: (1) Sudden death is common in areas where community water supplies are Mg-deficient. (2) Myocardial Mg content is low in people who die of sudden death. (3) Cardiac arrhythmias and coronary artery vasospasm can be caused by Mg deficiency and (4) Intravenous Mg reduces the risk of arrhythmia and death immediately after acute myocardial infarction. Because of these data, Mg supplementation has been proposed as a possible method of reducing the risk of sudden death. Suggested ways of supplementing Mg include public education to change dietary habits, addition of Mg to community water supplies, fortification of foods, and oral supplementation. Despite the substantial number of studies linking Mg deficiency with sudden death, no prospective studies have yet investigated whether large-scale Mg supplementation is useful for the primary prevention of sudden death.

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Biochemical mechanisms involved in the β-blocker–induced changes in serum lipoproteins

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The reported patterns in serum lipoproteins during treatment with β-adrenergic receptor blockers are still conflicting. However, some general features seem to emerge at least from short-term studies (up to 1 year). The β-blocker–induced changes in serum lipoproteins may indeed differ between the different classes of β-blockers and perhaps within each class (Table I). Nonselective β-adrenergic receptor blockers produce the most pronounced alterations in serum lipoproteins, whereas β_1-selective receptor blockers produce less marked alterations. Nonselective β-blockers with intrinsic sympathomimetic activity (ISA) produce variable changes.

Fig. 1 shows the effect of celiprolol, a β_1-selective blocker with partial β_2-agonist activity and direct vasodilating properties,[1] on serum lipoproteins. The overall results of published studies with celiprolol indicate either no change or a modest decrease in serum triglycerides, low-density lipoprotein (LDL) cholesterol, and total cholesterol; high-density lipoprotein (HDL) cholesterol levels are frequently increased. The precise mechanisms of the effect of β-blockers on the serum concentration of lipoproteins are at present poorly understood. In this article possible biochemical mechanisms involved in changing serum triglycerides and serum HDL and LDL cholesterol levels during β-adrenergic receptor blockade are discussed separately.

Effect of β-adrenoceptor blockers on serum triglycerides. The hormone-sensitive lipase in adipocytes is regulated by adrenergic receptors.[4] Stimulation of β_1- and β_2-receptors activates adenylate cyclase,[5] inducing lipolysis (Fig. 2). Adenylate cyclase activity directly regulates lipoprotein metabolism at the adipocyte by activating hormone-sensitive lipase[6] and at the liver by blocking triglyceride synthesis.[7] β-Blockade decreases adenylate cyclase activity.[4, 8, 9] Inhibition of adenylate cyclase by β-blockers in the adipocytes, however, probably cannot account for the

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