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Chapter 27

Epidemiologic Data on Magnesium Deficiency-associated Cardiovascular Disease and Osteoporosis: Consideration of Risks of Current Recommendations for High Calcium Intakes

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Summary

Surveyed here are epidemiologic data on Mg deficiency, alone and in association with Ca excess that indicate the importance of Mg adequacy on cardiovascular health. Mechanisms by which Mg deficiency affects the cardiovascular system adversely, and enhances intra-vascular coagulation, especially in conjunction with excessive Ca and/or estrogen replacement therapy, or in the pathogenesis of eclampsia, placental thrombosis and IUGR and pre-term births, have been considered elsewhere, where also considered have been findings that pertain to the need for Mg in bone matrix maintenance, and thus on resistance to bone fracture.[3,116–118] Epidemiologic data implicating Mg deficiency in calcific uroliths have been largely from studies of water.[1] The vulnerability of Mg deficient animals on high Ca diets to renal calcification and calcium oxalate stone formation, and the efficacy of Mg treatment in clinical calcific urolithiasis have been summarized elsewhere.[119] The provocative findings that Mg deficiency, intensified by Ca excess predisposes to cardiovascular disease, and that where cardiovascular disease is prevalent, so is osteoporosis – for which increased Ca intake is advised, suggest the need for reevaluation of how best to manage these serious public health problems. The evidence that high intracellular Ca/Mg levels are associated with insulin resistance, and with the associated disorders that comprise the GCVD: hypertension, arteriosclerosis, hyperlipidemia, aging, as well as obesity, suggest the desirability of exploring the influence of raising the dietary Mg intake on tissue Ca/Mg. The epidemiologic evidence of association of LBW with adult CVD, diabetes, and insulin resistance, suggests that the influence of Mg supplementation on prevalence of conditions leading to fetal malnutrition should be studied. Even before controlled Mg intervention studies are undertaken during pregnancy, in young high cardiovascular risk subjects, and in those prone to osteoporosis, because Mg supplementation is benign, and does not require life style or food habit change, public health measures to assure optimal Mg intake should be considered.

Key words: Epidemiology cardiovascular disease (or CVD), osteoporosis, calcific uroliths, insulin resistance, syndrome X, diabetes, obesity eclampsia, pre-term delivery, intrauterine growth retardation (or IUGR), low birth weight (or LBW) magnesium deficiency, calcium excess, dietary recommendations.

Introduction

There is experimental and clinical evidence that the amount of magnesium (Mg) in the typical western diet is insufficient to meet individual needs. Epidemiologic studies of the contributions of dietary Mg deficiency to disease, additional to those that derive from comparisons of hard and soft water,[1] provide insight into the importance of meeting Mg requirements to protect against cardiovascular disease (CVD). Both experimental[2] and clinical[3] studies of its intake have shown that Mg maintains cardiovascular integrity.[4] Higher Mg intakes, whether from food or supplements, protect against arterial and cardiac disease, that low intakes enhance. Substantial increases of calcium (Ca) intake can intensify Mg deficit. High intracellular (i.c.) Ca/Mg ratio in metabolic disorders has been associated with insulin resistance with and without diabetes, obesity, CVD, and even disorders of aging,[5–7] conditions that constitute a growing health problem in the industrialized world. There are fewer epidemiologic studies on Mg and osteoporosis, and complications of pregnancy that result in poor maternal and fetal outcomes (*infra vide*), but some of the findings, uncovered by studies not considering Mg, and experimental data, suggest that Mg insufficiency may be contributory.

Are magnesium intakes adequate?

There have been steady falls in Mg intakes and rises in Ca, phosphorus (P) and vitamin D intakes, as indicated by metabolic and dietary survey studies from 1922 to 1977[8–13] (Fig. 1). Dietary surveys in the industrialized world, in the last two decades of the 20th century, have shown that average Mg intakes are about 300–350 mg/day for women and men, respectively; for women, they are often lower.[14–24] Adequacy in dietary Mg is commonly presumed if hypomagnesemia or Mg deficiency manifestations, such as convulsions, do not develop. CVD with functional or structural pathologic changes, that resemble those produced by pure or relative Mg deficits in laboratory models, are a major health problem that is not often recognized by physicians or nutritionists as being related to human Mg deficiency. In 1998, the Food and Nutrition Board, in the United States (US), in determining recommended dietary allowances (RDA), went beyond preventing overt deficiencies and now consider current concepts about the role of nutrients in achieving long-term health.[25] This has led to increase of the RDA of Mg for women to 310–360 mg, and for men to 410–420 mg. The RDA for Ca for both sexes was also raised to 1000–1300 mg, and that for P to 700–1250 mg. But a new category: upper limits (UL), amounts that are deemed tolerable, has been created to provide guidelines for supplements and for fortification of foods. The UL for Ca is 2500 mg; that for P is 3500 mg,

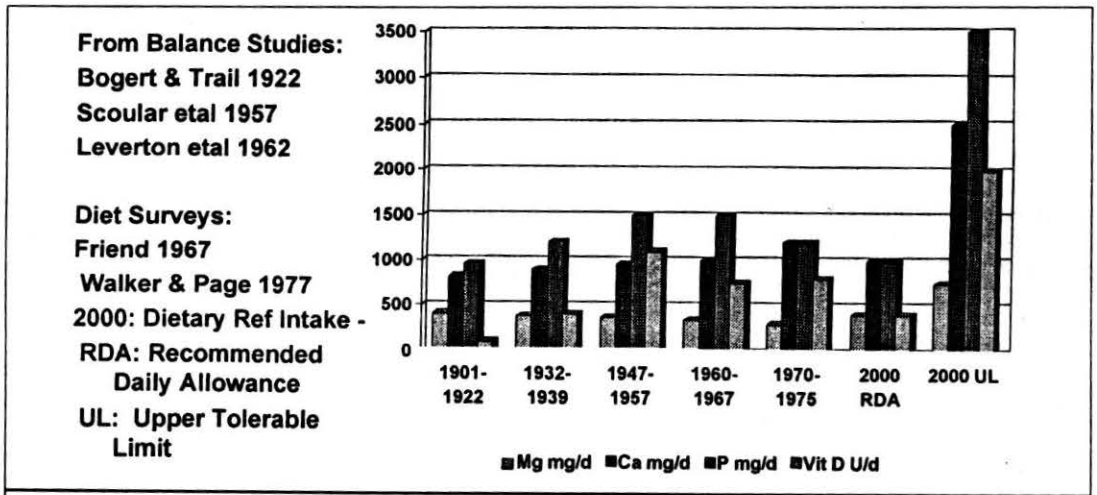

Fig. 1. Increasing dietary American Ca/Mg ratios from early 20th century with increasing PO_4 and vitamin D.

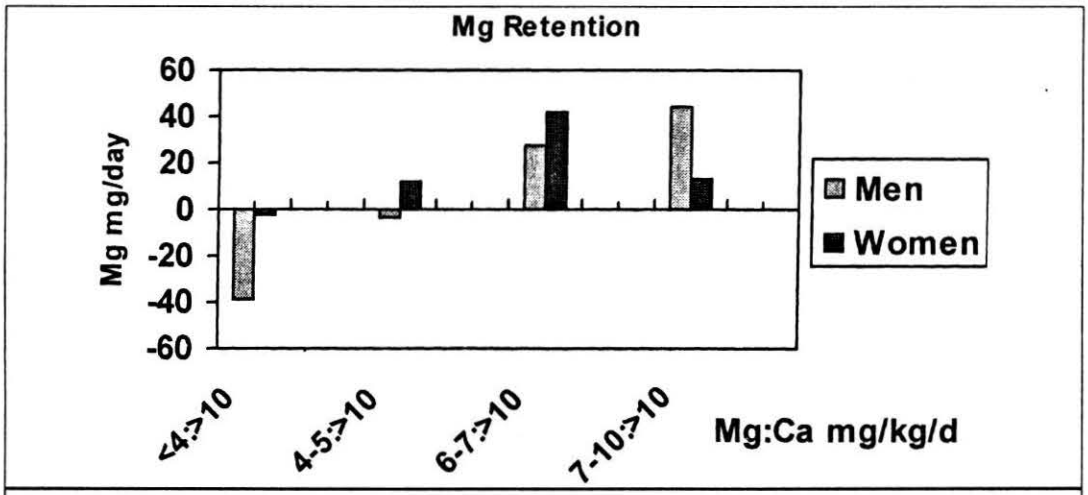

Fig. 2. High Ca intake effect on Mg balance in normal men and women on low to high Mg intakes. [Adapted from Seelig MS: Am. J. Clin. Nutr. *14:342–390, 1964.*

and are derived from diet and supplements. The UL of 350 mg for Mg that is just from supplements, can result in Ca/Mg ratios that are unphysiologic by those accepting the UL as amounts of Ca and vitamin D that are advised. RDA and UL figures are depicted in the last two banks of columns of Fig. 1, with the UL column for Mg derived from an average RDA plus 350 mg for supplements. A Ca/Mg ratio of 2/1, provided by daily Mg intake of 600 mg and a Ca intake of 1200 mg/day was considered suitable for maintenance of health by Schmidt and Greenberg in 1935,[26] on the basis of their extensive review of the literature. The current RDA allowances provide a Ca/Mg ratio of 3/1; the UL allows for 4/1 or higher ratios. Since P excess intensifies Mg loss,[27] the high UL for P can aggravate the problem. Since therapeutic amounts of Mg, even when given parenterally are generally safe, until there are definitive data as to optimal intakes under different physiologic and pathologic conditions, Mg intakes should be increased to not less than 6 mg/kg/d for young adults.[20,28,30]

Metabolic balance studies of magnesium; influence of calcium

Human metabolic balance studies have shown that high intake of Ca or Mg, each interferes with intestinal absorption and renal retention of the other, when low amounts are present. Early extensive Mg balance studies of normal young adults showed negative Mg and Ca balances at Mg intakes below 5 mg/kg/day, when Ca intakes are not high.[28–33] On Mg intakes below 300 mg/day, Mg balances were either negative or barely in balance at Ca intakes of 1 g/day. At 5–6 mg/kg/day of Mg, Ca intakes below 1 g/day allowed for positive Mg balances, that Ca intakes above 1 g/day diminished (Fig. 2). Very high Ca intakes, if the Mg intake is low, can result in negative Mg balance and positive Ca balance, but in such a circumstance the Ca deposition can be in soft tissues, rather than in bone. High Mg intakes do not interfere with Ca retention, and improve Ca retention unless the Ca intake is very low.[28,29,34]

Dietary magnesium and calcium and cardiovascular disease

Analysis of metabolic balance studies done worldwide, that disclosed better retention of Mg by young women than by men, and greater intake of Mg in the East than in the West, led to an hypothesis, presented in 1964,[35] that the greater prevalence of cardiovascular disease in young women than in men and in occidental than oriental men might partially stem from relative Mg inadequacy. That this might underlie the prevalence of CVD in industrialized nations has since been reiterated by the author, citing experimental, clinical and epidemiologic evi-

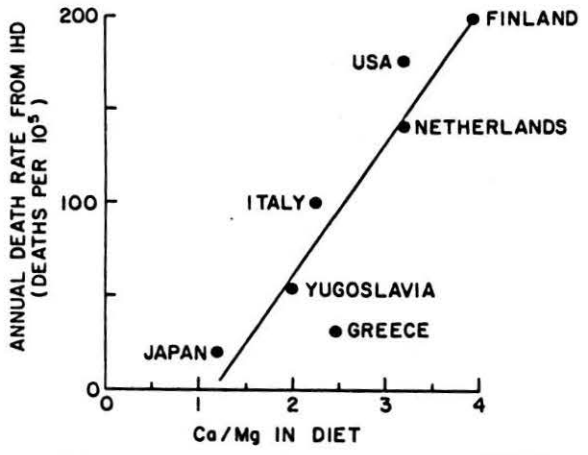

Fig. 3. Increase in IHD mortality with high Ca/Mg intake ratios.
[Reproduced with permission from Karppanen H, Pennanen R, Passinen L: Minerals, coronary heart disease and sudden coronary death. Adv Cardiol *25:9–24, 1978.]*

dence.[1–4,28,32,35,36] Anderson and his coworkers, before he related differences in rates of ischaemic heart disease (IHD) in Canadian men to water-borne Mg,[37] observed that before 1920 men and women were equally prone to CVD, but that fatal IHD rose dramatically in men thereafter.[38]

Ca/Mg ratios and CVD

The first to call attention to high dietary Ca/Mg ratios as a factor that plays an important role in the serious health problems caused by CVD worldwide, as well as in Finland, was Karppanen, *et al.*[39] The line graph (Fig. 3) depicts the increase in IHD mortality that occurs with high Ca/Mg intake ratios. Japan was shown to be lowest in both Ca/Mg ratio, and IHD mortality, in contrast to Finland which was highest in both. Kimura *et al.*[40] have shown that, as dietary Ca/Mg ratios have risen in Japan, to amounts close to those in the occident, CVD has become more prevalent. Age-adjusted increased mortality from IHD and strokes in Japan, between 1971 and1985 were shown by Sei *et al.*[41] to be correlated with increased Ca/Mg ratios, as well as with low dietary potassium (K). Both these groups of investigators attributed mineral intake shifts to departure from the traditional diet that is rich in fruit and vegetables. A study by Itoh *et al.*[42] in Japan found a high dietary Ca/Mg ratio to be more important than low Mg alone in hypertension development. A Chinese study by Lai *et al.*[43] showed high dietary Ca/Mg ratio to be a strong predictor of high systolic blood pressure.

CVD prevalence change with population moves that change Mg intakes

Jeppeson[44] considers the much lower incidence of CVD (as well as of diabetes, osteoporosis and uroliths) of Danes in Greenland, than in Denmark, to be due to their much lower dietary Ca, and their lower serum Ca/Mg ratios. Differences in CVD among men of the same racial or ethnic background, whose Mg intakes changed when they migrated to other lands, have been reported in other countries. Brown *et al.*[45] compared the high incidence of IHD of Boston men, with its lower and later development in their brothers who remained in Ireland. They had substantial dietary differences: more potatoes, cereals and butter and oil in Ireland, despite which there was less obesity, and more meat, fruit, vegetables and a higher ratio of mono- and polyunsaturated fatty acids to saturated fats in Boston. The Irish brothers ate more Ca-rich food daily (1644 mg Ca) than did those in Boston (1189 mg), but their daily Mg intake was also

higher: 404 mg in Ireland and 255 mg in Boston, yielding Ca/Mg ratios of 4/1 in Ireland, and almost 5/1 in Boston. The greater amount of alcohol drunk each day by the Boston brothers (36 g) than by the Irish brothers (16 g), lowered the amount of Mg retained. Another study found a low incidence of IHD in sons of European fathers,[46] living in North Dakota, despite their diets being the same: high salt, fat and Ca diet, and high alcohol ingestion, as it was in Finland, the country of origin of the Europeans (Enterline, personal communication). In this case, the likely protective factor was the high Mg content of the water from wells on the farms.

American nutrition/CVD Surveys

Ma *et al.*[47] reported relationships of dietary and serum Mg with prevalence of CVD, hypertension, diabetes, fasting insulin, and carotid wall thickness, in 15,248 subjects of both sexes in the US, from the Atherosclerosis Risk in Communities (ARIC) study. Serum and dietary Mg levels were significantly lower in those with CVD, hypertension and/or non insulin dependent diabetes mellitus (NIDDM), and were inversely associated with fasting insulin and glucose levels. Another group (Colditz *et al.*[48]) investigated the influence of nutrients on development of NIDDM in the Nurses Health Study of 84,360 US women, and reported reduced risk with diets high in Mg and/or K. Prospective study of the relation of dietary and serum Mg to development of IHD in 13,922 middle-aged subjects free of CVD, over 4 to 7 years, in the ARIC study,[49] disclosed that among 223 men and 96 women who developed IHD, the findings were suggestive that low Mg contributes to coronary atherosclerosis or acute thrombosis. Data from a19 year follow-up of 12,340 participants, 25 to 74 years of age (National Health And Nutrition Examination Survey [NHANES]), were examined by Ford,[50] who reported, in 1999, that there had been 1,005 IHD deaths, and 2,637 IHD hospitalizations or deaths, that were inversely associated with serum Mg levels.

Asian and European surveys and intervention studies of Mg and CVD

Singh *et al.*[51] reported results of a ten-year randomized study of 400 high CVD risk mostly male volunteers, 25 to 63 years of age. Group A (#206) were given Mg-rich diets (1,142 ± 233 mg/day); Group B (#194) stayed on their usual diet (418 ± 105 mg of Mg/day). At outset they had comparable NIDDM, hyperlipidemia, IHD, hypertension, diuretic treatment and smoking histories. At study end, group A had fewer total complications (28.6 per cent) than did Group B (60.3 per cent), among whom there were one and a half times more sudden deaths ($P < 0.001$). These investigators then surveyed 501 rural (270M; 231 F) and 505 urban (250M; 255 F) randomly selected north Indian subjects between 50–54 years of age, to determine association of Mg with risk of IHD.[52] IHD prevalence was threefold higher in urban than in rural subjects. Dietary intake of Mg was significantly higher in rural men (520 ± 58 versus 415 ± 47 mg/d) and women (432 ± 40 versus 316 ± 38 mg/d), and it was inversely correlated with serum Mg and IHD. The odds ratio for dietary Mg intake indicates a higher prevalence of IHD at lower Mg intakes in both rural (0.67, 95 per cent confidence interval [C.I.] 0.51 to 0.86) and urban (0.72, 95 per cent C.I. 0.54 to 0.90) subjects. Another study from India,[53] including 3575 subjects, 25–64 years old: 1769 rural and1806 urban subjects equally divided by sex, verified the threefold greater prevalence of IHD among urban than rural subjects, that was related to their lower Mg intakes. Subjects with low Mg intakes, had higher prevalence of hypertension, hypercholesterolemia and NIDDM. Singh *et al.*[53] suggest that increased intake of Mg to about 500 mg/day might be of benefit in the prevention of IHD. Elwood *et al.*[54] reported a dietary study of 2172 Welsh men aged 45–59 years, followed for ten years, among whom there were 269 IHD events, including 232 myocardial infarctions, of whom 96 were fatal. All had low Mg intakes, but of the 434 who had the lowest intakes (266 mg), 70 developed an IHD event; mean Mg intake of those who died of IHD was 253 mg. Those without IHD event had mean Mg intakes of 281 mg. Lasserre *et al.*[55] undertook a follow-up epidemiologic survey in Switzerland on 712 patients, including 52 with proven IHD who were matched with and compared to 52 coronary-prone subjects with similar major risk factors, and to 52 patients at low risk, but who were free

of overt IHD. Patients with IHD, below 60 years, had significantly lower red blood cell (rbc) Mg than did older subjects. More cardiac events occurred in the follow-up period in patients with lower rbc Mg, and they had more unfavourable outcomes. A 6 month open pilot trial of oral Mg supplementation (350 mg/day for three months followed by 250 mg/day for three months) of nine IHD patients who had low rbc Mg raised their Mg levels, decreased their anginal attacks and was associated with less ST segment depression by electocardiography on exercise testing.

Epidemiologic studies of hypertension and Mg

Among the studies, in different countries, on Mg intake or levels, in the pathogenesis of CVD, several have dealt only with hypertension. Kesteloot[56] correlated dietary Na, K, Ca and Mg with blood pressures and serum cation levels of 3814 Belgian men and women. There was significantly negative correlation between dietary Ca intake and diastolic blood pressure in men, and between dietary Mg and systolic pressure in women. A 1989 Chinese study of the relation between blood pressure and urinary cations (Na, K, Ca and Mg) among Yi people[43] found that those with most cultural advantage had most hypertension, that was positively related to a high urinary Ca/Mg ratio. In another part of China, Li *et al.*[57] found that reduced intake of Mg was associated with slightly increased systolic blood pressure. An intervention study in the US of four combinations of K, Ca and Mg by Sacks *et al.*[58] in 125 subjects did not prove combinations of cation supplements to be important in treatment of mild or borderline hypertension. A study by van Leer *et al.*,[59] of 20,921 women and men in the Netherlands showed that diets rich in Ca, K and Mg are associated with lower blood pressure, than diets poor in those cations. Geleijnse *et al.*[60] reported that of 3239 Dutch subjects over 55 years of age, increasing their Mg intake by 100 mg lowered blood pressure. Only in a subgroup of 1360 was increased Ca associated with lower diastolic blood pressure. On the other hand, a Russian study by Davydenko *et al.*[61] of 1556 urban men, aged 20–59 years, and evaluated for relations between mineral intakes and blood pressure, disclosed that high intakes of Ca or Zn were associated with more hypertension, and that hypertension was seen twice as often in those with low dietary intakes of Mg, as at high intakes. Singh *et al.*[62] found that of 1769 subjects in India, higher social classes, who had less hypertension than lower classes, also had higher dietary and serum Mg. In Japan, a high dietary Ca/Mg ratio exerted more influence on development of hypertension than did low Mg alone.[42]

Several large American studies prospectively studied effects of Ca and Mg on blood pressure. During four years' follow-up of 58,219 nurses, aged 34–59 years, 3,275 reported diagnosis of hypertension and the effects of 800 mg of Ca/day versus 400 mg Ca/day, and effects of 300 mg of Mg/day or more versus 200 mg of Mg (Witteman *et al.*, 1989[63]). Their findings of possible risks of high Ca/Mg intakes suggested randomized trials of dietary Ca and Mg on blood pressure control. In 1992, Ascherio *et al.*[64] of the same group, found that dietary fibre, K and Mg were each inversely related to blood pressure among 30,681 normotensive men 40–75 years old. During four years of follow-up, alcohol consumption was a strong predictor for development of hypertension. Ca affected risk only in lean men. Increased fibre and Mg intakes seemed of value in preventing hypertension. In an extended study [65] of 43,738 men, 40 to 75 years old, free of CVD or NIDDM, they associated low intakes of K, Mg, and cereal fibre, but not of Ca, with increased risk of ischaemic stroke.

The World Health Organization (WHO) has investigated the effect of Mg on blood pressure, in its Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study.[66–69] First, comparative studies of nutrients in two rural regions in Spain and Japan with low incidences of IHD suggested that their low blood pressures might be due to their Mg rich diets: rich also in K in the Mediterranean diet in Spain, and rich also in fish protein in Japan (Horie *et al.*).[66] In the CARDIAC study, which in 1990 comprised 45 centres in 20 countries, 100 men and 100 women of 50 to 54 years were randomly selected from each centre for blood pressure, urine,

and blood tests. Findings supported adverse effects of Na and obesity, but animal protein and Mg intakes seemed to have beneficial influence on blood pressure (Yamori *et al.*).[67] Four years later, with extension of the CARDIAC study to 55 centres in 24 countries, a significant inverse relation was found between 24-h Mg/creatinine excretion ratio and diastolic blood pressure in men (Yamori *et al.*, 1994).[68] Mizushima *et al.*[69] pointed out that seven of 12 studies showed a negative association Mg intake with blood pressures, indicating need for a systematic quantitative overview.

Low intracellular Mg/high intracellular Ca in hypertension and associated diseases

Resnick *et al.*[70] demonstrated that untreated patients with essential hypertension had lower rbc free Mg and elevated rbc Ca levels than did normal subjects, and in 1984, suggested that low i.c. Mg levels are important in the pathophysiology of hypertension. In Japan in 1988, Shibutani *et al.*[71] observed that serum Mg levels were significantly correlated with rbc Mg in both boys and girls in a survey of 380 junior high school students. Those with lower rbc Mg levels had higher blood pressures and more family history of hypertension than did students with lower rbc Mg. The authors suggested that i.c. Mg deficit is partially responsible for elevated blood pressure in children with familial hypertension, and that a genetic predisposition to hypertension may be closely related to Mg metabolism. Resnick *et al.*[5–7,72] correlated interrelations of i.c. cations with insulin resistance, which is seen in an important new complex of commonly familial diseases: hypertension, atherosclerosis, hyperinsulinemia, NIDDM, hyperlipidemia, and obesity, that has been named Syndrome X, Insulin Resistance Syndrome and that they suggest should better referred to as generalized cardiovascular metabolic disease (GCMD).

Low birth weight, CVD and magnesium

Evidence of low birth weight (LBW) infants = Susceptibility to CVD

Epidemiologic studies of the relationship of CVD to LBW in several thousand adults, in England, implicate intrauterine malnutrition in subsequent diseases, primarily of the cardiovascular system. Barker *et al.*[73–75] have correlated disorders, such as insulin resistance, NIDDM and Syndrome X, in children and adults who had been abnormally small at birth, with fetal malnutrition. They suggest that there may be programming of cardiovascular, endocrine and metabolic regulatory systems of unknown origin, to explain the greater vulnerability to CVD of these people, but this group has not considered the possibility that gestational Mg deficiency might be contributory to eclampsia which is an important cause of LBW.

Mg effects on eclampsia and on maternal and fetal outcome

Disregard of Mg in the studies of CVD vulnerability of people who had been LBW might reflect the delay in British acceptance of the strong American and German evidence of the value of Mg in improving maternal and fetal outcomes since the 1960s in the US,[76] and from Germany since the 1980s.[77,78] Wynn and Wynn[79] pointed out, in 1988, that 7.2 per cent of babies born in England and Wales in 1986 had birth weights below 2,500 g, and that there were European trials that found that oral Mg supplementation with physiological amounts of Mg during pregnancy reduces pregnancy induced hypertension and miscarriage, intrauterine growth retardation (IUGR) and pre-term birth. They referred to evidence that Mg intakes of many women in Europe and North America are too low to support a healthy pregnancy, and advocated Mg supplement trials and paying attention to Mg in nutritional advice given to pregnant women. A survey of 1007 British obstetric consultants, reported by Hutton *et al.* four years later,[80] disclosed that only 2 per cent used Mg to manage eclampsia. After a study of therapy of 1687 eclamptic women, The Eclampsia Trial Collaborative Group reported, in 1995, better maternal and fetal outcomes with Mg than with drugs in common use,[81] confirming American findings of thirty years before.[76]

Nutrition and medical studies have shown that Mg intakes, by pregnant mothers are commonly insufficient to meet their needs, and to prevent infantile disorders.[3,30,82-90] It has been recommended that the supply over the adult female requirement should be increased by at least 150 mg.[21,87] Most prenatal vitamin-mineral supplements provide 100 mg of Mg.[87] In Hungary, gestational Mg deficiency has been clearly associated with poor gestational outcomes, including high rates of spontaneous abortions and pre-term deliveries in regions where the water supply is very low in Mg.[1,91] Their intervention studies with oral Mg salt supplementation of pregnant women in those low Mg regions, have reduced the prevalence of spontaneous abortions and premature births.[92-95] Since Mg deficiency predisposes to complications of pregnancy that interfere with normal fetal development and growth, clinical investigators and epidemiologists should determine if Mg supplementation during pregnancy should be implemented widely, and if it might favourably impact even on adult CVD.

Osteoporosis and Mg: Needs for bone and cardiovascular system

Prevalence of osteoporosis, as affected by dietary intakes of Mg and Ca

Osteoporosis is widespread in Finland, despite lifelong high Ca/Mg intake ratios, where it has increased over the years, as indicated by studies through 1995 by Simonen[96] and Kannus *et al.*[97] In Sweden, where osteoporosis is prevalent, a dietary survey by Michaelsson *et al.*[98] of over 65,000 women indicated that high Ca intakes did not protect against development of osteoporosis, but that high dietary intakes of Mg and iron seemed protective. Angus *et al.*[99] studied the influence of 14 nutrients on bone mineral density (BMD) of the proximal femur and of hip and vertebrae of 159 white Australian women (23–75 years old). Their Ca intake was not correlated with bone mass at any site, but Fe was a positive predictor of BMD in femoral neck, and alcohol intake was a negative predictor of BMD in the trochanter of the proximal femur in premenopausal women. In that study, both low Mg and iron were significant predictors of decreased BMD in forearms in pre- and post-menopausal women. An American study of nutrient intakes of surviving members of the original Framingham Heart Study cohort, with BMD evaluation of their bones at three hip sites and at one forearm site, was reported by Tucker *et al.* in 1999.[100] They found that high K intake was significantly associated with greater BMD, and that high Mg intake was associated with greater BMD at one hip site for both sexes and in the forearm for men. Fruit & vegetable intake was also positively associated with BMD. Nine years earlier, Abraham and Grewal,[101] having found that high Ca intake exerted no significant effect on trabecular BMD, instituted a dietary program emphasizing Mg instead of Ca to manage 19 postmenopausal patients on hormonal replacement therapy, 15 of whom had BMD below the spine fracture threshold. The decision to achieve high Mg intake was to avoid soft tissue calcification, that might be a risk of high Ca intake. There was significantly increased BMD of calcaneous bone within one year, sufficient to be above the fracture threshold in eight, in contrast to seven control osteoporotic patients, who showed no bettering of BMD.

Before considering the few studies on administration of Mg supplements, it is well to make note of a possible source of error in studies that postulate a protective role for high dietary intakes of Ca in osteoporosis, and other diseases, that was pointed out by Holbrook and Barrett-Connor.[102] They analysed dietary patterns, differing by Ca intakes, of 957 men and women 50–79 years old in California. They found that adjusted intakes of several nutrients that affect bone: protein, vitamin D, P, and Mg, were significantly higher, and alcohol intakes were much lower in the high Ca-intake groups than in the low- and mid-Ca- intake groups.

Magnesium trials in osteoporosis

Cohen *et al.*, in Israel[103,104] and Driessens *et al.*[105] from The Netherlands and Czechoslovakia have diagnosed Mg deficiency in patients with osteoporosis. Ditmar and Steidl[106] reported favourable clinical results with oral Mg lactate alone in 37 osteoporotic patients, whose evaluation at three half-year intervals, for two years showed improvement in pain and spine

movement. Driessens *et al.*[105] affirmed the two year improvement, but found no further improvement with longer therapy. Stendig-Lindberg *et al.*,[107] in Israel, found that two years treatment of 31 post-menopausal osteoporotic women with $Mg(OH)_2$ (2–6 125 mg tablets/day for 6 months and two tablets for another 8 months) in an open, controlled therapeutic trial, improved trabecular BMD 1–8 per cent by one year in 22 (71 per cent), a benefit that persisted through the second year. The mean BMD of the responders increased significantly both after one year ($P < 0.001$) and after two 2 years ($P < 0.02$), while in controls: 23 comparable women who refused treatment, the mean BMD decreased significantly ($P < 0.001$). A group of American postmenopausal women given $Mg(OH)_2$ for two years to assess the effects of Mg on bone density, reported by Sojka and Weaver,[108] experienced no fractures and exhibited significantly increased bone density. Rude and Olerich[109] found that among 14 patients with malabsorption eight had low rbcMg^{2+} and subnormal BMD of the lumbar spine and proximal femur. Five of the eight were given 504–576 mg of $MgCl_2$ or Mg lactate, and were followed for two years; they exhibited significantly increased BMD in femoral neck and total proximal femur, that correlated positively with increased rbc Mg^{2+}.

Co-existence of osteoporosis and cardiovascular disease

The widespread emphasis on increasing Ca intake, in order to increase mineralization of bone, can result in even higher Ca/Mg ratios than Karppanen and his co-workers[39] have correlated with the high incidence of IHD in Finland (4/1, see Fig. 3), where there is also wide prevalence of osteoporosis. Prevalence of atherosclerosis in association with osteoporosis in the aged has been correlated with three dietary factors: excess vitamin D, high fat intake, and Mg inadequacy.[110] Abbott, Nadler & Rude[111] consider alcoholism another factor, that increases risk of both arteriosclerosis and osteoporosis, since it increases Mg loss, and point out several mechanisms by which the Mg deficiency can contribute to osteoporosis: abnormal vitamin D and parathyroid metabolism, and to arteriosclerosis: increased thrombogenesis. Among the conditions with high i.c. Ca/Mg ratios, that exist as an integral part of the GCMD Syndrome (*supra vide*), are several known to increase vulnerability to osteoporosis: NIDDM, aging-both in men and women, as well as Mg-wasting alcoholism – both acute and chronic.

Osteoporotic men and women over the age of sixty were reported, in 1971, to have significant calcification of the aorta,[112] an observation that was confirmed in 1991 in a Czech study that disclosed aortic calcification in 98 per cent of women with osteoporosis.[113] A 1997 study in Japan showed carotid artery plaques scores to be correlated with low bone density in post-menopausal women,[114] an interesting observation in view of the 1991 study by Browner *et al.*,[115] in California, that strongly associated low BMD with strokes. For each S.D. decrease in BMD, there was a 70 per cent increase in stroke mortality.

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