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Magnesium Research (1990) **3**, 3, 197–215 REVIEW ARTICLE

Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment

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Summary: Prophylactic treatment of postmenopausal osteoporosis with oestrogen and calcium, often in combination, disregards the likelihood that an excess of each agent may increase magnesium requirements and decrease serum Mg levels. Relative or absolute Mg deficiency, which is likely in the Occident where the Mg intake is commonly marginal, can militate against optimal therapeutic bone response, Mg being important for normal bone structure, and can increase the risk of adverse effects. Although oestrogen has cardiovascular protective effects (expressed by the lower incidence of heart disease in premenopausal women than in men, and also in postmenopausal women given low dosage oestrogen replacement treatment), high dosage oestrogen oral contraceptives have caused increased intravascular blood clotting with resultant thromboembolic cardio- and cerebrovascular accidents. This might be contributed to by the oestrogen-mediated shift of circulating Mg to soft and hard tissues, which in persons with marginal Mg intakes may lead to suboptimal serum levels. If the commonly recommended dietary Ca/Mg ratio of 2/1 is exceeded (and it can reach as much as 4/1 in countries with low to marginal Mg intakes), relative or absolute Mg deficiency may result, and this may increase the risk of intravascular coagulation, since blood clotting is enhanced by high Ca/Mg ratios. Mechanisms by which Ca activates the various steps in blood coagulation that are also stimulated by oestrogen are considered here, as are the multifaceted roles of Mg that favourably affect blood coagulation and fibrinolysis, through its activities in lipoprotein and prostanoid metabolism.

Key words: Alcoholic, bone structure, calcium therapy, Ca/Mg ratio, combination therapy, diabetic, intravascular coagulation, malabsorption, Mg deficiency, Mg lipoproteins, Mg requirements, oestrogen therapy, osteoporosis prophylaxis, postmenopausal, prostanoids.

Introduction

Far less appreciated than calcium in the treatment or prevention of osteoporosis is the importance of magnesium. Osteoporotic bone has subnormal Mg content, such as is found in Mg deficiency. Many factors interact in the vulnerability to relative or absolute Mg deficiency of those prone to the development of osteoporosis. Low Mg intake, decreased Mg absorption, and hormonal changes that influence the distribution of magnesium and its effects on vitamin D metabolism are major factors in the elderly. In postmenopausal women, among whom are found most of the cases of osteoporosis, loss of oestrogen – which affects distribution of both Ca and Mg – is the predominant factor. The marginal Mg content of many Western diets can be contributory. Other conditions in which osteoporosis has developed, such as chronic alcoholism, disease- or therapy-induced Mg malabsorption or renal wasting, and poorly controlled diabetes mellitus increase Mg deficiency, the latter by increasing urinary Mg output and decreasing its tissue uptake. Since Mg deficiency causes changes in bone structure, the effect on Mg of agents used in prevention and treatment of osteoporosis should be considered. Oestrogen replacement delays onset and retards progression of postmenopausal osteoporosis, partly by antagonizing mobilization of both Ca and Mg by parathyroid hormone (PTH). The effect of oestrogen in lowering serum Mg by shifting Mg to

soft tissues and bone could be implicated in the thromboembolic side effects of high doses of synthetic oestrogens. Since many of the steps in coagulation are Ca-dependent and are antagonized by Mg, might an increase in the serum Ca/Mg ratio in persons whose diets are low or marginal in Mg favour intravascular coagulation? Would adding Mg to oestrogen-Ca treatment of osteoporosis decrease that possibility?

Factors that increase magnesium inadequacy in those at risk of osteoporosis

Dietary magnesium deficiency
Mg intakes below the USA recommended daily allowance (RDA) of 300 mg/day are common[1–12]. Yet such an intake is below the recommendable daily intake of 6 mg/kg.day[1,4,7–10]. It has been customary to advise a dietary Ca/Mg ratio of 2/1, but with the frequently advised intake of 1200 mg/day of Ca or more for the elderly, the ratio may be at least 4/1. Excess of fat, sugar, phosphates, Ca, and vitamin D can each increase Mg requirements, and can lead to relative Mg deficiency[1,4–7]. The elderly, who are prone to involutional osteoporosis, often have reduced food intake[13,14], impaired intestinal Mg absorption[15,16], and increased urinary Mg excretion[17] – factors that increase the likelihood of Mg deficiency. Their hormonal changes can contribute to Mg loss[14] (Fig. 1).

Magnesium deficiency and decreased bone magnesium in osteoporosis
Markedly increased retention of Mg after a parenteral Mg load – one of the most reliable tests for Mg deficiency[9,18–20] – has been found in postmenopausal patients with osteoporosis[21,22]. A study of Mg levels in serum and bone biopsy specimens of 10 elderly women (68.9 ± 6 years) with osteoporosis, compared with serum Mg of age-matched women free of bone disease and with necropsy bone of women who had died suddenly, showed marginally low serum Mg in the controls (1.74 mEq/litre) and low Mg (1.64 mEq/litre) in the osteoporotic women[23]. The bone Mg of the osteoporotic women (1.54 ± 0.29 mg/g) was lower than that of sudden death victims (1.75 ± 0.25)[23].

There was Mg malabsorption in 12 of 20 postmenopausal osteoporotics[15]. Loss of trabecular bone (in which the bone crystals are abnormal[21,24]) is associated with decreased trabecular bone Mg in postmenopausal and senile osteoporosis[15,21,22,24], in alcohol-associated osteoporosis[25], and in diabetics[21,26]. The abnormalities were not seen in oestrogen-treated women[21]. Patients with non-alcoholic cirrhosis (without osteoporosis) had low Mg in bone cortex rather than in trabecular bone.[27]

The acidity of bone extracellular fluid has been postulated to fall when Mg deficiency depresses the Mg-dependent ATPase H^+–H^+ pump in osteocytes.[28]

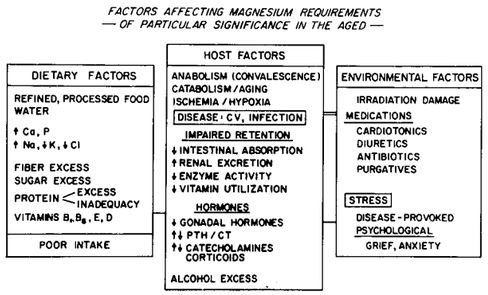

Fig. 1. Factors affecting magnesium supplements, of particular significance in the aged (from M.S. Seelig[14]).

It is suggested that, as a result of lowered pH of the bone extracellular fluid, octacalcium phosphate formation in bone falls, although resorption proceeds – a possible way in which long term Mg deficiency may lead to osteoporosis[28].

Conditions that increase magnesium needs, associated with osteoporosis

Magnesium malabsorption and renal wasting — Magnesium deficiency, manifested by low bone Mg and low bone Mg/Ca ratios, as well as by negative Mg balance, has been detected in patients with sprue, steatorrhea, inflammatory bowel disease, intestinal resections, and genetic isolated Mg malabsorption[29–36]. Malabsorption was associated with slight generalized bone thinning in a 67-year-old man with malabsorption[32], and with evidence of demineralization in a black 56-year-old woman[36]. Vertebral osteoporosis was seen in a young man with Mg deficiency secondary to intestinal resection[30]. Juvenile osteoporosis has been reported in Bartter's syndrome, a genetic renal Mg wasting condition[37]. Mg malabsorption[15] and renal Mg wasting[38] have been diagnosed in postmenopausal osteoporosis.

Alcoholism — Alcoholics' poor food intake, and their malabsorption, in addition to the increase of urinary Mg output caused by alcohol, even when consumed in moderate amounts[39–41], can cause severe enough Mg deficiency to cause overt signs: Mg-responsive tremors, hallucinations, convulsions, and arrhythmias[41–43]. Chronic Mg deficiency of alcoholism[9] may contribute to development of osteoporosis[25].

Pregnancy — Pregnancy increases the need for both Mg and Ca, because of both fetal and maternal requirements[5,44]; osteoporosis can be a risk among women who have had multiple pregnancies. In such women, repeated drains on Mg, as well as on Ca, may contribute to hyperparathyroidism of pregnancy (see below) which is so common as to be termed 'physiological'[5,45], and which mobilizes bone minerals.

Diabetes mellitus — Diabetes mellitus is a disease that is characterized by Mg depletion, caused by complex mechanisms[9]. The extent of the Mg loss in diabetics is related to the severity of the disease. Osteoporosis is not infrequent in insulin-dependent diabetics[21,46]. Severe hypomagnesaemia has long been associated with decompensated diabetes[47]. Less profound reductions in serum Mg have been demonstrated in juvenile diabetics[48,49]. Contributory to the Mg deficiency of diabetes mellitus is glycosuria, which increases Mg output in the urine even in normal subjects given glucose loads[41,50]. Insulin is important in cellular uptake of Mg[51,52]; in its long term inadequacy or with refractoriness to its activity, diminished tissue Mg – including that of bone – is likely.

Interrelations between magnesium and calcium

High calcium intake with marginal or low magnesium intake
To compensate for the loss of Ca from osteoporotic bone, oral treatment with Ca and vitamin D as a calcaemic agent is common, without taking into consideration the effect of these agents on Mg requirements, or the importance of Mg in maintaining normal bone matrix[5]. High dietary Ca/Mg ratios interfere with Mg absorption, partially because Ca and Mg share a common intestinal absorption pathway[34,53,54]. Vitamin D favours Ca over Mg absorption[55]. Metabolic studies have shown interference by high dietary Ca with Mg retention of normal young women[1], and of patients with osteopathies (Fig. 2)[34,56,57]. Moderately high Ca intake (1270 to 2360 mg/day) had little effect on the Mg balance of elderly men[58]. Similarly, addition of 900 mg Ca/day to young men's diets containing 700 mg Ca had little effect on Mg balance[59]. However, even though the Mg balance was not affected by up to 2 g/day of Ca in normal young men, their plasma Mg levels fell[60].

	MEN		WOMEN	
DAILY MAGNESIUM INTAKE (mg)	234	273	202	179
DAILY CALCIUM INTAKE (mg)	<1200	>2600	<1200	>2600
FECAL MAGNESIUM (% OF INTAKE)	74%	120%	73%	115%
URINARY MAGNESIUM (% OF INTAKE)	37%	35%	37%	30%

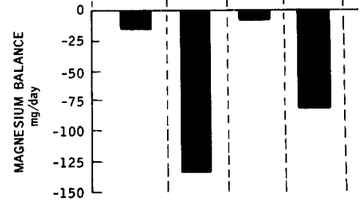

Fig. 2. Effect on magnesium balance of calcium supplementation in patients with osteopathies (adapted from D. Amioco, D.J. Hioco, J. Durlach: *J. de Med.. Besancon* **5**, 371–378, 1969, in M.S. Seelig[5].)

Effect of magnesium supplementation on hypocalcaemia
Persons subject to osteoporosis who have low Mg dietary intakes are prone to low serum levels of both cations. Raising Mg intake increases Ca absorption in normal young men on adequate Ca intake[61]. The restoration by parenteral or oral Mg treatment of responsiveness to vitamin D and parathyroid hormone (PTH) (see below) is important in Mg-deficient patients. It corrects hypocalcaemia as well as hypomagnesaemia[31,33,55].

Interrelation of magnesium with parathyroid hormone — Low Ca levels, despite adequate dietary Ca, may result from Mg deficiency, as well as from Ca deficiency. It has long been known that hypocalcaemia can be a manifestation of severe Mg deficiency in adults[30–33,47,62,63], as well as in infants with convulsive hypocalcaemia responsive to Mg but not to Ca[5,64,65]. Their refractoriness to calcaemic therapy is caused by impaired release of PTH and target organ (bone and kidneys) resistance to PTH[66–71]. However, early or less severe Mg deficiency increases PTH secretion, which increases bone mineral mobilization not only of Ca but of Mg *in vitro*[68] and *in vivo* in humans[36,63,69]. Studies of adults with hypocalcaemia secondary to Mg deficiency showed that most had both impaired PTH secretion and end-organ resistance to PTH[69–71]. Mg is required for activity of adenylate cyclase in parathyroid tissue[72], in kidney[73], and in bone[74]. That enzyme converts ATP to cyclic AMP (cAMP)[75], which is needed for PTH secretion[69]. Defective cAMP generation may thus be responsible for both target organ resistance to PTH and for its impaired secretion in severe Mg deficiency[69–71].

Vitamin D interrelations with magnesium — Vitamin D deficiency impairs not only Ca absorption, but that of Mg[53,76,77]. Formation of the active hormonal metabolites of vitamin D partially depends on enzymes that are Mg-dependent[78,79]. Thus the Mg status affects the calcaemic response to vitamin D treatment of osteoporotic patients. Hypocalcaemic patients with Mg deficiency have not responded to the addition of vitamin D to Ca therapy in refractory hypoparathyroidism[80], in malabsorption or alcoholism[81], or in refractory rickets[82–84] until Mg was provided. It is important to note that the provision of excess Ca or vitamin D and phosphate without correction of a Mg deficit can cause bone to be hypermineralized and brittle[5]. The effect of acute Mg deficiency on production of the active vitamin D metabolites is inconsistent, possibly due to the biphasic effect of Mg on the 1-α-hydroxylase activity[85,86]. Both normal and low levels of the vitamin D metabolites have been found in

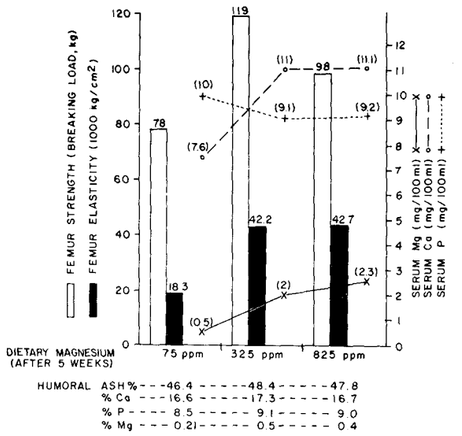

Fig. 3. Serum and bone Mg, Ca, P; bone strength and elasticity in pigs on excess vitamin D, and low, optimal and high Mg intakes (derived from E.R. Miller *et al*[76], reproduced from M.S. Seelig[5], page 296).

Mg-deficient patients treated with vitamin D[87,88]. Prolonged (up to 20 days) Mg administration, sufficient to raise the level of PTH (the trophic hormone for α-hydroxylation), has raised low levels of calcitriol and serum Ca[88].

The significance of interrelations between vitamin D and Mg as regards bone disease requires further study. An important effect of meeting the increased Mg requirement of baby pigs treated with high dosage vitamin D was that of significantly increasing bone elasticity, which resulted in some increased resistance to breakage[76] (Fig. 3).

Interrelations of oestrogen with PTH, vitamin D, and magnesium

Oestrogen treatment; antagonism of PTH

Prolonged replacement oestrogen therapy, preferably with low dose conjugated oestrogens (Premarin), alternating with a progestin, is useful in prophylactic and therapeutic treatment of postmenopausal osteoporosis – whether associated with spontaneous or iatrogenic cessation of oestrogen secretion[89–98]. Inferential evidence that hyperparathyroidism is a factor in postmenopausal osteoporosis is its increased frequency at and after the menopause[99,100], and its greater severity in hyper- than in hypoparathyroid women[101]. Oestrogen antagonizes PTH-induced bone resorption *in vitro*[102,103], and bone of overiectomized rats is more sensitive to PTH – as measured by Ca and hydroxyproline content and decreased bone thickness[104]. Loss of oestrogen at menopause causes negative Ca balance, and greater bone responsiveness

Table 1. Plasma, bone and muscle magnesium and calcium levels in rats treated with ethinyloestradiol +/− progestin (adapted from Charnot, Gozan & Peres[113])

	Plasma (mg/dl)		Femur (mg/g)		Muscle	
(μg/g)	Mg	Ca	Mg	Ca	Mg	Ca
Control	2.5	8.5	1.8	120.4	212.2	70.2
Ethinyl oestradiol	2.4	10.4	2.6	133.5	286.5	43.0
Norethisterone	1.8	11.9	2.1	106.2	154.0	57.4
Combination	1.7	10.0	2.4	167.6	366.2	46.3

to the Ca-mobilizing effect of PTH, and decreased formation of calcitriol[105]. These findings, and the evidence that oestrogen inhibits the bone-resorbing effect of PTH[101,106], support the clinical use of oestrogen in osteoporosis. It is possible that the loss of the protective effect of oestrogen on bone – mediated both by its effects on PTH release and PTH-induced demineralization – is the cause of postmenopausal osteoporosis. Both of these effects may be influenced by the effects of oestrogen on Mg[5,107].

Oestrogen effect on vitamin D metabolism – role of

The evidence, from metabolic balance studies, that young women retain Mg better on marginal Mg intakes than do young men has suggested that the effect of oestrogen on Mg might contribute to their greater resistance to arterial and cardiac disease[1,4,5,107]. There are some data indicating shift of blood Mg to tissues under the influence of oestrogen: soft tissue[108–113] and bone [114–116] (Table 1). Circulating Mg levels are higher in young men than in young women, particularly when oestrogen levels are highest, such as during ovulation or during oral contraceptive use [115–128], and when pregnant (see below). Oestrogen-induced lowering of serum Mg is not associated with increased urinary Mg output or decreased Mg absorption, which supports the premise that oes-

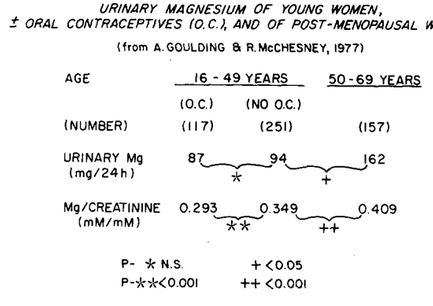

Fig. 4. Urinary magnesium of young women using oral contraceptives (O.C.) and of post-menopausal women (derived from A. Goulding & McChesney[126]; reproduced from M.S. Seelig[14]).

trogen shifts Mg to tissues. After the menopause, women lose more Mg in their urine than do young women, whether or not they are taking oral contraceptives[126–128] (Fig. 4). Oestrogen/progestogen treatment can reduce Mg loss and may thereby be beneficial in postmenopausal osteoporosis[127,129].

Even when corrected for haemodilution, serum Mg is lower in pregnant than in non-pregnant women[5,130–132]. During pregnancy, meeting fetal Mg needs is the major factor in predisposing to maternal Mg deficiency, but the high oestrogen levels probably contribute to the fall in serum Mg early in pregnancy. Magnesium deficiency has been implicated in the pathogenesis of pre-eclampsia[5,44,134–138], in part through increased blood coagulation[135–138].

Oestrogen effect on vitamin D metabolism – role of magnesium

Low calcitriol levels, and low activity of enzymes involved in its formation, are associated with old age and with involutional osteoporosis[139–144], but the response of the disease to its administration is inconsistent[143]. The need for more parathyroid stimulation for normal vitamin D metabolism by women with osteoporosis, and the lesser response of the elderly to calcitriol[144], has been correlated with possible Mg deficiency[145]. The level of calcitriol has been raised during physiologically increased oestrogen, for example during pregnancy[146], and during use of oestrogen[147]. It has been suggested that impaired activation of 1-α-hydroxylase might be responsible for the oestrogen deficiency-induced decreased formation of the active vitamin D metabolite[148]. On the grounds that low levels of the active form of vitamin D were found in Mg deficiency[87], and that oestrogen increases Mg retention (see above), it is suggested that the increase in calcitriol formation caused by oestrogen might be mediated by increased tissue Mg.

Worth exploring is the relationship to osteoporosis of the lower serum Mg and decreased urinary Mg loss by women on oestrogen therapy in comparison with those not so treated. Does this reflect a shift to bone, as in rats[113–116]? Does increased urinary Mg of postmenopausal women reflect their inability to retain Mg? It has been noted that low trabecular bone Mg, and abnormal bone crystals, seen in pelvic crest biopsies of osteoporotic patients are not present in postmenopausal women receiving oestrogen[21].

Magnesium deficiency-associated thromboses; mechanisms

Magnesium/calcium in blood coagulation

That Ca activates blood clotting, and that Mg antagonizes this effect, has been known since 1944; it was assumed to result from competitive inhibition by Mg of Ca-dependent conversion of prothrombin to thrombin[149]. Since then, the need for Ca by many steps leading to fibrin formation and polymerization in clot formation[150,151] has been further defined. Review of published evidence on counteraction by Mg of Ca-stimulated steps in coagulation focused on the effect of Mg on prothrombin and Factors V, VII, and IX, as well as on its enhancement of fibrinolysis[152] (Table 2). Mg stabilizes fibrinogen and decreases fibrin formation; it also increases fibrinolysis[152]. Mg also slows thrombin generation, both *in vitro* and *in vivo*[152,153].

Platelet aggregation requires both Mg and Ca, but is largely Ca-dependent. *In vitro* studies have yielded conflicting results as to the effect of Mg on platelet structure and function; at low, but not at higher than physiological concentrations, the Ca/Mg ratio is an important determinant[154,155]. When Ca was missing or low in concentration, Mg inhibited aggregation[151,155–161]. Addition of Mg to blood samples has reduced ADP-induced platelet clumping. It has been suggested that Ca is required for aggregation and Mg is required to maintain the shape of platelets and for deaggregation. Serotonin, the release of which from aggregating platelets is dependent on Ca and inhibited by Mg[162–164], accelerates divalent cation-induced platelet clumping[165]. Mg is released from platelet granules[165]; it inhibits both further platelet release reactions[154] and steps in blood coagulation (Table 2) by competitive inhibition of Ca. Mg deficiency increases serotonin release from platelets[166,167]. Serotonin-induced vascular muscle contraction is also inhibited by Mg[168,169].

Experimental magnesium deficiency

Partial thromboplastin and thrombin clotting times were significantly shortened in Mg-deficient calves, but their prothrombin time, their platelet counts, and

Table 2. Contrast between Ca and Mg effects in blood coagulation; comparison with oestrogen effect

	Calcium	Magnesium	High oestrogen
Factor VII to protease	Dependent*	?	?
Factor X activated	Dependent**	?	?
Prothrombin → thrombin	Dependent**	Inhibited	?
Prothrombin time consumption	Shortened Increased	Lengthened, +− Decreased	Shortened Increased
Fibrinogen to fibrin	Increased	Decreased	?
Platelet adhesiveness	Increased (aggregation)	Decreased (deaggregation)	Increased (decr count)
Serotonin release (increases platelet clumping	Increased	Decreased	?
Fibrinolysis	?	Increased	Decreased
Fibrinolysis-inhibition	?	Decreased	Increased

* +Lipoprotein tissue factor. ** +Phospholipid.

platelet aggregation were unaffected[170]. Hypercoagulability of blood of Mg-deficient rats, produced by feeding diets rich in saturated fat to animals (see below), decreased coagulation time and increased prothrombin consumption and could be prevented by adding Mg to the diet[171,172].

Prostacyclin and thromboxane — There is some evidence that Mg deficiency inhibits synthesis of prostacyclin (a vasodilating, anti-platelet-aggregating, anti-hypertensive prostaglandin[173–176]), and increases release of thromboxane A2 and B2 (TXB2), which are vasoconstrictive, pro-aggregating prostaglandins[175,176], from platelet aggregates. It has been hypothesized that the accelerated platelet clumping produced by platelet-active collagen (as a model of the bared subendothelial collagen of damaged vascular intima) in Mg-deficient lambs was mediated by diminished production of prostacyclin[177].

The release of increased amounts of arachidonic acid, the precursor of prostanoids, from thymocytes of Mg-deficient rats[178] led to study of the effect of Mg deficiency on these derivatives of phospholipid metabolism in blood[179]. Prostacyclin, as measured by its stable metabolite 6-keto-PGFa1, was increased twofold; PgE2 was increased threefold, but TXB2 was increased more than 10-fold. These increases were attributed to increased Ca levels in Mg-deficient rats, since the enzyme responsible for liberation of arachidonic acid is Ca-activated phospholipase A2[180]. The depression of cyclic AMP seen in Mg deficiency may also participate directly in the markedly increased TXB2 synthesis of Mg deficiency, since cyclic AMP inhibits TXB2 production by platelets[181]. Fatty acid metabolism is altered in Mg deficiency[182–188], with arachidonic acid production diminished as a result of slowed conversion of linoleic acid to arachidonic acid[188,189], a finding pertinent to the role of prostanoids in blood coagulation.

Dietary Mg depletion of humans has recently been shown to increase platelet aggregation and TXB2 release, effects that were reversed by Mg infusion[189]. A nine-fold increase in serum TXB2 was seen in a marathon runner immediately after racing, when his serum Mg was lowest (1.07 mEq/litre), as compared with the pre-race value[190].

Interrelations of fat intake, hyperlipaemia and coagulability — High fat intakes, in experimental Mg deficiency, increases Mg requirements, as expressed by the anticoagulative and cardiovasculo-protective effects of adding Mg to thrombogenic, hyperlipidaemic, or infarctoid diets[3,5,6,171,172,191–207]. Experimental Mg deficiency has long been known to affect serum lipoproteins[191–199]. Mechanisms involved in Mg/lipid interrelations, as they affect coagulation and vascular disease, are being elucidated[182–187]. Mg deficiency of weanling rats has caused hypertriglyceridaemia with increases in very low density lipoproteins (VLDL), and low density lipoprotein (LDL) fractions, with

Table 3. Effect of magnesium on lipids in rats on high fat diet (Adapted from Vitale, Heilerstein, Nakamura *et al.*[193,194])

Fat intake	Serum lipids			
	Cholesterol (mg %)		Lipoproteins	
	Low Mg	High Mg	Low Mg	High Mg
20% Saturated	115	97	α : 15.9 —	7.7
			β : 11.8 —	6.3
20% Unsaturated	115	102	α : 8.1 —	4.0
			β : 8.5 —	4.8

increased cholesterol in those fractions, but decreased cholesterol in the high density lipoproteins (HDL)[182,184–187,202–204] (Fig. 5). Defective triglyceride removal from the blood in Mg-deficient rats[183] is associated with reduction of plasma lecithin cholestryl acyl-tranferase (Fig. 6), and of lipoprotein lipase[203–206].

Magnesium deficiency-associated thromboses; clinical aspects and treatment

Marginal clinical magnesium deficiency

Patients with latent tetany of marginal Mg deficiency have developed thromboses and emboli; new events were prevented by Mg supplements, and recurred when supplements were discontinued[122,207–211].

Postoperative; magnesium-containing anaesthetics

An early study showed that blood taken from surgical patients, who had been anaesthetized with an Mg-containing preparation, clotted but then liquefied completely within 2 hours; blood of such patients at autopsy 12 hours after death was liquid[212,213]. Because there were no cases of phlebothrombosis or emboli among 120 survivors of major surgery so anaesthetized, the investigator undertook clinical trials of the presumed thrombolytic effect of Mg. Patients with deep vein phlebothrombosis responded to parenteral Mg therapy; oral Mg therapy was prescribed prophylactically, with resultant decreased platelet aggregation and inconsistent thrombolysis. In a confirmatory study of the improved recovery of patients with thrombophlebitis or phlebothrombosis, treated with intramuscular or oral Mg (providing 80 mg/ampoule and 50 mg/tablet), blood coagulation indices (clot formation, prothrombin times, antithrombin) were unaffected, but fibrinolysis increased substantially[214].

Pregnancy-associated thrombotic disease

Pregnancy and puerperium — Pulmonary embolism is a major cause of death during pregnancy and the puerperium[215], which suggests that the naturally high oestrogen secretion at that time increases intravascu-

Table 4. Lipids in experimental magnesium deficiency in dogs

Mg intake	Fat intake		Reference
(0.08%) of diet	Butter fat (8% of diet)	→ % Esterified cholesterol fatty acids No change in total serum lipids	Kruse *et al.*[191]
0	Corn oil (9% of diet)	No change in blood cholesterol	Vitale *et al.*[194]
80 ppm		Aortic lesions → serum cholesterol	Bunce *et al.*[195]
180 ppm	Animal fat (20% of diet)	No aortic lesions → serum cholesterol	
0 (Also free of K. High in Vitamin D; Ca, PO_4, protein)	Animal fat	Cardiopathogenic → serum cholesterol	Sos *et al.*[197]

lar coagulation. Comparison of incidence of postpartum phlebothrombosis treated with parenteral Mg, followed by oral Mg (200 mg three times/day for 3–10 days postpartum), provided after delivery, was compared with the phlebitic events during a prior year in which that regimen was not followed. Those treated with Mg exhibited substantial reduction in postpartum thrombosis, after spontaneous or operative delivery (Table 5)[216].

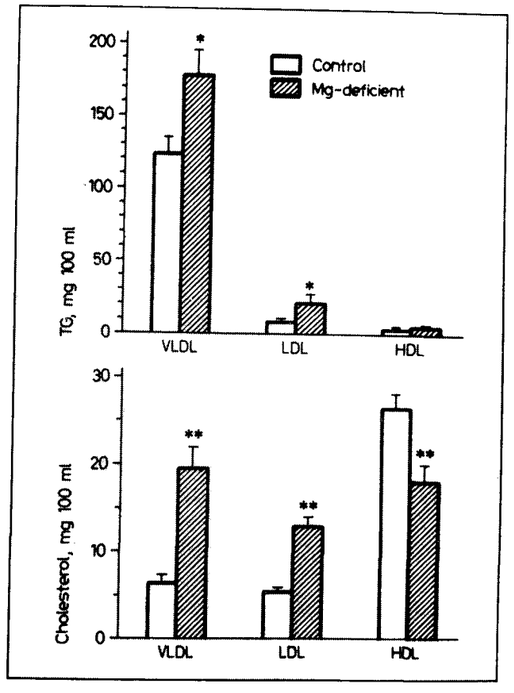

Fig. 5. Effects of magnesium deficiency on triglycerides and cholesterol (in rats) (reproduced from Y. Rayssiguier[185]).

Pre-eclampsia and eclampsia — Hypercoagulability of blood has been associated with pre-eclampsia and eclampsia, and with associated placental abnormalities[5,134–138,217–219]. Abnormalities that increase the risk of thrombosis in eclampsia include decreased plasminogen activation and decreased fibrinolysis, with resultant decreased thrombolytic potential. Also found were lowered platelet counts – which suggests their consumption as a result of intravascular coagulation[218]. (See above for interaction with prostanoids.)

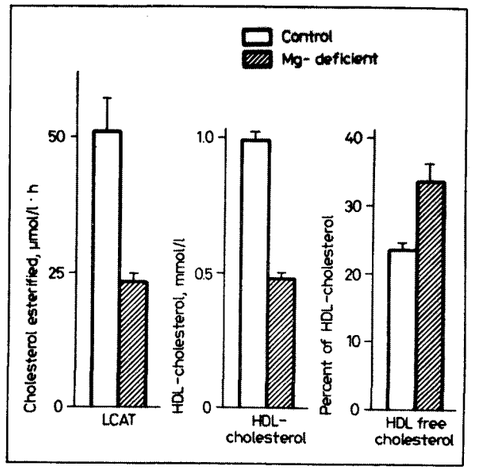

Fig. 6. Effects of magnesium deficiency on LCAT and HDL-cholesterol (in rats) (reproduced from Y. Rayssiguier[185]).

Table 5. Incidence of thrombosis: post-partum, surgical patients treated with magnesium *vs* earlier use of anticoagulants (from B. Schnitzler[216])

Delivery	Incidence of thrombosis			
	Mg treatment (1955)		Anticoagulant treatment (1952)	
	Number	Percent	Number	Percent
Spontaneous	562	0.89	660	1.21
Surgical	77	1.3	114	4.4
Vaginal surgery	115	2.6	170	7.7

Parenteral magnesium treatment of eclampsia; anticoagulant effect — Hypomagnesaemia, which is characteristic of pre-eclampsia and eclampsia before renal failure, is associated with comparable increases in coagulation (see above). Administration of pharmacological amounts of Mg is the time-honoured means of treatment of eclamptic convulsions and hypertension[5,220,221]. It is used as a drug, but much of it is retained[134,220] – suggesting repair of underlying Mg deficiency. That the effect of Mg in eclampsia may also entail its antithrombotic effect was postulated on the basis of the rapid reduction of markedly increased platelet adhesiveness after intramuscular Mg in eclamptic women, and the combination of many factors that predispose to Mg deficiency in pregnancy[135–138]. When Mg deficiency produced eclampsia with glomerular microthrombi and decreased lowered platelet counts in pregnant ewes, the theory was extended to encompass the lowered prostacyclin/TXB2 ratio seen both with pregnancy and Mg deficiency[137,138] (Fig. 7).

A decreased prostacyclin/TXB2 ratio has been implicated in the pathogenesis of toxaemias of pregnancy[222]. The relationship of the Mg deficiency of eclampsia to this change in prostanoids was suggested soon thereafter[138,223,224]. The inhibitory effect of Mg on both platelet aggregation and hypertension in toxaemias of pregnancy has been attributed to its stimulation of prostacyclin production[223]. That the antihypertensive effect of Mg might be mediated by prostacyclin was suggested by the increase in prostacyclin production induced by Mg infusion of normal subjects[225].

Migraine, oestrogen and prostacyclin/TBX2 — Of particular interest as regards interrelations of oestrogen with Mg is the strong association of migraine with eclampsia[136,226,227]; eclampsia was 220 times more prevalent in pre-eclamptics with histories of migraine than in those without. Migraine was found 2.5 times as often in patients with pre-eclampsia before the 34th week of pregnancy as it was in those with normal pregnancy[228]. Favourable results have been reported in 80% of 3000 women given 200 mg/day of Mg for the prophylaxis of eclampsia and migraine when they

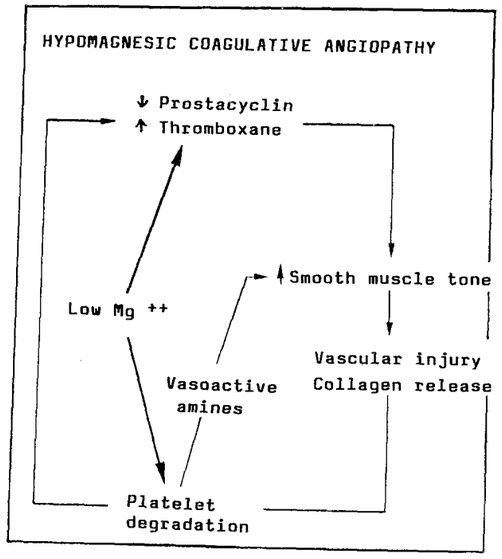

Fig. 7. Proposed interaction of low magnesium and prostanoids leading to eclampsia and migraine (reproduced from K. Weaver[137]).

were taking oral contraceptives or were pregnant[136,226].

Support for the premise that Mg deficiency is involved in the pathogenesis of migraine derives from its higher incidence among those prone to hypomagnesaemia, and relates it with association of the effect of Mg on prostanoids and thrombogenesis[136,226,229] (Fig.7). Several specific interrelationships of vascular factors that seem to be involved in migraine that pertain to Mg deserve mention. Prostaglandin metabolism has been correlated with migraine[230] (see above for Mg and prostanoids). Increased serotonin release from platelets[231], which occurs in migraine[232], may contribute to cerebral vasospasm; it is enhanced by Ca and inhibited by Mg[162–165]. Ca channel blockers are effective in prophylaxis of migraine[233]; Mg has been proposed as a physiological Ca channel blocker[234], on which basis Mg treatment was proposed for migraine[235].

Myocardial infarction; coronary artery disease; cerebral thrombosis

Blood coagulation, fat intake, hyperlipaemia, and magnesium requirements — Increased platelet adhesiveness has long been recognized in ischaemic heart disease[236], and is known to be intensified by hyperlipaemia due to high intake of saturated fatty acids[237–240] and that found in clinical arteriothrombotic disease[241].

Table 6. Blood lipid changes in 50 patients with ischaemic heart disease after treatment with 2 ml 50% $MgSO_4$ at 5 day intervals × 12 (derived from R.S. Parsons, T.C. Butler & E.P. Sellers[244])

	Reduced	No change	Increased
Cholesterol	82%	12%	54%
Lecithin/cholesterol	0	14%	86%
α-lipoproteins	40%	28%	32%
β-lipoproteins	66%	28%	6%
Changes in fibrinolytic potential after Mg treatment			
Plasmin activation	18%	38%	44%
Plasmin inhibition	62%	34%	4%

Magnesium treatment in ischaemic heart disease; effects on lipoproteins — Reported as long ago as the adverse effects of saturated fats on blood coagulation in patients with ischaemic heart disease was the favourable response to (uncontrolled) Mg treatment of several hundred patients with ischaemic heart disease (IHD), with and without recent myocardial infarction[242,243]. Their reduction in angina, in association with lowered serum β-lipoproteins, persisted as long as the Mg treatment was maintained, but rose when it was discontinued. Clinical confirmation was provided in another series of patients, who experienced clinical improvement on similar treatment with $MgSO_4$ (2 ml 50%, intramuscularly every 5 d for 12 injections): marked reduction of β-lipoproteins occurred, with no change in α-lipoproteins[244,245] (Table 6).

Effects on coagulation and fibrinolysis of magnesium treatment of ischaemic heart disease — In the foregoing uncontrolled study of the anti-anginal efficacy AMg, and the lowering of β-lipoproteins of patients with ischaemic heart disease by intramuscular Mg, it was found that Mg markedly reduced the increased plasmin inhibition, and functioned synergistically with heparin in management of patients who had suffered recent myocardial infarction[244,245]. In another study, platelet adhesiveness was studied in 25 patients within 48 h of myocardial infarction and was found to be markedly increased; their mean serum Mg on the third day was marginally low (1.7 mEq/litre), *versus* a control normal mean of 2.36 (Table 7)[245]. There is increasing clinical evidence that Mg deficiency predisposes to clinical cardiovascular disease, including myocardial infarction[5,20,247–254], and that Mg treatment improves the post-infarction course by reducing risk of arrhythmias[5,234,249,250–252,255–263].

Increasing serum Mg only to 2.1 mEq before partial occlusion (by suture) of coronary arteries of animals markedly diminished platelet aggregation at the site of injury and distal to it[264]. This suggests that Mg treatment in ischaemic heart disease might protect against thrombosis formation on atherosclerotic

Table 7. Platelet adhesives and serum Mg in myocardial infarction (Adapted from C. Prakash *et al.*, Proc. Intl. Mg Sympos. 1971/1973)

Day after MI	Myocardial infarction patients			Normals
	3rd d	6th d	9th d	
Platelet adhesive index	1.39	1.36	1.34	1.14
No/cmm: Adhesive platelets	76 000	73 000	71 000	49 000
Ser Mg (mg/dl)	2.02	2.08	2.17	2.63
(mEq/litre)	1.69	1.73	1.81	2.36

arteries and microthrombi associated with arteriospasms[264]. The anti-arrhythmic effect of Mg is implicated in the improved survival of post-myocardial infarction patients treated with Mg infusions; its antithrombotic effect may also participate.

Cardiovascular protection by oestrogen

The lower cardiovascular disease death rate in premenopausal women than in men suggests that oestrogen has a protective effect. It is proposed that this effect might be mediated by the improvement in Mg retention caused by oestrogen[1,3,5,107]. Experimental animals treated with oestrogen[265,266], and pregnant animals with high oestrogen levels, have increased resistance to induced arterial and cardiac damage[267–269]. Epidemiological studies showing either no effect on[270] or lowered coronary disease risk of elderly women receiving replacement low dosage oestrogens[271–275] support the premise that oestrogen is protective against cardiovascular lesions.

Thrombophlebitis on high dose synthetic oestrogens — However, high levels of oestrogen have been reported to have been associated with intravascular coagulation[5]. Men treated with oestrogens for prostatic carcinoma had more thrombosis-associated cardiac disease than those not so treated[276], although the degree of atherosclerosis seems not to have been affected[277]. The venous thrombophlebitic events in women on high dosage oestrogen-containing oral contraceptives[278–280] (Fig. 8), and in women given oestrogens to inhibit lactation[281,282], led to study of the increased coagulation caused by oestrogens. The synthetic oestrogens, especially in high doses, but not the conjugated oestrogens (in lower doses), shorten prothrombin time[283], increase prothrombin consumption[284], and increase platelet adhesiveness[284,285]. In low doses they exert little or no effect[286]. Premarin showed no significant increase of clotting tendency in women given 1.25 mg/d for a month[287]. An epidemiological study has shown no increased risk of stroke in postmenopausal women on low dose replacement oestrogen[288].

High dose oestrogen-induced thrombophlebitis; due to lowered serum magnesium? — It has been hypothesized that high dose oestrogens increase the risk of thromboem-

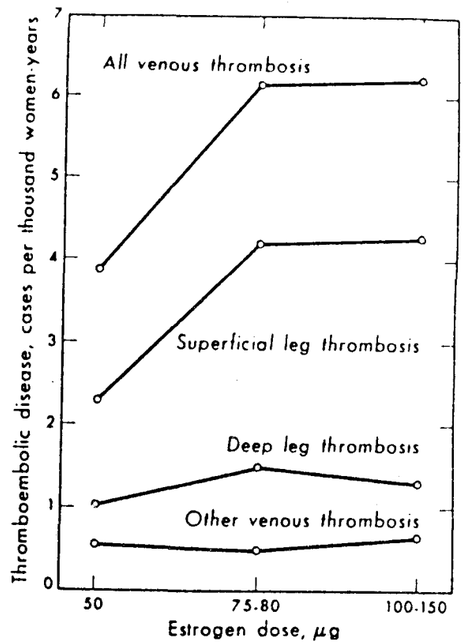

Fig. 8. Association of thromboembolic disease with oestrogen dose (from C.R. Kay[280], reproduced from N. Goldsmith[116]).

bolism and phlebothrombosis as a result of oestrogen-induced shift of circulating Mg to tissues, lowering serum Mg levels[115,289]. The recent report that oral contraceptive users who smoke have increased platelet aggregation and decreased prostacyclin levels[290], and the interrelationships of Mg with prostacyclins (see above), provide more insight into additional mechanisms by which oestrogen may affect blood coagulation through its effects on Mg. It has been advised that during any long term oestrogen therapy the Mg status should be monitored and deficits corrected to reduce the risk of phlebothrombosis[9,122,211].

Conclusions

This correlation of multiple interrelations among the factors that increase the likelihood of development of osteoporosis, and among the treatments of that disease (that currently emphasize administration of oestrogen and Ca), calls attention to the mechanisms by which such combination therapy may increase Mg requirements. Patients who take enough Ca supplements to exceed the commonly recommended Ca/Mg ratio of 2/1, especially in those with the marginal Mg dietary intake that is common in the developed world, may develop relative or absolute Mg deficiency, with suboptimal serum Mg levels. Combined Ca and oestrogen treatment of such patients might lower serum Mg, thereby increasing the risk of intravascular coagulation. Postmenopausal women who are treated with low dose replacement oestrogen to prevent or slow osteoporosis are not considered to be at risk of thromboembolic events such as have been associated with use of high dosage synthetic oestrogens. Ca activates many steps in blood coagulation; Ca supplementation, in conjunction with oestrogen, might contribute to an increased possibility of intravascular blood clotting. Mg counteracts some of the Ca-activated steps in blood coagulation, and even has some fibrinolytic activity. Furthermore, it has been shown to participate in activities that may function to correct the lipid and prostanoid abnormalities associated with Mg deficiency and that increase the risk of thrombosis. Thus Mg supplementation is suggested to reduce the risk of intravascular coagulation, and possibly to improve the anti-osteoporotic therapeutic effect.

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Besoin magnésique accru par l'utilisation d'estrogène et de calcium associés dans le traitement de l'ostéoporose

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Résumé: Le traitement prophylactique de l'ostéoporose post-ménopausique: estrogène et calcium (Ca), souvent associés, dissimule la probabilité qu'un excès de l'un ou de l'autre agent accroît le risque de besoins magnésiques accrus et d'hypomagnésémies sériques. La déficience magnésique relative ou absolue qui est probable en Occident où l'apport magnésique est fréquemment marginal peut intervenir en mal vis-à-vis d'une réponse thérapeutique osseuse optimale, le magnésium étant important pour une structure normale de l'os et doit accroître le risque d'effets secondaires néfastes. Bien que les estrogènes puissent avoir des effets protecteurs cardiovasculaires (dont té-moigne la plus faible incidence des affections cardiaques chez la femme avant la ménopause que chez l'homme ou chez les femmes âgées sous traitement par de faibles doses palliatives d'estrogènes), les traitements contraceptifs par de hautes doses orales d'estrogènes ont provoqué une augmentation de la coagulation sanguine intravasculaire avec comme résultante des accidents thromboemboliques cardio- et cérébro-vasculaires. Ils peuvent dépendre d'échanges induits par les estrogènes entre magnésium circulant et tissus mous et durs, ce qui face à des apports magnésiques marginaux peut amener à des concentrations sériques suboptimales. En dépassant le rapport ingéré habituellement recommandé de 2/1 pour Ca/Mg (et qui d'ailleurs peut atteindre 4/1 dans les régions à faible ou marginal ingesta magnésique), on peut augmenter le risque de coagulation intravasculaire, la coagulation sanguine étant augmentée par des taux élevés du rapport Ca/Mg ingéré. Les mécanismes par lesquels le Ca active de multiples étapes de la coagulation sanguine sont aussi stimulés par les estrogènes. Ils sont analysés comme le sont les rôles à multiples facettes due Mg favorables sur la coagulation sanguine et la fibrinolyse, à travers ses activités sur les métabolismes des lipoprotéines et des prostanoïdes.

Mots clés: Alcoolisme, besoins magnésiques, calcithérapie, coagulation intravasculaire, déficience magnésique, diabète, lipoprotéines, magnésium, malabsorption, postménopause, prévention de l'ostéoporose, prostanoïdes, rapport Ca/Mg, structure de l'os, traitement estrogénique.

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