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Elwood PC, Pickering J

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Magnesium and Cardiovascular Disease: A Review of Epidemiological Evidence

P. C. Elwood, J. Pickering

Magnesium (Mg) is an essential element with numerous biological functions. Its relevance to disease is, however, uncertain. Both dietary Mg intake and serum Mg appear to be negatively related to the incidence of ischaemic heart disease events and stroke, but the evidence is both sparse and inconsistent. Perhaps the most persuasive data come from the *post-mortem* examinations of heart muscle: low tissue Mg levels being consistently found in myocardium taken from subjects whose death had been attributed to vascular disease. The clinical aspect which has received the greatest attention in recent years is the value of an infusion of Mg given early to patients with acute myocardial infarction. The evidence on this is inconsistent and a further trial is being set up in an attempt to resolve some of the uncertainties. The most pressing needs in the evaluation of Mg and health are, however, for more prospective evidence on dietary Mg intake and the risk of myocardial infarction, and for randomised controlled trials of the effect of an increase in Mg intake on vascular disease mortality. *J Clin Basic Cardiol 2002; 5: 61–66.*

Key words: magnesium, myocardial infarction, stroke, diet, supplements

n a challenging paper Neutra [1] has pointed out that a limitation in research on magnesium (Mg) is that concepts have been driven by metabolic studies conducted with a handful of subjects. Epidemiologists have certainly played a very small role in recent years, compared with the intense activity by cellular biologists working with a very wide range of animals and other organisms. Neutra went on to indicate that the most important deficiencies in knowledge about Mg are those that relate to public health and he recommended that further research should relate to possible public health actions.

There are several important hypotheses relevant to Mg and human health. One of the most important is that tissue Mg is predictive of cardiovascular disease, a low Mg level increasing the risk of a vascular disease event. A second is that supplementary Mg, given in the acute phase of a myocardial infarction, reduces mortality. A third is that long-term dietary Mg supplementation reduces the risk of cardiovascular morbidity and/or mortality. The issue of Mg in acute cardiac infarction has certainly generated a very great interest, and much controversy in recent years. Nevertheless, of the three hypotheses, the first is by far the most relevant to public health, that is, that low Mg levels are a risk factor for cardiovascular disease and death from vascular causes. The other two hypotheses follow from this, the more important relating to prevention by long-term dietary supplementation.

In the following, evidence relating to these three hypotheses will be reviewed in the context of a series of questions of increasing importance:

- 1. How best is body Mg status assessed in epidemiological studies?
- 2. What are the mechanisms that might be involved in cardiovascular disease?
- 3. Is there *post-mortem* evidence that body Mg is relevant to cardiovascular disease?
- 4. Is there prospective evidence that dietary Mg intake, or body Mg is relevant to vascular disease?
- 5. Is there experimental evidence that Mg supplementation is beneficial during infarction?
- 6. Is there experimental evidence that long-term Mg supplementation reduces the future risk of vascular disease events and/or death?

1. How Best is Body Mg Assessed in Epidemiological Studies?

Tissue Mg is clearly the measure most likely to be relevant to cardiovascular disease, especially if the tissue is myocardium. It is possible to obtain bone and heart muscle during surgery but samples from groups of subjects likely to be representative of a community can normally be obtained only at *post-mortem* examination. Skeletal muscle on the other hand, can be biopsied during life, but the procedure is unlikely to be acceptable for large epidemiological studies. This also applies to the Mg loading test, even in the one hour shortened form of the test [2].

Only about 0.3 % of body Mg is carried in the serum and the level appears to differ widely between subjects. In the National Health and Nutrition Examination Study (NHANES) the range in serum Mg levels was 0.41 to 1.45 mmol/l [3]. There appears, however, to be little correlation between dietary intake and serum Mg. In Atherosclerosis Risk in Communities (ARIC) study, the correlation coefficient was 0.09 in men and 0.04 in women [4] and in the men in the Caerphilly cohort [5] it was 0.05. Although all these coefficients are statistically significant, they imply that less than one percent of the variation in serum Mg levels can be explained by differences in dietary intakes. This raises the question as to the value of one or other of these variates. Furthermore, Altura [6] has repeatedly and persuasively argued that it is free Mg ions (Mg²⁺) that are biologically active and that it is these that induce the array of pathophysiological effects. Unfortunately, no epidemiological study to date appears to have used this measure.

It can be argued, however, that in relation to issues of public health the most relevant measures relate to dietary intake and estimates of these can be made in large numbers of subjects, representative of defined populations. Estimates of intake can also be made from chemical analyses of duplicate diets provided by selected subjects, and balance studies can be used to estimate requirements. Neither of these types of studies are appropriate for studies based upon large population samples of subjects, but the valuable evidence they give is reviewed elsewhere in this issue (see, Vormann and Anke, this issue).

From the Department of Epidemiology, Statistics and Public Health, University of Wales College of Medicine, Cardiff <u>Correspondence to:</u> Prof. Peter Elwood, Llandough Hospital, Penarth, S. Glam, CF64 2XW, U.K.; e-mail: pelwood@doctors.org.uk

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In large epidemiological studies, the most appropriate way of estimating dietary intake of a nutrient is by dietary questionnaire. While estimates obtained from questionnaires are crude, an advantage with Mg is that dietary intakes of Mg vary enormously, and probably have a greater range than most other dietary elements. For example: the range of Mg intakes in the Honolulu Heart Study [7] was 38 to 1,429 mg Mg per day. A range in a nutrient anything as large as this should make it relatively easy to detect a relationship with disease, if there is one.

Estimations of the dietary contribution of any nutrient carry many uncertainties. These arise from variability in the content of the nutrient in different food items, variability in the dietary pattern of individuals from time to time, and possible interactions between food items leading to variability in the absorption of the nutrient. Furthermore, like many elements, Mg is widely distributed throughout the diet and any measure of Mg content could in effect be acting simply as a surrogate for other nutrients. Nevertheless, valid conclusions about the role of any single dietary element in a disease; decisions as to advice to be given to patients; and decisions as to possible preventive public health actions are best based on measures that relate in a meaningful way to food consumption within a community.

In fact, as far as can be judged, estimates of the dietary intake of Mg appear likely to have some validity as there appears to be a reasonable degree of stability in intake within individual subjects over time. In the Caerphilly cohort study of over 2,000 older men [5], the mean daily Mg intake on two occasions, five years apart, was $264 \pm \text{SD } 84$, and $265 \pm \text{SD } 78 \text{ mg Mg/day}$, and the correlation coefficient between individual intakes on the two occasions was 0.49 (p < 0.001).

The point that dietary Mg could simply be acting as a surrogate for other nutrients is especially important in relation to fruit and vegetables, and to alcoholic drinks. Fruit and vegetables are protective against cardiovascular disease, and they both make substantial contributions to dietary Mg intake. In the average diet in the UK, about one quarter of the total Mg intake comes from fruit and another quarter from vegetables [5].

Another source of Mg, and one that raises difficulties in the evaluation of Mg and ischaemic heart disease, is alcoholic beverages. The contribution from beer and wine to the total dietary Mg intake ranges in different individuals from less than 20 mg to over 300 mg per day. In the Caerphilly cohort study of older men [5] the correlation between total dietary Mg intake and alcohol consumption was found to be high (r = 0.59, p < 0.001) and the quarter of men with the highest alcohol intakes increased their Mg intake through drinking by an average of 63 %. In an experimental study of beer drinking [8], small amount of beer, only 330 ml daily, raised plasma Mg by over 10 %. Alcohol intake, being itself negatively associated with heart disease risk, is therefore an important confounding factor. On the other hand, one of the mechanisms by which alcohol reduces risk could be through its Mg content. If this latter is the case, then adjustment of the Mg-cardiovascular risk for alcohol intake represents over-control.

A considerable impetus was given to studies on Mg by the observation, repeated in numerous studies in different areas, of a strong and negative association between Mg in drinking water and cardiovascular mortality. It has been estimated that a 'hard' drinking water can increase the Mg intakes of residents by up to one quarter of the total intake [9], and persons living in areas with a hard water supply appear to have a risk for cardiovascular disease that is about 30 to 40 % lower than subjects living in areas with soft water supplies. Nevertheless, evidence on hard water and health is so confounded by social and life-style factors that it is not considered further here, but the relevant studies have been well reviewed elsewhere [10, 11].

2. What Are the Mechanisms That Might be Involved in Cardiovascular Disease?

There are many cardiac mechanisms and processes which are sensitive to Mg level, including coronary vasodilatation and a reduction in arterial spasm, calcium channel blocking and a reduction in reperfusion injury, reduction of catecholamine production, and a suppression of platelet activity. The mechanism which appears to be appealed to most frequently in relation to Mg, appears to be a reduction in ventricular instability, leading to a reduction in ventricular ectopic contractions, and protection from ventricular fibrillation and death. The observational evidence on this, both from intervention and nonintervention studies is somewhat inconsistent, making it difficult to draw firm conclusions. In addition to supportive laboratory and animal studies, three large randomised controlled trials (RCTs) of Mg supplementation showed a reduction of around 50 % in ventricular arrhythmias [12], and in a study of 930 patients with acute myocardial infarction, intravenous Mg administration was associated with a 58 % reduction in ventricular tachycardia and fibrillation [13]. In yet another small RCT 16 % of 135 patients given a Mg infusion during the acute phase of infarction had an arrhythmia during the following 7 days, compared with 27 % of patients given no additional Mg [14]. On the other hand, no reduction was seen in either ventricular fibrillation or cardiac arrest in the huge Fourth International Study of Infarct Survival (ISIS-4) trial [15], nor, in a small study of 800 patients with acute MI, was admission serum Mg predictive of later ventricular fibrillation [16].

It is significant, however, that the authors of the largest successful trial of Mg in the reduction of myocardial infarction failed to find any evidence of a reduction by Mg in arrhythmias by Holter monitoring [17]. In fact, these authors comment elsewhere that in the light of trial and experimental evidence a reduction in reperfusion injury is likely to be the main mechanism of the therapeutic action of Mg [18].

On the other hand, hypomagnesaemia appears to be a relatively common finding in heart failure. Patients with hypomagnesaemia appear to have more frequent ventricular premature complexes and episodes of ventricular tachycardia than patients with normal serum Mg levels, and in one follow-up study patients with low Mg levels had a significantly worse one-year survival [19]. It is further of relevance that there is evidence suggesting that both intravenous and oral Mg reduces the occurrence of ventricular arrhythmias in heart failure, and a number of studies have been reviewed in Sueta et al. [20].

The relevance of a possible effect of Mg on platelet activity is uncertain. In one small laboratory study [21] an Mg infusion in 14 healthy volunteers was found to decrease aggregation to adenosine diphosphate and to collagen (p < 0.04) and to give a marked increase in bleeding time (from 8.0 to 11.8 minutes; p < 0.005). The relevance of platelet aggregation to vascular disease has, however, been questioned, and in the large Caerphilly cohort study neither platelet aggregation in platelet rich plasma, nor in whole blood, nor bleeding time were found to be predictive of MI [22]. That Mg may still be relevant to platelet function is suggested by work by Shechter et al. [23] who reported that the degree of platelet dependent thrombosis onto an exposed porcine arterial wall was negatively related to intracellular Mg level, while no direct effect of Mg on platelet aggregation was detected.

A relationship between Mg and blood pressure, and a reduction with Mg supplementation is also controversial. The evidence is reviewed elsewhere [24], but the best epidemiological evidence appears to have come from the Honolulu study [7]. In this, the relationships of 61 dietary variables with blood pressure were examined. Of all the nutrients, dietary Mg intake appeared to have the strongest relationship with blood pressure, and this was manifest with both dietary intake and with the use of Mg supplements. The fifth of men with the highest Mg intakes had systolic and diastolic pressures which were 6.4 and 3.1 mmHg lower than in the fifth of men with the lowest intakes. On the other hand, a randomised controlled trial of the administration of supplements of Mg, calcium and potassium, separately and together, in 300 women with low usual intakes of these elements, gave evidence of a lowering of blood pressure by potassium, but not by Mg [25].

Among the many other mechanisms which may be beneficially affected by Mg are oxidative stress and lipid peroxidation, a reduction in peripheral vascular resistance, a dilatation in coronary arteries, a reduction in the release of catecholamines, and protection in ischaemia-reperfusion injury. Evidence for these and other possible mechanisms is reviewed in Rayssiguier et al. [26], Woods [27] and Muir [28].

3. Is There *Post-Mortem* Evidence That Body Mg is Relevant to Cardiovascular Disease?

This would appear to be a most important source of evidence and a large number of studies have reported lower tissue Mg levels in samples of myocardium taken *post-mortem* from subjects whose death has been certified as due to ischaemic heart disease, compared to the levels in samples taken from subjects whose deaths had been attributed to other causes. An important possible factor which could negate these findings is that Mg leaches out of the myocardium into the pericardium after death. The largest of the studies attempted to allow for this by including the time between death and the sampling of the myocardium in the statistical analysis. The study was based on 1,236 samples taken at *post-mortem* examinations conducted in 28 hospitals in England and Wales [29]. The mean myocardial Mg level in 489 subjects whose deaths had been sudden, and due to ischaemic heart disease (IHD), was $159 \pm \text{SD } 29 \,\mu\text{g}$ Mg/g myocardium, and this compared with a mean of $177 \pm \text{SD } 32 \,\mu\text{g}$ Mg/g in 611 subjects whose deaths had been certified as due to causes other than IHD. After adjusting for confounding by age, cause and mode of death ('sudden' or 'lingering'), and time between death and the taking of the sample, the difference was $23 \pm \text{SD } 1.7 \,\mu\text{g}$ Mg/g (p < 0.001).

A more recent study [30] has reported Mg levels in the abdominal aortas taken from 28 patients who had died in acute myocardial infarction and 26 patients whose deaths had been from ischaemic heart disease without recent infarction. The Mg content in both these groups (678 \pm SD 143 and 833 \pm SD 151 mg Mg/g dried aorta) was very much lower than the Mg content in the subjects whose deaths had been accidental (1,021 \pm SD 220 mg Mg/g).

4. Is There Prospective Evidence That Dietary Mg, or Body Mg is Relevant to Vascular Disease?

Evidence on estimated dietary Mg intake and the occurrence of subsequent cardiovascular disease events comes from a number of cohort studies. The results of the various studies are certainly not consistent but suggest that the highest dietary Mg intakes are associated with about a 30 % reduction in cardiovascular disease events (Tables 1 and 2). The data from the ARIC study [4] presents perhaps the greatest inconsistency, in that the total IHD incidence was reduced in the quarter of men with the highest dietary Mg intakes, but increased in the women with the highest intakes. In both the Caerphilly cohort [5], and the cohort in the DART study [31] there is evidence suggestive of a reduction in risk in the men with the highest intakes, but significance is lost upon adjustment for confounding factors. Nevertheless, overall, the data from these three studies suggest a possible 30 % reduction in cardiovascular risk in the men with the highest Mg intakes.

Table 1. Prediction of ischaemic heart disease events by dietary magnesium intake

Study	No. of subjects	Years of follow-up	Number of outcome events	Results (as relative risk of a vascular event in groups of men defined by dietary Mg)	Comments
ARIC [4]	14K	4–7	IHD (223 men)	RR in lowest fourth: 1.0 RR in highest fourth: 0.64 $p < 0$	Adjusted for age, race, field centre, 0.01 waist/hip ratio, smoking, drinking, education, sports index, fibrinogen,
			IHD (92 women)	RR in lowest fourth: 1.0 RR in highest fourth: 1.32 <i>n.s.</i>	total and HDL cholesterol, triglycerides, diuretic use, hormone replacement
Caerphilly [5]	2.5K	13	All IHD (376)	RR in lowest fifth: 1.0 RR in highest fifth: 0.66 <i>n.s.</i>	Adjusted for age, smoking, prior IHD, energy intake and alcohol intake
	2.5K	13	Sudden IHD death (155)	RR in lowest fifth: 1.0 RR in highest fifth: 0.70 <i>n.s.</i>	
DART [31]	459	2	IHD deaths (120)	RR in lowest fifth: 1.0 RR in highest fifth: 0.66 <i>n.s.</i>	Adjusted for age, smoking, energy intake and alcohol consumption

 Table 2. Prediction of stroke by dietary magnesium intake

Study	No. of subjects	Years of follow-up	Number of outcome events	Results (as relative risk of a vascular event in groups of men defined by dietary Mg)	Comments
Health Professionals Follow Up [32]	44K	8	Stroke (328)	RR in lowest fifth: 1.0 RR in highest fifth: 0.70 $p < 0.03$	Adjusted for smoking, alcohol, past MI, etc.
Nurses' Health Study [33]	86K	14	Ischaemic stroke (386)	RR in lowest fifth: 1.0 RR in highest fifth: 0.84 $p < 0.31$	Adjusted for age, smoking, BMI, total calorie intake, alcohol intake, history of hypertension
Caerphilly [5]	2.5K	13	Ischaemic stroke (146)	RR in lowest fifth: 1.0 RR in highest fifth: 0.70 <i>n.s.</i>	Adjusted for age, smoking, calorie intake and alcohol consumption

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In view of the likely effect of Mg mechanism on ventricular fibrillation it would be of interest to consider acute IHD deaths separately from all IHD events. Adequate data on the mode of death are rarely collected, but these are available (unpublished) for the Caerphilly cohort, in which 155 sudden deaths occurred. While the trend between death rates and decreasing Mg intakes is probably stronger for these acute deaths than for all IHD deaths, the significance of the trend is lost on allowing for the effects of confounding factors. Nevertheless, the relative risk of sudden death is around 0.77 in the fifth of men with the highest Mg intakes (397 men), compared with the fifth of men with the lowest Mg intakes, but with adjustment for differences in age, smoking, prior IHD, energy intake and alcohol consumption, significance is lost.

DÄRT [31] involved 2,033 men, followed for two years after a myocardial infarct. Six months after their initial infarct, estimates of dietary Mg intakes were made from 7-day weighted dietary records kept by 459 men (unpublished). The mean dietary Mg intake in 19 of these men who died from an IHD event during the following eighteen months was 290 mg/day, and this differed, though not significantly, from the mean intake in men who survived with no IHD event (317 mg/day). However, the intakes of men who experienced a nonfatal IHD event (318 mg) was virtually identical to the mean intake in men with no incident IHD event. The men were followed for a further five years, and further IHD deaths identified (unpublished). Again, although the difference is not significant, the dietary Mg intakes of the 62 men who died had been 281 mg/day and in those who survived 323 mg/day.

In ARIC [4] and Caerphilly [5] the relationships with Mg intakes were adjusted to allow for alcohol intakes. As has already been indicated, this raises a major difficulty. The inclusion of adjustments for alcoholic beverages which led to the figures in Table 1 for these studies may represent, on the one hand, the best available evidence, but on the other hand, it may have led to an underestimate of the relationships.

Evidence on dietary Mg intakes and stroke is of interest because if the main protection from Mg arises through a suppression of ventricular arrhythmias, then an association with stroke would not be expected. Despite this, there was a significant negative trend in stroke incidence with Mg intake in each of three cohort studies. In the Health Professionals Follow-up Study (HPFU, [32]) the relative risk of a stroke was 0.7 in the fifth of men with the highest, compared with men with the lowest Mg intakes. Both the Nurses' Health Study [33] and the Caerphilly study (unpublished data) show closely similar reduction in risk in the subjects with the highest Mg intakes, but in neither of these studies was the trend significant. Again, however, the suggested reduction in stroke incidence is around 30 % (Table 2). In view of the lack of correlation between dietary intake and serum level of Mg, and the fact that only about 0.3 % of body Mg is in the serum, one would not expect to find relationships between serum Mg and disease. Thus, serum Mg on admission to hospital of patients with acute MI does not predict death or re-infarction [34] and no difference was found in serum Mg between patients who died, and those who survived an acute myocardial infarction [35].

Nevertheless, a number of prospective studies do appear to show a relationship between serum Mg and IHD (Table 3). In over 12,000 subjects in the NHANES I study, the hazard ratio for IHD death in the third of subjects with the highest serum Mg levels, 'adjusted for other explanatory variables', was 0.69 (p < 0.002) [36]. In a more extensive examination of the same data, the association with IHD deaths was confirmed, but only a small and non-significant relationship was found with total IHD incidence [3]. In ARIC [4] base-line serum Mg had been 0.8 mmol/l in the 223 men who subsequently experienced an IHD event compared with 0.82 mmol/l in 6,000 men who remained IHD free (p < 0.01). On the other hand, data on serum Mg showed no convincing prediction in the Caerphilly cohort [5].

5. Is There Experimental Evidence That Mg Supplementation is Beneficial During the Infarction Process?

There has been prolonged discussion in the journals about the value of Mg given during the acute phase of infarction. While a number of small trials suggested benefit from intravenous Mg given early in the acute infarction process, recent discussion has focussed largely on the differences between the results of two very large RCTs. LIMIT-2 [18] involved 2,316 post-MI patients, half of whom received an infusion of Mg sulphate shortly after the onset of symptoms of infarction, followed by a further 24 hour infusion. In this, as in six small trials which had been reported earlier, there was a substantial reduction in clinical outcomes: 90 deaths in the patients given Mg, 118 in the other patients: a 24 % reduction (95 % CI 1–43 %). Also of relevance are the results of a more recent trial [37] in which intravenous Mg had been given very early during infarction. In-hospital mortality was 4.2 % compared with 17.3 % in the patients not given Mg, but this reduction appeared to be due to a lower occurrence of cardiogenic shock and congestive failure, and not through any effect detected on arrhythmias. ISIS-4 [15], however, was a huge factorial, multi-centre trial in which over fifty-eight thousand patients were enrolled and in this the patients given a Mg infusion experienced a 7.6 % mortality during the five weeks after infarction, compared with 7.2 % in 29,039

Table 3. Prediction of cardiovascular disease events by serum magnesium

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Study	No. of subjects	Years of follow-up	Number of outcome events	Results		Comments
NHANES I [3]	8K	10	ISH (492)	RR in lowest third: RR in highest third:	1.0 0.68 p < 0.005	Adjusted for age, sex, race, smoking, cholesterol, BP, antihypertensive medication, diabetes, BML activity
NHANES I [36]	12K	19	IHD deaths (1005)	RR in lowest quarter: RR in highest quarter	1.0 :: 0.69	and alcohol consumption
			All IHD (2637)	RR in highest quarter	: 0.92	
ARIC [4]	14K	4–7	IHD (223 men)	RR in lowest fourth: RR in highest fourth:	1.0 0.84 <i>n.s.</i>	Adjusted for age, race, field centre, waist/hip ratio, smoking, drinking, education, sports index, fibrinogen.
			IHD (96 women)	RR in lowest fourth: RR in highest fourth:	1.0 0.55 p < 0.05	total and HDL cholesterol, triglycerides, diuretic use, hormone replacement
Caerphilly [5]	2,5K	13	IHD (244)	RR in lowest third: RR in highest third:	1.0 0.96 <i>n.s.</i>	Adjusted for age, smoking, prior IHD, energy intake and alcohol intake

who received standard treatment (odds ratio = 1.06; p = 0.07).

The inconsistency between these two excellent trials, LIMIT-2 and ISIS-4, led to a long debate on technical aspects of the studies. It also led to a most useful discussion on statistical aspects of trials and overviews. While chance may well have played a part in the different outcomes of these two major trials, the consistency in the seven small trials which had been published earlier can possibly be explained by publication bias leading to the reporting of only the trials in which benefit had been observed [38].

Nevertheless, uncertainties persist and arguments about the difference between LIMIT-2 and ISIS-4 focus on a number of uncertainties: the timing of the Mg infusion, the dose of Mg, the duration of the infusion, the basic level of risk of the patients and heterogeneity in the data from the different centres which were pooled in ISIS-4. *Post-hoc* discussion will never resolve the arguments, and a further RCT with the acronym MAGIC may resolve some of the uncertainties, in particular those relating to the relevance of the timing of the Mg infusion (see [39]).

Two trials in stroke have suggested benefit from the early, and continued administration of Mg [40, 41]. These were very small and the results did not achieve significance (odds ratio of death or disability 0.71; 95 % CI 0.71–1.37). It is of interest therefore, that as with acute MI, the need for further evidence is accepted, and a major trial in stroke is now planned [42].

6. Is There Experimental Evidence That Long-Term Mg Supplementation Reduces the Incidence of Vascular Disease Events and/or Death?

On the recommendation of Neutra [1] that further research should be related to possible public health actions, this is surely the most pressing of all questions about Mg. Yet only one *ad-hoc* RCT seems to have been reported. Galloe et al. [43] gave a supplement of 15 mmol of Mg oxide per day for one year in a randomised trial based on 289 male and 178 female survivors of an acute MI. There was no evidence of any subsequent reduction of risk of sudden death or non-fatal IHD event (Table 4) and the authors concluded that 'Mg supplementation cannot be recommended'. This conclusion is unreasonable in view of the quite inadequate power of the trial. A more realistic, long-term trial should therefore be conducted as a matter of urgency.

It may, however, be important to distinguish between a nutrient given as an isolated supplement, and a diet which is naturally rich in that nutrient. The clinical effects of the two approaches to enrichment which these represent can be dramatically different, as has been shown in the case of beta-carotene supplements and foods which contain this nutrient [44].

It appears that only one RCT gives evidence at present on the effect of an increase of Mg intake through a dietary change, and this evidence is somewhat indirect. DART [31] tested the effect on cardiovascular disease events of three dietary changes in 2,033 post-myocardial infarction patients over a two year period. One of the interventions was advice to increase dietary cereal fibre. Food items which are high in cereal fibre are also rich in Mg, and the thousand patients in DART 1 who were randomised to this food item increased their intakes of Mg *pari passu* to a mean of 353 mg/day. This represents an average increase of 24 % above the 277 mg/day taken on average by the thousand patients randomised to the other dietary interventions (fish, low-fat and a 'control' diet). During the following two years neither deaths nor total IHD incidence differed in those with, and those without the increased dietary Mg intakes (Table 4).

The only other evidence of relevance is a possible effect of Mg in delaying re-stenosis after coronary angioplasty [45]. A daily supplement of 600 mg of a Mg salt was given to 49 patients and a non-significant trend towards a lower rate of restenosis was noticed on repeat angiography, compared with 50 control patients who received no additional Mg (p = 0.10).

On the other hand, it is important to note that the authors of two trials in which the administration of Mg was followed by a beneficial effect, both suggest that the Mg may have had a therapeutic effect, and the benefit may not have been due to the correction of an underlying deficiency of the element. In their discussion of the 24 % reduction in mortality in LIMIT-2, the authors suggest that 'magnesium is acting pharmacologically rather than correcting a deficit' [18]. Similarly, England et al., who reported a large and significant reduction in ventricular dysrhythmias following cardio-pulmonary surgery, commented: "It is also conceivable that the efficacy of magnesium administration in decreasing postoperative morbidity may be related to the pharmacologic properties of magnesium and unrelated to the normalisation of circulating magnesium concentrations" [46]. These interpretations are only suggestions, but if true, then it would be difficult to sustain a case for a long-term trial of Mg and vascular disease events.

Conclusions

The evidence from the prospective studies of dietary Mg intakes and serum levels of Mg, suggests that levels of Mg deficiency which are associated with an increase in the risk of cardiovascular disease are prevalent in the community. At the same time, the inconsistencies in the evidence from the different cohorts are worrying and suggest either that there may be residual confounding by factors not yet identified, or that Mg may simply be a marker for other nutrients which are beneficial. However, the one group of studies that cannot be dismissed on these grounds, is those which have found a reduced Mg content in the myocardium of subjects whose deaths had been attributed to IHD.

An assessment of the clinical relevance of Mg can be summarised as follows:

1. Biological plausibility: It has been established beyond all reasonable doubt that Mg is an essential element and that numerous cardiac, neurological and other mechanisms are dependent upon adequate tissue levels.

 Table 4. Prevention of cardiovascular disease by increased magnesium intake

Study	No. of subjects	Years of follow-up	Number of outcome events	Results	Comments
Galloe et al. [42]	468	1	Cardiac event (41) Sudden death (13) Non-fatal IHD (27)	RR in survivors: 1.0 RR: 1.40 <i>n.s.</i> RR: 1.22 <i>n.s.</i> RR: 1.36 <i>n.s.</i>	15 mmol of magnesium oxide per day
DART [31]	2K	15	IHD deaths (643)	RR in men with no extra fibre: 1.0 RR in men receiving extra Mg: 1.1 <i>n.s.</i>	Dietary magnesium intake: 353 mg/day in men advised to increase cereal consumption; 277 mg/day in controls

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2. Strength of association and evidence of a dose response relationship: Inconsistencies in the evidence from cohort studies makes it impossible to judge the relevance of Mg to disease, let alone the strength of any such association between a measure of Mg and a clinical outcome. Only in the largest cohort study [32] and only for stroke, is there evidence of a significant dose-response relationship between a measure of Mg and the incidence of a disease.

3. Coherence between different approaches and consistency in different studies: There is broad coherence in that most studies of tissue myocardial Mg level and cause of death, studies of Mg in drinking water and cardiovascular disease, studies of disease prediction by dietary Mg, and by serum Mg, and many animal studies suggest that Mg intake is relevant to vascular disease. At the same time, within each of these approaches there are inconsistencies.

4. Experimental confirmation: Evidence from trials of Mg infusions in acute myocardial infarction is hopelessly confused and no firm conclusion can be drawn. To date there appear to have been only two studies of the effect of a long-term increase in Mg intake on cardiovascular disease. Both are limited in design and seriously inadequate in power.

Finally, the question that would seem to be the most directly relevant to public health is whether or not, in the community, there is a degree of dietary Mg deficiency which contributes to the risk of cardiovascular disease, and whether an increase in dietary Mg intake will remove this excess risk. The first part of this question can be examined in further prospective epidemiological studies, the second can only be answered in randomised controlled trials. Both kinds of study are urgently required.

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