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Magnesium Fortification of Drinking Water Suppresses Atherogenesis in Male LDL-Receptor-Deficient Mice

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Key Words
Magnesium · Atherosclerosis · Drinking water · Cholesterol

Abstract
Magnesium, an important cofactor of more than 300 enzymes, has previously been found to modulate blood lipid levels, atherogenesis and atherosclerosis in rabbits, when added to their diet. The aim of this study was to examine whether magnesium fortification of drinking water, without a change in diet content, can affect atherogenesis. The study included six groups of LDL-receptor-deficient mice. The mice received either distilled water or water containing 50 g of magnesium sulfate per liter. In the first (12 weeks) and second (6 weeks) stages of the experiment, the mice received low- and high-cholesterol diets, respectively. At the end of each stage, blood was drawn for the determination of plasma magnesium, calcium and lipid levels. In addition, the extent of atherosclerosis was determined at the aortic sinus. In both males and females, magnesium fortification was associated with higher levels of plasma magnesium (50 and 37% increase, respectively), without any differences in plasma calcium content. The extent of atherosclerosis at the aortic sinus in the male mice that received high levels of magnesium was a third of that of the male mice that received distilled water. However, these differences were not found in the female groups. Surprisingly, the female mice that received water fortified with magnesium had higher levels of cholesterol after stage 2, whereas no differences regarding plasma lipid levels were found among the male mice. These results confirm that magnesium fortification of drinking water is capable of inhibiting atherogenesis in male LDL-receptor-deficient mice. The mechanisms of action are yet to be discovered, and are probably not related to diminished lipid excretion, but possibly to the prevention of calcium influx into vascular smooth muscle cells, elevated antioxidative capacity, or other yet undetermined mechanisms.

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Introduction

Magnesium is the fourth most abundant cation in the human body. It plays an important role as a cofactor of more than 300 enzymatic reactions, including glycolysis, ATP metabolism, transmembrane transport of other cations such as sodium, potassium and calcium, protein and nucleic acid synthesis, muscle contraction and nerve reactions [1]. Though the National Research Council has recommended a minimum daily consumption of 400 mg of Mg for adults [2], the average Western diet does not provide this amount of Mg and as a consequence, Mg deficiency is very common in Western populations [2, 3]. The association between cardiovascular mortality and morbidity and Mg deficiency is well established [4], and, correspondingly, Mg has some beneficial effects with respect to the cardiovascular system, such as antihypertensive and antiarrythmic actions, and reducing the size of myocardial infarction [5]. Moreover, Mg supplementation of diet was found to modulate blood lipid levels, atherogenesis and atherosclerosis in rabbits [6, 7]. These studies emphasized that both Mg aspartate hydrochloride and Mg sulfate were equipotent in atherogenesis inhibition. The finding that only Mg aspartate hydrochloride lowered serum cholesterol levels suggests that Mg affects atherogenesis by a mechanism other than lowering plasma cholesterol levels [6, 7].

The potential importance of nutritional factors and preventive medicine in the development and treatment of cardiovascular diseases led us to examine the effect of Mg fortification of drinking water on the development of atherosclerosis in cholesterol-fed mice. As Mg has been suggested as an agent potentially capable of aiding atherosclerosis prevention [4], the aim of this study was to test whether Mg fortification of drinking water (without a change in Mg diet content, as in previous studies [6, 7]) can inhibit early atherogenesis in an animal model.

Methods

Mice and Diets

Three-week-old LDL-receptor-deficient mice were bred in the local animal house of the Institute of Lipid and Atherosclerosis Research (Sheba Medical Center, Tel-Hashomer, Israel). The mice were produced by homologous recombination as described by Ishibashi et al. [8]. These mice develop atherosclerotic lesions throughout the arterial tree that have many similarities with human atherosclerosis with regard to the distribution pattern and morphological features [8]. On a low-cholesterol diet (chow diet), the mice do not develop significant atherosclerotic lesions, whereas on a high-cholesterol diet the mice develop marked hypercholesterolemia and lesions throughout the aorta within 3–4 months [9]. Two groups of 10 male mice (groups A and B), two groups of 10 female mice (groups C and D) and two groups of 5 male mice (groups E and F) were studied. The mice were 3 weeks old when the study was commenced. They were on 12-hour dark/light cycles and were allowed access to food and water ad libitum.

The study included 2 stages: stage 1 lasted 12 weeks in which all of the mice were fed a normal chow diet containing 4.5% fat by weight and 0.02% cholesterol. Groups A, C and E were allowed access to distilled water (Mg concentration: <1 mg/dl), while groups B, D and F were given water containing 50.0 g of Mg sulfate per liter. At the end of stage 1, in which no significant atherosclerotic lesions were expected, the mice of groups E and F were sacrificed. Stage 2 lasted 6 weeks, and in this period the mice were fed an atherogenic Paigen diet containing 1.25% cholesterol, 7.5% casein and 0.5% sodium cholate, and there was no change with respect to the Mg content of their drinking water. At the end of stage 2, all mice were sacrificed. The mineral content of both diets was measured with an ICP machine (Spectro, Germany): the chow diet contained 2,470 mg/kg of food of Mg and 15,400 mg/kg of food of Ca, while the Paigen diet contained 1,430 mg/kg of food of Mg and 6,600 mg/kg of food of Ca.

The weight of each mouse was determined at the beginning and at the end of the study and once every 2 weeks during its course. Moreover, since mice of the same group were in the same cage, mean food and water intake was roughly estimated for each group of mice.

Plasma Mg and Ca Levels

Blood was collected from the retroorbital plexus of the mice at the end of stage 1; 1,000 U of heparin per ml of blood was added to each sample for plasma Mg determination. At the end of stage 2, blood was obtained by cardiac puncture, and plasma Mg and Ca were determined using the same method. In short, 10 µl of plasma was deposited on either Mg or Ca slides (Vitros Chemistry Products), which have a correlation coefficient of 0.999. Mg from the sample, both free and protein-bound, reacts with the formazan dye derivative in the reagent layer. The high Mg affinity of the dye dissociates Mg from its binding proteins and the Mg-dye complex formed is read at a wavelength of 630 nm. Ca forms a complex with Arsenazo III dye and this complex is read at a wavelength of 680 nm.

Lipid Profile

At the end of both stages 1 and 2, blood was collected from the retroorbital plexus and by cardiac puncture, respectively, after 12 h of fasting. One milligram of EDTA per ml of blood was added to each sample. Total plasma cholesterol and triglyceride levels were determined using an automated enzymatic technique (Boehringer Mannheim, Germany) [10].

Assessment of the Extent of Atherosclerosis at the Aortic Sinus

Quantification of atherosclerotic fatty streak lesions was carried out by calculating the lesion size in the aortic sinus as previously described [11], with a few modifications. Briefly, the heart and upper section of the aorta were removed from the animals and the peripheral fat carefully removed. The upper section was embedded in OCT medium and frozen. Every second section (5 µm thick) throughout the aortic sinus (400 µm) was taken for analysis. The distal portion of the aortic sinus is recognized by the three valve cusps which are the junctions of the aorta to the heart. The sections were evaluated for fatty streak lesions after staining with oil red O. The number of lesion

areas per section was counted by an observer unfamiliar with the tested specimen using a grid.

The extent of atherosclerosis was evaluated at the level of the aortic sinus. Processing and staining of the tissue was carried out according to Paigen et al. [11]. Lesion area was quantified by the modified method of Rubin et al. [12].

Statistical Analysis

Statistical analysis was carried out using Students' t test. $p < 0.05$ was considered as statistically significant.

Results

Body Weight, Diet and Water Consumption

Average daily dietary intake did not differ much between groups: in all groups the mice consumed approximately 4.98–6.75 g of food per day (p values for groups A and B, C and D, and E and F were 0.22, 0.71 and 0.89, respectively). However, average water consumption differed greatly between the treatment groups: mean daily water intake for a mouse in groups A and B was 5.6 ± 0.7 versus 3.1 ± 0.9 ml (mean ± SD) ($p < 0.001$); in groups C and D it was 3.7 ± 0.4 versus 2.2 ± 0.5 ml ($p < 0.001$), and in groups E and F it was 7.4 ± 0.7 versus 8.9 ± 1.5 ml ($p = 0.03$). All mice gained weight from the beginning of the study at the same rate, and no weight loss was noticed (fig. 1).

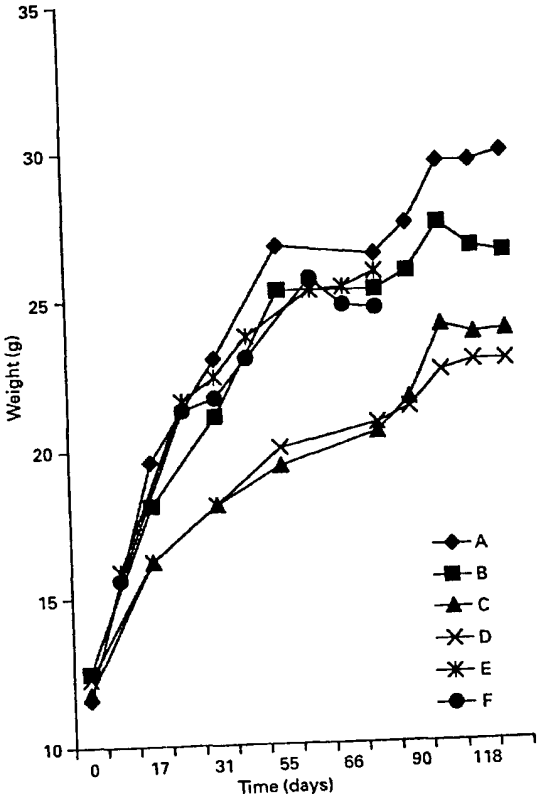

Fig. 1. Average body weight in the different groups of mice.

Plasma Mg and Ca Levels

At the end of stage 1, plasma Mg levels were 32.2 ± 5.3, 41 ± 10.9, 32.3 ± 9.7, 29.8 ± 4, 46 ± 4.1 and 64 ± 6.6 mg/l (mean ± SD) for groups A–F, respectively. The higher Mg level in group B compared with group A was not statistically significant ($p = 0.17$; Student's t test), whereas groups E and F differed significantly ($p < 0.001$). Similarly, Ca levels did not differ between the groups. However, at the end of stage 2 a highly significant elevated Mg concentration was found in groups B and D compared with groups A and C (63.6 ± 5.5 and 55.4 ± 7.0 mg/l vs. 42.3 ± 2.7 and 40.4 ± 1.7 mg/l, respectively; $p < 0.001$ for both). As at the end of stage 1, Ca levels were similar between the groups: 98.2 ± 7.8, 97.6 ± 3.8, 102.2 ± 6.9 and 104.8 ± 13.2 mg/l for groups A–D, respectively (fig. 2).

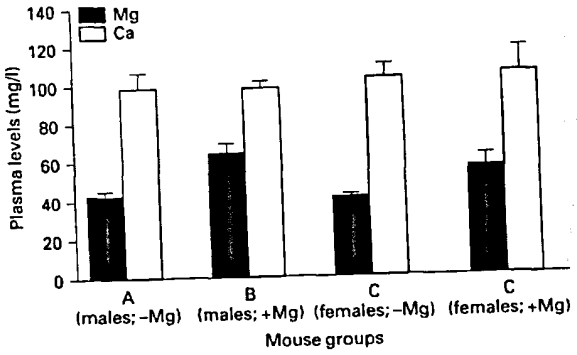

Fig. 2. Average Mg and Ca levels at the end of stage 2. $p < 0.001$ comparing Mg levels between groups A and B, and groups C and D.

Lipid Profile

Lipid levels were determined at the end of stages 1 and 2. Significant differences in cholesterol levels were found between groups E and F after stage 1 ($p = 0.044$), and between groups C and D after stage 2 ($p = 0.007$). In addi-

tion, groups C and D differed significantly ($p = 0.004$) with respect to triglyceride level at the end of stage 1. Table 1 summarizes lipid levels in all mice groups.

Atherosclerosis Extent

The extent of atherosclerosis at the aortic sinus differed significantly between the male groups A and B: 192,000 ± 43,000 versus 64,000 ± 25,000 μm^2 ($p < 0.001$). Though cholesterol levels in group D were higher than in group C, a trend towards reduction of atherosclerosis was found in female mice that received Mg, compared with those that did not receive it (55,000 ± 26,000 vs. 72,000 ± 19,000 μm^2, respectively), but this trend was statistically insignificant ($p = 0.14$) (fig. 3). As expected, groups E and F, which received only low-cholesterol diet, had minimal atherosclerosis, and the differences between them were insignificant (5,000 ± 4,000 vs. 14,000 ± 12,000 μm^2, respectively; $p = 0.23$). Representative photographs of the differences in the extent of atherosclerosis in the aortic sinus between groups A and B are shown in figure 4.

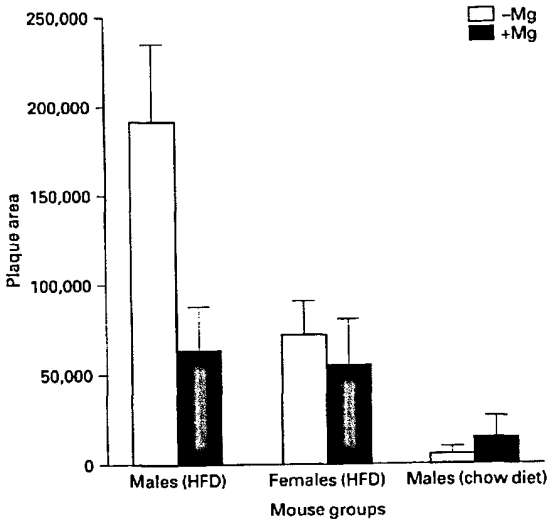

Fig. 3. Average atherosclerosis area at the aortic sinus. HFD = High-fat diet.

Discussion

The National Research Council has recommended a minimum daily consumption of 400 mg of magnesium for adults [2]. The recommendation stems from the important role of magnesium: it serves as a cofactor of more than 300 enzymatic reactions. Among its beneficial effects are those relating to the cardiovascular system. These can be roughly divided into acute and chronic effects. Regarding the former, administration of magnesium immediately before, during or up to 45 min after a coronary occlusion may reduce the size of the infarct by increased cardiac levels of Mg ions [13], reduction of coronary vasospasm and constriction [14], or increased cardiac tissue oxygenation [13]. Mg also has antiarrhythmic effects: it prolongs the PR interval and the sinuatrial conduction time, increases the AV nodal refractory period, and reduces automaticity [15]. Therefore, it is not surprising that magnesium is successful in the termination of supraventricular tachycardia [16], atrial fibrillation [17], intractable ventricular arrhythmia [18], multifocal atrial tachycardia [19] and torsades de pointes [20, 21].

Another beneficial action of magnesium in cardiovascular morbidity and mortality depends on its long-term

Table 1. Plasma lipid levels according to groups of mice (mg/dl)

Group	Chow diet (stage 1)		High-cholesterol diet (stage 2)	
	cholesterol	triglycerides	cholesterol	triglycerides
A (m; -Mg)	291 ± 96	254 ± 159	2,370 ± 380	195 ± 157
B (m; +Mg)	314 ± 173	261 ± 103	2,256 ± 255	107 ± 14
C (f; -Mg)	204 ± 53	112 ± 25*	2,012 ± 542**	79 ± 37
D (f; +Mg)	247 ± 64	143 ± 14*	2,682 ± 360**	75 ± 20
E (m; -Mg)	210 ± 21	192 ± 41		
F (m; +Mg)	317 ± 97	142 ± 51		

* $p < 0.05$ comparing triglyceride levels of groups C and D after a chow diet (stage 1).
** $p < 0.05$ comparing cholesterol levels of groups C and D after a high-cholesterol diet (stage 2).

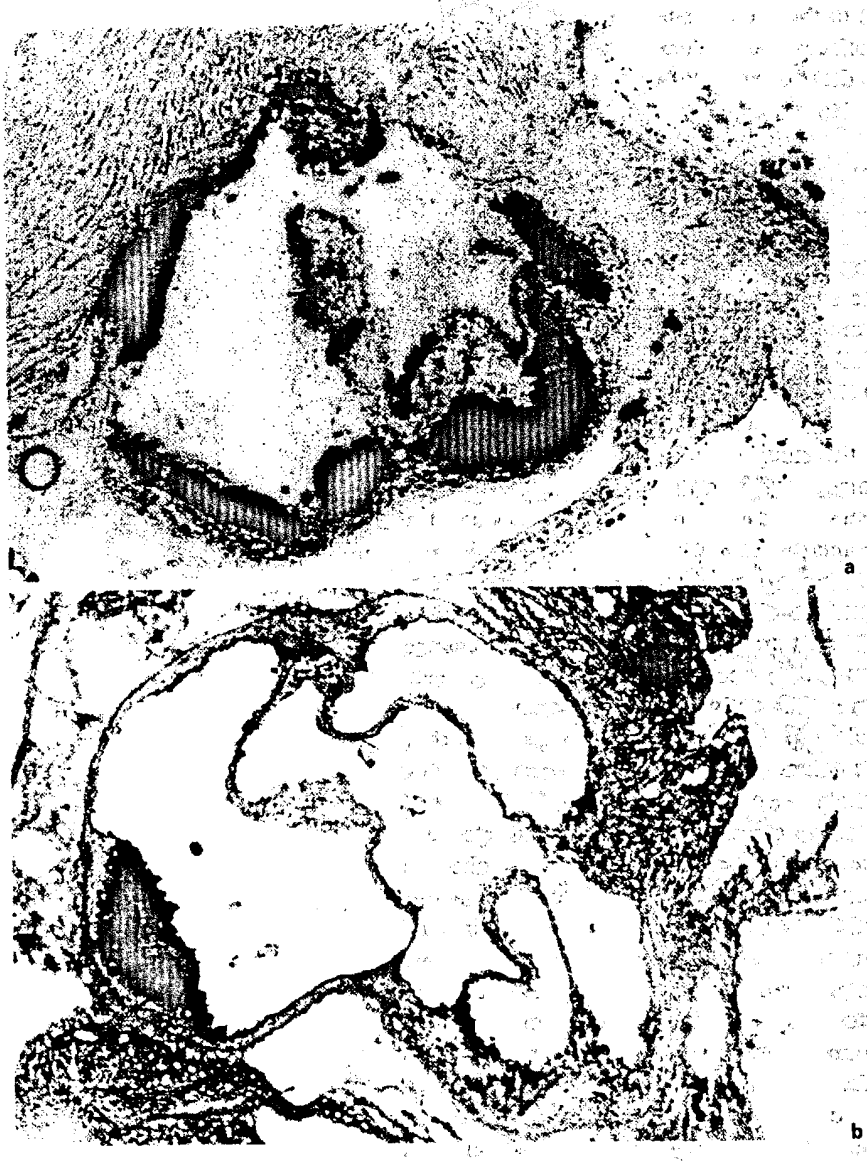

Fig. 4. Sections from the aortic sinus stained with oil red O demonstrating the difference in atherosclerosis extent between male mice without Mg (**a**) and with Mg (**b**).

consumption. It is well known that magnesium deficiency is associated with myocardial injury, by decreasing the body's antioxidative capacity and tissue resistance to free radicals [22, 23]. Thus, magnesium deficiency may be associated with cardiomyopathy [24]. Moreover, magnesium deficiency has also been found to be associated with sudden death [25]. Similarly, an epidemiological study demonstrated an inverse relationship between the odds ratios of death from acute myocardial infarction to the amount of magnesium in drinking water. These findings are further strengthened by the ability of magnesium to modulate blood lipid levels and atherosclerosis in rabbits [6, 7]. It has been found that magnesium deficiency can augment atherogenesis in these animals, while magnesium supplementation can suppress it. Altura et al. [7] have reported both a reduction in the extent of atherosclerosis in the aorta, and a reduction in serum cholesterol and triglycerides in rabbits fed with a higher Mg content. The Mg salt used in that report was Mg aspartate hydrochloride, while the Mg salt used by Ouchi et al. [6], as well

as in the present study, was Mg sulfate, which failed in both cases to modulate plasma lipid levels, but succeeded in decreasing atherosclerosis.

Here we present similar results: Mg inhibited early cholesterol-induced atherosclerosis in LDL-receptor deficient mice. These mice develop atherosclerotic lesions that have many similarities to human lesions, but on a chow diet, they do not develop significant lesions in the first 6 months of life [8]. This finding is best confirmed by the small area of atherosclerotic lesions in the mice of groups E and F, which were sacrificed after stage 1 (chow diet). On the contrary, on a high-cholesterol diet (parallel to stage 2), the mice developed marked hypercholesterolemia and lesions throughout the aorta within 3–4 months. In this study, the mice were sacrificed after 6 weeks on the Paigen diet, in order to find differences in early atherogenesis, and hence the aortic sinus lesions, from which the lesions progress, were chosen as the most appropriate site for comparison of the extent of atherosclerosis. The presented results emphasize two important facts: Mg fortification of drinking water (without any change in diet content of Mg) is capable of inhibiting atherogenesis, and Mg can significantly inhibit atherogenesis (by two thirds) in male LDL-receptor-deficient mice. Even though the average extent of atherosclerosis was slightly less also in the female mice that received Mg, this difference did not reach statistical significance. It is of interest that the baseline level of atherosclerosis is much higher in male than in female mice (as evident from the comparison of groups A and C). In fact, the Mg succeeded in diminishing the atherosclerosis extent of male mice to a level similar to that of female mice. Nevertheless, the difference in the average extent of atherosclerosis, albeit small, between the female groups, suggests that Mg might have an antiatherogenic effect in them as well, and in another experimental design (i.e. different diet, duration of feeding, or murine model) this difference might reach statistical significance. As gathered from figure 1, the three pairs of groups of mice gained weight at a similar rate, as is also evident from the similar food intake. This is not trivial, as Mg is used as a laxative in humans. The higher water consumption in the groups of mice that received only distilled water compared with the groups that received water fortified with Mg was expected, as the water with Mg was salty. One of the explanations for the lack of a clearly antiatherogenic effect of Mg in the female mice might thus be the decreased consumption of water with Mg of the female compared with the male mice.

The exact mechanism for the inhibitory effect of magnesium on the development of atherosclerosis is not yet known, but suggested mechanisms are increased excretion of lipids, decreased calcium influx into vascular smooth muscle, and decreased oxidation of LDL. Increased excretion of lipids cannot explain the beneficial effect of Mg, since Mg sulfate did not decrease plasma lipid levels. An alternative hypothesis is the prevention of calcium influx into vascular smooth muscle cells [26]. As Mg is a calcium antagonist, this can also explain its antiaggregate effect. The lack of difference in Ca levels between groups does not contradict this theory, as the presence of hypermagnesemia associated with normocalcemia on the one hand, and decreased Ca levels within the aortic wall on the other hand, have been reported by Ouchi et al. [6]. However, in this study the degree of early noncalcified atherosclerotic lesions was compared, and hence Ca influx into the vessel wall probably did not play a role in this early stage of atherogenesis. Finally, as a decrease in lipid oxidation has been reported in the presence of elevated Mg [27], decreased oxidation of LDL can also be involved in the prevention of atherogenesis, and should be further investigated in this setting.

In conclusion, the presented data combined with previous reports further emphasize that Mg fortification of drinking water inhibits atherosclerosis. It is not known why this beneficial effect of Mg was not observed in the female mice, but since these mice developed less atherosclerosis than males, it is possible that a longer duration of feeding with a high-cholesterol diet would strengthen the trend observed (reduction of atherosclerosis extent), and result in a significant difference in the females as well. Even though there are some theories to explain this effect, more research should be carried out in order to elucidate the exact mechanism. These results raise the question of whether chronic exposure to higher Mg levels in drinking water would have a similar suppressive effect on human atherosclerosis, and consequently on cardiovascular morbidity and mortality.

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