

## Iron, magnesium and ischaemic heart disease

BY PETER C. ELWOOD

*MRC Epidemiology Unit, Llandough Hospital, Penarth,  
South Glamorgan CF64 2XW*

Interest has focused recently on a number of micronutrients which are of likely relevance to ischaemic heart disease. Two of these, Fe and Mg, are essential trace elements and the importance of both in ischaemic heart disease is at present under close scrutiny.

### IRON

There are a number of ways in which Fe could be of relevance to ischaemic heart disease (IHD). A high dietary intake can raise circulating haemoglobin level and lead to an increase in blood and plasma viscosity, which in turn are strong predictors of IHD events (Yarnell *et al.* 1991). On the other hand, a low circulating haemoglobin level consequent on anaemia has been shown to be associated with a proliferation in the anastomotic network of the coronary vessels (Zoll *et al.* 1951) which could be life-saving in coronary thrombosis. A further way in which Fe is of relevance to heart disease arises from the possibility that Fe may promote free-radical production, particularly during reperfusion of the anoxic myocardium following infarction (Biemond *et al.* 1986). Others have also suggested that free Fe may be more generally involved as a catalyst in free-radical generation and, therefore, in the promotion of atherosclerosis through the oxidation of lipids within the vessel wall (Cross *et al.* 1987; Salonen *et al.* 1992).

There are a number of measures of body Fe status, and it is of interest to examine the predictive power of each of these for IHD events. Measures include dietary Fe intake, Fe in transport (serum Fe and transferrin saturation), Fe in haemoglobin (haemoglobin concentration and packed cell volume), and storage Fe (usually estimated from serum ferritin). Fe is widely distributed throughout the diet and consequently it is difficult to estimate total intake. A further difficulty comes from the fact that dietary Fe involves two groups of sources, inorganic salts and haem-, or protein-bound Fe in meat and other animal food products. These are seldom distinguished in dietary intake studies, and this is perhaps unfortunate because haem-Fe is absorbed with much greater efficiency than inorganic Fe. Perhaps because of the difficulties in estimating dietary Fe, there have been few attempts to examine associations with IHD. Only one, the Kupio study (Salonen *et al.* 1992), has detected a significant association of a 5% increase in the risk of an IHD event for each 1 mg of dietary Fe intake. This result, however, is based on a relatively small cohort of 1931 men in whom only fifty-one heart-disease events occurred during a 3-year follow-up, while three larger cohort studies failed to find any such association (Ascherio *et al.* 1994; Morrison *et al.* 1994; Sempos *et al.* 1994). In other studies, estimates of Fe status have been based on serum Fe or transferrin saturation (Magnusson *et al.* 1994; Morrison *et al.* 1994; Sempos *et al.* 1994). The evidence from these studies on associations with IHD are totally inconsistent.

The easiest measures of Fe status are, of course, haemoglobin level and packed cell volume, and the relationships between these variables and IHD have been examined in

Table 1. *Haemoglobin level and heart disease based on 2334 men aged 45–59 years being followed in the Caerphilly Prospective Study of Heart Disease and Stroke*

(Estimates of haemoglobin level were made at baseline and 312 heart disease events (ischaemic heart disease (IHD) death or myocardial infarction) occurred during 10 years of follow-up)

Fifths of Hb level	Relative odds of an IHD event	Relative odds standardized for age, smoking and prevalent heart disease
Highest	1.0	1.0
2nd	1.0	1.1
Middle	1.0	1.0
4th	1.6	1.6
Lowest	1.3	1.2

Hb, haemoglobin.

numerous studies. An overall interpretation is difficult because in many of the earlier studies inadequate attention was paid to the effect of possible confounding factors, in particular smoking, which is associated with elevated haemoglobin and packed cell volume levels, and an increased risk of IHD. Most of the major recent studies of male cohorts, including the Honolulu Heart Program (Carter *et al.* 1983), the follow-up of NHANES I (Sempos *et al.* 1994) and the Health Professionals Study (Ascherio *et al.* 1994) failed to find any association once allowance had been made for relevant confounding factors. Our own cohort study, the Caerphilly Prospective Study of Heart Disease and Stroke, also gives no evidence (Table 1), indeed there is a suggestion that lower levels of haemoglobin may indicate a higher risk of IHD (not significant).

In conclusion, although no formal meta-analyses seem to have been done, an epidemiologist is unlikely to be impressed by the evidence on body Fe status, however measured, and risk of IHD.

#### MAGNESIUM

Mg is the second most abundant intracellular cation, next to K. It is in highest concentration in the most active tissues, i.e. brain, heart, liver and kidney, and about one-third of the total body Mg is in skeletal and cardiac muscle (Rude, 1989). Within the heart, it slows conduction through the atrioventricular node with a reduction in clinically significant arrhythmias after acute myocardial infarction (Woods, 1991). It may also protect the myocardium both against ischaemic injury and against reperfusion injury (Woods, 1991). Further effects of Mg which are likely to be protective include an inhibition of platelet function (Adams & Mitchell, 1979) and coronary vasodilatation possibly through the inhibition of the contraction of smooth muscle and the production of endothelium-derived relaxing factor (EDRF) (Gold *et al.* 1990).

The estimation of body Mg status is undoubtedly difficult and has not been studied widely. The element is largely intracellular and, thus, serum levels are likely to be of little clinical relevance. On the other hand, it is highly mobile in the tissues and, for example, it rapidly moves out of infarcted tissue. Dietary Mg, however, comes from a relatively small number of food items, and the consumption of these particular food

Table 2. Sources of dietary magnesium: the average contribution (%) to the total dietary Mg intake made by various food items, based on 2398 food-frequency questionnaires given to men in the Caerphilly Prospective Study of Heart Disease and Stroke\*

Fruit and vegetables	24
Bread	24
Eggs and dairy produce	17
Alcoholic drinks	14
Meat	8
Fish	3
Other foods	10

\* In some areas Mg in hard water can increase total daily intake by at least 20% (Anderson *et al.* 1975).

items can be estimated with fair precision. Table 2 lists the main sources of Mg and indicates the average contribution of each to the total intake in a representative population sample of men in Wales. While the estimation of a dietary item cannot be said to be precise, estimations of Mg intake are certainly likely to be better than those of Fe intake. Furthermore, within the cohort of men in Wales, estimations of intake made from 7-d weighed intake records were found to correlate reasonably well with estimates based on a food-frequency questionnaire ( $r$  0.4,  $P < 0.001$ ) and estimates made from the latter appear to be fairly stable within individuals over time ( $r$ , between two sets of estimations, made 5 years apart, 0.4,  $P < 0.001$ ).

Epidemiological evidence relating Mg to IHD comes from several sources. First, a number of studies have shown that tissue Mg, estimated in samples of myocardium taken post-mortem, is substantially reduced in subjects whose death had been certified as due to IHD (Iseri *et al.* 1952; Chipperfield & Chipperfield, 1973; Elwood *et al.* 1980). Second, a number of clinical trials have demonstrated a reduction in mortality following myocardial infarction from an intravenous infusion of a Mg salt. The most important of these is the trial known as the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), in which 2316 post-infarct patients were randomized to receive either an intravenous Mg salt, or physiological saline (9 g NaCl/l; Woods *et al.* 1992). The primary outcome measure was 28 d mortality post-infarction, and this was reduced by 24% in the group of patients given Mg. The evidence from this trial, and from a number of smaller previous trials which indicated benefit from Mg, has been challenged by the results of ISIS-4, which tested the effect of a Mg infusion in over 50 000 post-infarction patients (ISIS Collaborative Group, 1993). In this, an excess of 4% deaths by 35 d after infarction (statistically not significant) contrasts sharply with the reduction reported from the LIMIT-2 (Woods *et al.* 1992) and other trials.

To nutritionists and to epidemiologists, however, the question of greatest interest is whether or not Mg is protective in normal subjects in the general population. Relevant evidence seems to be extremely sparse, and to date it would seem that dietary Mg intake data have been reported from only one large cohort study (The Caerphilly and Speedwell Collaborative Group, 1984). The Caerphilly Prospective Study is based on a cohort of 2512 older men who have been followed for 10 years. While preliminary evidence suggested a protective role for Mg, further examination of the data suggests that a negative association between dietary Mg intake and subsequent IHD events, may be totally explained by confounding variables, in particular alcohol intake (Table 3).

Table 3. *Dietary magnesium and heart disease: mean Mg intakes for men in the Caerphilly Prospective Study of Heart Disease and Stroke cohort who died from an acute myocardial infarction (ICD 410; MI), suffered a non-fatal myocardial infarct, or experienced no myocardial infarction during a 10-year follow-up*

Outcome	Mean Mg intake (mg/d)		
	1	2	3
Acute MI death	242	256	265
Non-fatal MI	259	256	260
No IHD event	265	265	264

1, Standardized for age and smoking; 2, alcohol intake added; 3, energy intake added; IHD, ischaemic heart disease.

Table 4. *Serum and erythrocyte magnesium and heart disease based on 2046 men, aged 45–59 years, followed for 5 years\**

Outcome	<i>n</i>	Serum Mg	Erythrocyte Mg
Acute MI death	38	0.82	5.43
Non-fatal MI	93	0.81	5.57
No IHD event	1905	0.83	5.32
		(SD 0.06)	(SD 0.53)

MI, myocardial infarction; IHD, ischaemic heart disease.

\* Mg levels estimated at baseline.

Further confirmatory evidence comes from an absence of any predictive power of estimations of serum and erythrocyte Mg, made 5 years into the study and, hence, evaluated against incident events during 5 years of follow-up (Table 4).

#### CONCLUSION

IHD is a multifactorial disease, and it is likely that many dietary factors are involved. The current interest in free radicals and in dietary antioxidants enormously heightens expectations of important associations with dietary items.

Wide media attention has been focused recently on Fe, following the report of an association between a measure of storage Fe (serum ferritin) and myocardial infarction (Salonen *et al.* 1992). Two larger studies gave no confirmation, however, and a wide range of studies of other measures of Fe status have given inconsistent, but largely negative, results.

It is even more difficult to assess the evidence on Mg and IHD. Expectations of benefit arise from a very large number of animal and laboratory studies, but two large trials of the beneficial effect of Mg in patients at high risk of death from heart disease have given results which are totally inconsistent. Preliminary evidence on the relevance of Mg in the general population is limited at present to a single cohort study and this gives no evidence of prediction for death by dietary Mg, once allowance has been made for the effects of confounding factors, in particular alcohol.

## REFERENCES

- Adams, J. H. & Mitchell, J. R. A. (1979). The effect of agents which modify platelet behaviour and of magnesium ions on thrombus formation *in vivo*. *Thrombosis and Haemostasis* **42**, 603–610.
- Anderson, T. W., Neri, L. C., Schreiber, G. B., Talbot, F. D. F. & Zdrojewski, A. (1975). Ischaemic heart disease, water hardness and myocardial magnesium. *Canadian Medical Association Journal* **113**, 199–203.
- Ascherio, A., Willett, W. C., Rimm, E. B., Giovannucci, E. L. & Stampfer, M. J. (1994). Dietary iron intake and risk of coronary disease among men. *Circulation* **89**, 969–974.
- Biemond, P., Swaak, A. J., Beindorff, C. M. & Koster, J. F. (1986). Superoxide-dependent and -independent mechanisms of iron mobilization from ferritin by xanthine oxidase: implications for oxygen-free-radical-induced tissue destruction during ischaemia and inflammation. *Biochemistry Journal* **239**, 169–173.
- Carter, C., McGee, D., Reed, D., Yano, K. & Femmermann, G. (1983). Haematocrit and the risk of coronary heart disease: the Honolulu Heart Program. *American Heart Journal* **105**, 674–679.
- Chipperfield, B. & Chipperfield, J. R. (1973). Heart muscle magnesium, potassium and zinc concentrations after sudden death from heart disease. *Lancet* **ii**, 293–296.
- Cross, C. E., Halliwell, B., Borish, E. T., Pryor, W. A., Saul, R. L., McCord, J. M. & Harman, D. (1987). Oxygen radicals and human disease. *Annals of Internal Medicine* **107**, 526–545.
- Elwood, P. C., Sweetnam, P. M., Beasley, W. H., Jones, D. & France, R. (1980). Magnesium and calcium in the myocardium: cause of death and area differences. *Lancet* **ii**, 720–722.
- Gold, M. E., Buga, G. M., Wood, K. S., Byrns, R. E., Chaudhuri, G. & Ignarro, L. J. (1990). Antagonistic modulatory roles of magnesium and calcium on release of endothelium-derived relaxing factor and smooth muscle tone. *Circulation Research* **66**, 355–366.
- Iseri, L. T., Alexander, L. C., McCaughey, R. S., Boyle, A. J. & Myers, G. B. (1952). Water and electrolyte content of cardiac and skeletal muscle in heart failure and myocardial infarction. *American Heart Journal* **43**, 215–227.
- ISIS Collaborative Group (1993). ISIS-4: randomised study of intravenous magnesium in over 50,000 patients with suspected acute myocardial infarction. *Circulation* **88**, Suppl. I, 292.
- Magnusson, M. K., Sigfusson, N., Sigvaldason, H., Johannesson, G. M., Magnusson, S. & Thorgeirsson, G. (1994). Low iron-binding capacity as a risk factor for myocardial infarction. *Circulation* **89**, 102–108.
- Morrison, H. I., Semenciw, R. M., Mao, Y. & Wigle, D. T. (1994). Serum iron and risk of fatal acute myocardial infarction. *Epidemiology* **5**, 243–246.
- Rude, R. (1989). Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *American Journal of Cardiology* **63**, 31G–34G.
- Salonen, J. T., Nyssönen, K., Korpela, H., Tuomilehto, J., Seppänen, R. & Salonen, R. (1992). High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. *Circulation* **86**, 803–811.
- Sempos, C. T., Looker, A. C., Gillum, R. F. & Makuc, D. M. (1994). Body iron stores and the risk of coronary heart disease. *New England Journal of Medicine* **330**, 1119–1124.
- The Caerphilly and Speedwell Collaborative Group (1984). Caerphilly and Speedwell collaborative heart disease studies. *Journal of Epidemiology and Community Health* **38**, 259–262.
- Woods, K. L. (1991). Possible pharmacological actions of magnesium in acute myocardial infarction. *British Journal of Clinical Pharmacology* **32**, 3–10.
- Woods, K. L., Fletcher, S., Roffe, C. & Haider, Y. (1992). Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* **339**, 1553–1558.
- Yarnell, J. W. G., Baker, I. A., Sweetnam, P. M., Bainton, D., O'Brien, J. R., Whitehead, P. J. & Elwood, P. C. (1991). Fibrinogen, viscosity, and white blood cell count are major risk factors for ischaemic heart disease. The Caerphilly and Speedwell Collaborative Heart Disease Studies. *Circulation* **83**, 836–844.
- Zoll, P. M., Wessler, S. & Schlesinger, J. (1951). Inter-arterial coronary anastomoses in the human heart with particular reference to anaemia and relative cardiac anoxia. *Circulation* **4**, 797–815.