Nutritional Status and Requirements of Magnesium

with Consideration of Individual Differences and Prevention of Cardiovascular Disease

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Summary

How much magnesium is required for optimum health has remained controversial. The amount listed as the Recommended Dietary Allowance (RDA): 300 and 350 mg/day for young women and men, with 450 mg/day indicated during pregnancy, is under review — with consideration of lowering the recommendation, to an amount closer to the actual (low) consumption of magnesium. The risks of decreasing the daily intake are considered here. Particular attention is paid to the role of magnesium and the other dietary constituents with which it interacts, and which are likely to increase its requirements. How imbalances of such nutrients participate, with magnesium, in the pathogenesis of cardiovascular complications is presented in this paper. The effect of genetic differences, not only in handling magnesium but in vulnerability to deficiencies of vitamins that have magnesium dependent enzymes, are proposed as partial explanations of individual differences in magnesium requirements and in clinical expressions of its deficiency.

Résumé

La question de quantité de magnésium nécessaire pour une santé optimale reste toujours contradictoire. Les quantités suivantes indiquées dans le «Recommended Dietary Allowance» (recommandations des Etats Unis pour le nutriment), c'est à dire 300 et 350 mg par jour pour jeunes femmes et hommes, 450 mg par jour pendant la grossesse, sont en train d'être révisées, il est envisagé de baisser ces recommendations vers une quantité plus proche de la consommation actuelle (basse) de magnésium. Les risques de réduire l'apport quotidien sont discutés ici. En particulier, beaucoup d'attention a été prêté au rôle du magnésium et des autres substances nourrissantes interactives avec le magnésium qui augmentent probablement le besoin de magnésium. En plus, la participation de ces substances nourrissantes avec le magnésium dans la pathogenèse de complications cardiovasculaires est traité dans cet article. Les effets de différences génétiques, pas limitées au traitement de magnésium, mais aussi à la vulnérabilité quant à la manque de vitamines ayant des enzymes dépendents de magnésium sont proposés comme explications partielles pour les différences individuelles du besoin de magnésium et pour les expressions cliniques différentes d'une manque de magnesium.

Zusammenfassung

Wieviel Magnesium für einen optimalen Gesundheitszustand benötigt wird, ist widersprüchlich geblieben. Die in den Recommended Dietary Allowances (= US-amerikanische Empfehlungen zur Nährstoffzufuhr) aufgeführten Mengen: 300 und 350 mg Mg pro Tag für junge Männer bzw. Frauen und 450 mg während der Schwangerschaft — werden überarbeitet — und es wird diskutiert, die empfohlenen Mengen zu erniedrigen auf Werte, die näher an der aktuellen (niedrigen) tatsächlichen Zufuhr liegen. Die Risiken, die sich hieraus ergeben, werden diskutiert. Besonders wird eingegangen auf die Rolle von Mg und anderer Nahrungsbestandteile, mit denen Wechselwirkungen bestehen und die wahrscheinlich den Bedarf erhöhen. Weiter wird behandelt, wie solche Nahrungsbestandteile zusammen mit Mg in der Pathogenese kardiovaskulärer Komplikationen mitwirken. Genetische Unterschiede, die nicht nur im Mg-Metabolismus, sondern auch hinsichtlich der Empfindlichkeit gegenüber dem Mangel an Vitaminen, die Mg-abhängige Enzyme besitzen, relevant sind, werden als teilweise Erklärung dafür diskutiert, daß unterschiedliche individuelle Bedarfsanforderungen bestehen und sich ein Mg-Mangel klinisch unterschiedlich manifestieren kann.

Introduction

The recommended dietary allowances (RDA) for magnesium, have been designated by the National Research Council in the United States since 1980 as 300 and 350 mg a day for young women and men, respectively, with an extra 150 mg a day during pregnancy [20]. These values derive from metabolic balance studies of healthy young adults, and have been used as an indication of "known nutritional needs". Surveys have shown that the magnesium intakes of most Americans and Canadians fall below these values [79, 126, 132, 133]. Such survey results, and uncertainty as to reliability of the 1980 RDAs or of the methodology used in determining the requirements, have raised questions as to whether it might not be better to lower the RDAs to reflect "minimal nutritional needs" [71]: amounts below which symptoms and signs of deficiency of nutrients may develop, and/or other evidence of nutritional inadequacy can be elicited by specific tests. In the case of magnesium, difficulties in demonstrating early manifestations of deficiency — whether by symptoms, signs, or even clinical laboratory parameters — would unquestionably lead to disagreement as to what minimal needs might be. In Canada, the official recommendation for magnesium has already been reduced to minimal levels (personal communication, *J. R. Marier*).

To lower the recommendations for magnesium intake has inherent risks. Optimal intakes of magnesium in the normal subject may well be higher than the present

RDAs, particularly during conditions of growth and physical or psychological stress. Presented here is evidence that some of the nutrients that interact with magnesium can influence its requirements. The macronutrients: calcium and protein, and the micronutrients: vitamins B6, B1, and D are discussed in some detail because their adequacy, relative to individual needs, influences and is affected by the magnesium status. Less attention is given the phosphates, which have been considered elsewhere [107–109], and to micronutrients which have less clearly defined effects on magnesium. Interrelationships that influence magnesium needs are considered in the context of the disorders to which its deficiency, with and without deficiencies and/or excesses of the other nutrients, can contribute.

Magnesium Requirements for Protection Against Disease, as Affected by Other Nutrients

Metabolic studies of nutritional requirements usually deal with a single nutrient, often as affected by one other nutrient. Even studies of the lesions produced experimentally by excess or deficiency of a single nutrient limit the number of factors affecting its needs. Though expedient, such an approach does not mirror the multiplicity of interreacting factors that affect requirements, and that provide the basis for nutritionally caused diseases. Surveyed below are some of the ways in which nutrient interactions can affect magnesium requirements. Genetic enzymatic defects, mostly with disturbances of the nervous system, that affect the need for vitamins requiring magnesium as a cofactor, are extremes of individual differences in requirements.

Magnesium Requirements Determined by Metabolic Balance Studies

The 1964 analysis of magnesium metabolic balance data disclosed that most young men require at least 6 mg of magnesium/kg/day to remain in equilibrium; young women require a little less [113]. Most of the strongly positive magnesium balance data derived from oriental studies of balance on customary dietary intakes. Subsequent studies with free-living volunteers, with and without altered concentrations of nutrients that had been shown in early studies to affect magnesium retention, confirmed the 6 mg/kg/day requirement for healthy young adults [53, 63, 109]. Adolescents require as much as 10–16 mg/kg/day [104, 109], an amount probably needed by others forming new tissue, such as pregnant women, infants, and those undergoing tissue repair.

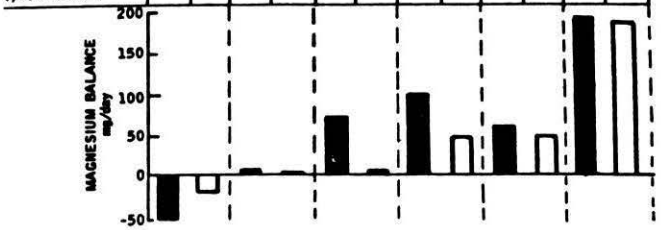
Few develop manifestations of such severe magnesium deficiency as have long been considered the hallmarks of magnesium lack: audiogenic seizures of experimental magnesium depletion (Review [28]). However, comparable severe manifestations have been seen among humans with the combination of high requirements and minimal supply, such as infants (often premature — and thus born with subnormal magnesium levels [107, 112]) with hypomagnesemic hypocalcemia, those receiving long-term parenteral fluids lacking magnesium [34], patients suffering alcohol withdrawal [34], and women with toxemias of pregnancy [107, 112]. Some of these conditions will be mentioned below, as probably associated with combined nutritional imbalances. It is likely that long-term relative and absolute magnesium insufficiency contributes to many chronic diseases [27, 107]. Interrelations that pertain to cardiovascular disease are developed here.

Effects of Macronutrients on Magnesium Requirements

Dietary macronutrients that affect magnesium utilization are calcium and protein, fat and sugar, and phytates and inorganic phosphates (Reviews [106–108, 113]). Calcium and protein are discussed below. Evidence that high intakes of fat or sugar increase magnesium needs have been considered elsewhere [93, 94] and at this Conference [86, 92]. Some pertinent points are mentioned in the next section. The loss of magnesium caused by high dietary phosphate/magnesium, or by iatrogenic phosphate loads (i.e. for treatment of kidney stones) was considered a potential risk because of animal studies showing phosphate-intensified renal and cardiovascular lesions, that were protected against by magnesium [14, 35, 73, 80]. The possibility that the combination of low magnesium and high phosphate plus vitamin D (in cow's milk-fed infants) might establish early cardiovascular lesions was then proposed [107, 108].

Calcium: Interrelationships of magnesium and calcium are complex, entailing interactions with vitamin D, phosphate, parathyroid hormone and calcitonin (Review [107]). Of particular importance, in regard to magnesium requirements — in these days of widespread promotion of self-medication with high doses of calcium — is the reduced magnesium retention that is caused by calcium supplementation of those on low magnesium intakes [113]. Metabolic balance studies with normal young adults on magnesium intakes below 4 mg/kg/day showed that they lost magnesium, whether their calcium intakes were low or high (over 10 mg/kg/day) (Figure 1). On low magnesium intakes: below 5 mg/kg/day — which surveys have shown to be the customary magnesium intake, the calcium balance was found also to be negative, unless supplementation to over 10 mg calcium/kg/day was

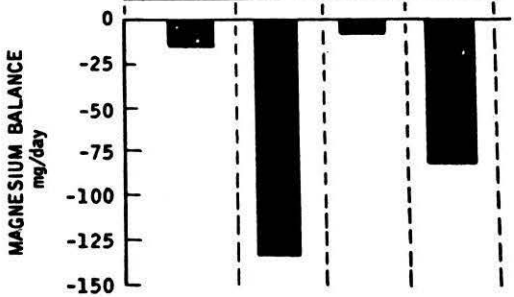
Mg INTAKE mg/kg/day	<4		4-4.9		5-5.9		6-6.9		7-10		>10	
Ca INTAKE mg/kg/day	<10	>10	<10	>10	<10	>10	<10	>10	<10	>10	<10	>10
FECAL Mg (% OF INTAKE)	81	69	61	60	54	59	58	60	62	60	58	60
URINE Mg (% OF INTAKE)	39	41	38	40	27	40	22	37	23	38	22	20



Adapted from M.S.Seelig, Am.J. Clin. Nutr. 14: 342-390 (Fig.3), 1964

Fig. 1: Influence of calcium intake on magnesium balance in normal adults

	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%



Adapted from D.Amiot, D.J.Hioco, and J.Durlach (Int'l Congr. on Mg, Argentina, April 1968)

Fig. 2: Effect on magnesium balance of calcium supplementation in patients with osteopathies

provided. On magnesium intakes from 5–10 mg/kg/day, the magnesium balances were positive regardless of the calcium intake, as were the calcium balances. As regards the positive calcium balance in those on low magnesium intakes, such a balance indicates retention, whether the calcium is deposited in bone or soft tissues as calcinosis — such as has been produced in experimental animals fed magnesium deficient diets high in calcium. They develop renal tubular lesions and calcinosis, and arteriosclerosis [9, 14, 107, 119].

Studies of the effect on magnesium retention of calcium treatment of patients with osteopathies or hypercalciuria [5, 85] showed that increasing the calcium intake, from about a gram a day to about 2½ grams, substantially increased their magnesium loss (Figure 2). Higher magnesium intake (344 mg/day), providing over 2 grams a day of calcium decreased the magnesium retention, but not to negative values. Balance studies in healthy young men showed that increasing the calcium intake from 780 to 2800 mg/day exerted no effect on magnesium balance [41]. A one year long study of young and older free living men and women [63] showed that, as in the previous study, a low magnesium diet (260 mg/day) did not affect magnesium retention in the young women. The older women, however, showed increased magnesium excretion with higher calcium intake. A two month long study of healthy young women on a diet providing a calcium/magnesium ratio of 3.5/1 showed strong negative magnesium and positive calcium balances [53]. A study of middle aged and elderly ambulatory hospitalized men showed that increasing the calcium intakes from 210 to 3000 mg/day reduced the retention of magnesium, but not to negative values; increasing the magnesium intake to about 600 mg/day caused strong positive magnesium balance even on 2 gram daily intake of calcium [123].

Protein: Whether the amount of dietary protein causes positive or negative magnesium balance seems to depend on the relative amounts of each in the diet, the source of the protein, and the rate of growth or tissue repair. Both young adults and adolescents on low intakes of both magnesium and protein exhibit negative magnesium and ni-

trogen balance (Review [109]. With low magnesium intakes, increasing the protein intake from very low to marginally adequate improved the magnesium retention; further increase impaired magnesium retention. Among adolescents on sufficient magnesium for growth and development (10–16 mg/kg/day), the amount of dietary protein exerted little effect on magnesium loss [104]. When the protein intakes were either very low or high, the magnesium intake had to be over 10 mg/kg/day to maintain magnesium equilibrium in older adolescents. In a study of men on a low magnesium diet (250 mg) in a stable metabolic unit, moderate alteration of the protein intake exerted no influence on magnesium balance [69]. Free-living middle aged women, studied for a year on self-selected diets, that were comparably low in magnesium, lost more urinary magnesium on moderately high protein intakes than they did on lower protein diets [63]. In contrast, magnesium retention of young women was not affected by moderate changes in protein intake.

The source of the protein influenced the magnesium balance during weight reduction on very low calorie reducing diets [33]. Obese men lost most magnesium on collagen protein; those on soy protein as the sole food source, that provided 116 mg/day of magnesium, had a cumulative positive magnesium balance over the 40 day weight loss program, when the balance was corrected to allow for the amount of magnesium released during lean tissue catabolism.

Magnesium and Micronutrients

Magnesium is a nutrient that is necessary for the activity of many enzyme systems [135] that are also dependent on several vitamins and trace minerals. Among them are most of the apoenzymes of vitamins B6 and B1 (Figure 3, Table 1) and

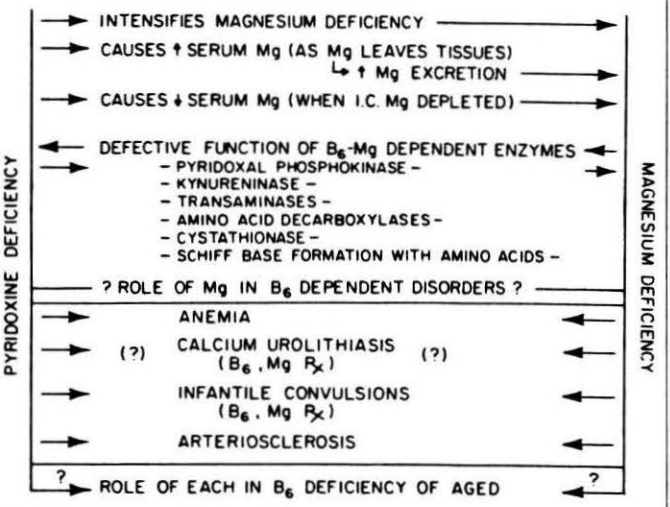


Fig. 3: Pyridoxine-magnesium interrelations

the enzymes that act on phosphorylated substrates: phosphokinases, synthetases, and phosphatases, and virtually all that catalyze phosphate transfer from adenosine tri- and diphosphate and other transphorylating enzymes, such as hexokinase [135]. It is not surprising, therefore, that functional and organic changes of magnesium deficiency can be intensified by deficiencies of vitamins that are dependent on magnesium for the full expression of their activities, and that correction of the deficiency of one may ameliorate the symptoms of deficiency of the other.

Pyridoxine: The prime example of mutually enhancing nutrients is that of magnesium and pyridoxine (Review [26, 27]. Their comparable activities relate to the numerous enzymes that are dependent on both (Figure 3). There are many clinical disorders that are caused by deficiencies of one that are at least partially responsive to administration of the other and that are treated best by both. Pyridoxine deficiency intensifies that of magnesium [62], since it requires increased amounts of magnesium as a co-factor of the enzymes. At first it causes transitory increased serum magnesium as the cellular magnesium falls and then causes depletion of intra- and extracellular magnesium [26, 97]. Worth exploring is whether the conditions associated with biochemical evidence of pyridoxine deficiency, which includes pregnancy and use of oral contraceptives [90], and high protein diets [15], would benefit from increasing magnesium intake.

Some children with neurological disorders (autism, Down's syndrome and hyperactivity) who respond to megadose B6 therapy [10, 19, 64, 67, 99], have developed hypomagnesemia (personal communication, *H. Bhagavan*), and respond better when magnesium is added to the B6 regimen [19, 64]. Other inborn errors of metabolism, that increase pyridoxine requirements because of abnormalities in B6-requiring apoenzymes, might also have increased magnesium requirements. The homovalinic acid response to massive doses of B6 of about a third of autistic children [67], and their response also to magnesium alone [64] and with B6

b. 1:

terrelations between magnesium and iamine

B1 and Mg are metabolized interdependently

Mg deficiency → B1 deficiency

B1 repletion of double deficiency → ↓ Mg

l-dependent enzymes requiring Mg:

pyruvate dehydrogenase
α-ketoglutarate dehydrogenase
transketolase

g requirements for steps in B1-conversions

$B_1 \xrightarrow[B_1 \text{ pyrophosphokinase}]{Mg +}$

thiamine pyrophosphate (TPP or cocarboxylase)

$TPP \xrightarrow[\text{phosphoryl transferase}]{Mg +}$

thiamine triphosphate (TTP)

TTP hydrolysis to free thiamine by:
B1 triphosphatase (needs Mg)
B1 diphosphatase (needs Mg)
B1 Monophosphatase (needs Mg)

19] has suggested the possibility hat the combined dependence reects a "vitamin insufficiency" [67] hat becomes manifest in the abence of adequate magnesium. some improvement in neurological nanifestations has been achieved with doses as high as 500 to 1,000 mg B6 daily [21, 67]. Adding magnesium has improved the response [64, 99] (p. c. *M. Coleman*). Defects in the gamma-aminobutyric acid (GABA) system, in kynurinase and in cystathione synthetase: enzymes with B6 and magnesium requirements, have been identified in infants with convulsions and/or mental retardation [67]. Homocystinuric infants also develop premature atherosclerosis, which has led to implication of lesser degrees of this enzymatic abnormality in more common forms of atherosclerosis (infra vide).

Thiamin: Another vitamin that has important interactions with magnesium is thiamin. They participate in many activities conjointly (Table I). This is reflected by impairment of clinical response to B1 when there is also magnesium deficiency [127, 142], and lowering of tissue B1 levels [54, 57] in magnesium deficient animals. High dosage of only the vitamin when there is double deficiency intensifies magnesium deficiency. It is possible that the requirement for magnesium by B1-enzymes can deplete marginal amounts of magnesium when B1 repletion is provided in excess. Among the adverse effects of magnesium deficiency that are intensified by thiamin excess are excess serotonin (5-HT) release, and inhibition of its oxidative metabolism [55]. Interrelations of the two nutrients also may be germane to lipid metabolism [56]. Most of the clinically relevant data on the relationship of magnesium and thiamine pertain to central nervous system effects — as regards hepatic encephalopathies [127, 142], and the Wernicke-Korsakoff syndrome. Since diminished binding of thiamin triphosphory lase (TTP), with abnormalities of transketolase that are only partially responsive to B1 therapy, have been reported in patients with the syndrome, and since magnesium plays a role in binding B1 to protein and in increasing neuronal transketolase levels [60], its addition to the treatment seems justified. It has been suggested that Wernicke-Korsakoff patients might have vitamin B1 dependency that develops only when alcohol intake is heavy [11]. Does the magnesium deficiency that alcohol induces [65] participate? Possibly the lethal genetic disorder, Leigh's Syndrome, or subacute necrotic encephalopathy (SNE), in which there is an inhibitor of triphosphorylation of thiamin that results in a deficiency in the brain of TTP [67], might also show some response to addition of magnesium to the therapeutic regimen.

Vitamin D: The interrelationships that exist between magnesium and vitamin D are complex (Figure 4). Vitamin D, in individually appropriate amounts (which can differ widely from those with vitamin D dependent rickets to those with vitamin D hyperreactivity [114]), is important in intestinal absorption, not only of calcium but of magnesium [77, 78]. When its supply is insufficient, the magnesium need is increased. Paradoxically, mag-

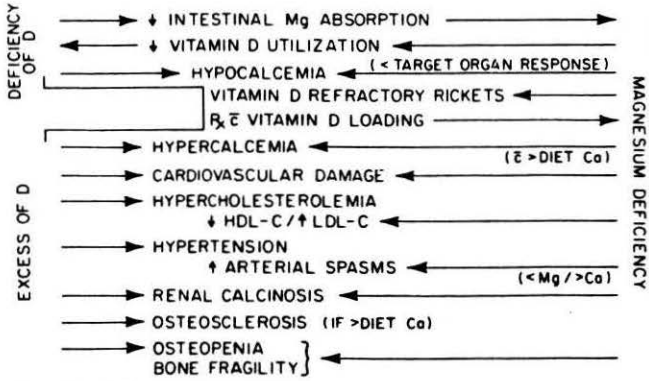


Fig. 4: Vitamin D and magnesium

nesium requirement may also be increased with hypervitaminosis D, which increases urinary magnesium loss [137,107]. Magnesium deficiency interferes with vitamin D utilization [76, 96], and has been implicated in a form of refractoriness to vitamin D that is expressed by vitamin D refractory rickets or osteopenia in adults until the magnesium supply is increased [76, 91, 107]. The increased responsiveness to vitaminen D on repair of magnesium deficiency makes it necessary to reduce the amount of vitamin D given to those with latent tetany of marginal magnesium deficiency [26] or to infants with hypomagnesemic hypocalcemia [107].

Some of the interactions that might explain the adverse effects of vitamin D excess — some of which might be associated with the increased need for magnesium — are depicted on Figure 4 and Figure 7 (infra vide). This is not to imply that increased magnesium intake will protect against overdosage with vitamin D (which may be no more than 2–3 times the recommended dose of 400 I. U. in those with genetically high vulnerability to vitamin D toxicity [114]).

Vitamins E and C; Zinc, Copper and Selenium: Other micronutrients that have activities that overlap with those of magnesium in disorders to which magnesium deficiency contributes, or in which magnesium exerts beneficial effects, are those that affect free radicals. Deficiency of vitamin E has induced magnesium deficiency [39], and lowered tissue magnesium levels [143]. Vitamin C excess has also caused lowering of tissue magnesium [59]. Like the trace mineral anti-oxidants: selenium and zinc, magnesium stabilizes membranes [8, 16, 31, 68, 131] (Figure 5). Copper increases free radical release [45, 50]. Possible interrelations of antioxidants with magnesium, in disorders that affect the immune system and the aging and neoplastic

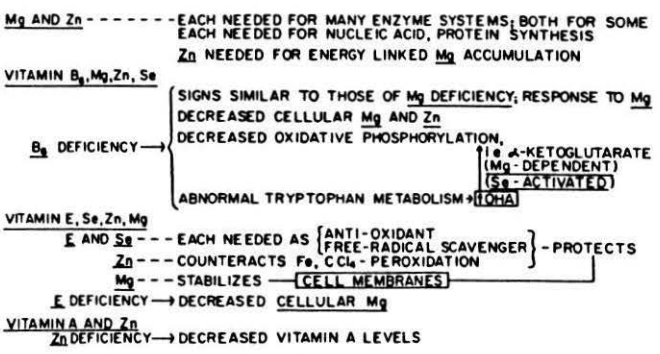


Fig. 5: Magnesium interactions with nutrients that affect free radicals

processes have been considered elsewhere [106a, 110, 111].

Magnesium Requirements, as Influenced by Other Nutrients, in Prevention of Cardiovascular Disease

Studies of experimental magnesium deficiency have shown that there are many ways in which magnesium deficiency can damage the heart and arteries (Reviews [115, 116]). The relevance of these findings to the sex difference and to East/West incidences of cardiovascular disease was first suggested by analysis of worldwide metabolic balance studies [113]. The greater retention of marginal intakes of magnesium by young women than by men, and the greater customary magnesium content of the oriental than the occidental diets suggested that the common denominator in these disparate examples of resistance to the most common killer in the Western world, might be adequacy of magnesium intakes. This premise has been supported by epidemiologic studies [6, 58, 70, 82] and by further experimental and clinical data [3–5, 27, 48, 53, 93, 120]. Imbalances of many nutrients — including excess fat and sodium — affect magnesium requirements. Deleterious excesses and deficits increase need for the protective effects of magnesium (Figure 6).

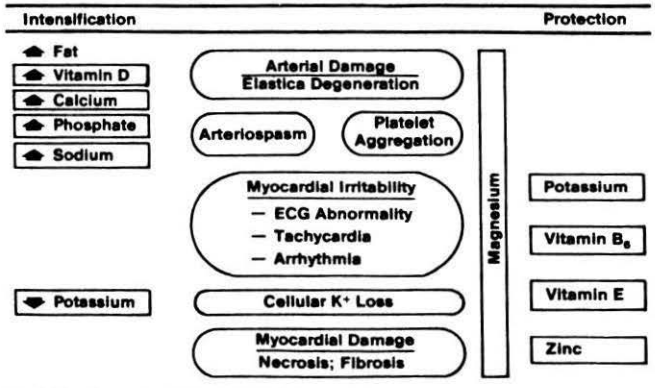


Fig. 6: Cardiovascular effects of magnesium deficiency

Tab. 1: Similarities of infantile cardiovascular disease to lesions of experimental magnesium deficiency and of hypervitaminosis D

Clinical infantile cardiovascular disease	Experimental magnesium deficiency	Experimental vitamin D toxicity
Arteriosclerosis of the small coronary arteries intimal edema, thickening elastica degeneration: fat streaks, calcification medial edema: necrosis medial hyperplasia	Arteriosclerosis of the small coronary arteries intimal edema, thickening elastica degeneration: lipid droplets, calcification (±) medial edema: necrosis medial hyperplasia	Atheriosclerosis and arteriosclerosis of the larger coronary arteries and aorta intimal plaques elastica degeneration, calcification
Endocardial fibroelastosis	Endocardial fibrosis (rare)	Endocardial fibroelastic thickening*
Valvular malformations (usually stenotic)		Supravalvular aortic stenosis
Coronary thrombosis (rare)	Myocardial perivascular focal infiltration, edema, necrosis	Myocardial focal necrosis
Conduction abnormalities'	Electrocardiographic abnormalities	
Hyperlipidemia''	Hyperlipidemia	Hyperlipidemia
Hypercalcemia''		Hypercalcemia
Hypertension''		Hypertension
Generalized arteriosclerosis''		
Supravalvular aortic stenosis''		Magnesium loss, intensification of magnesium deficiency

* young of rabbits with vitamin D toxicity during pregnancy; ' possibly contributory to sudden infant death; '' in later infancy, childhood

)enefical nutrients, that in optimal mounts act in concert with magesium, thereby logically decreasng its needs, may also increase its equirement initially (i.e. as poenzymes requiring it are actiated, in the case of prior defiiency). Excesses of vitamin D, calium, phosphate, and sodium — dded to a diet low in magnesium, otassium and chloride, has been ound to produce spontaneous nyocardial infarctions in several nimal species [98, 121]. Up to ivefold increased magnesium inake, with adequate potassium and hloride, mitigated the hyperholesterolemia, hypercoagulability and elevated blood pressure, as well as the arterial lesions produced by the cardiomyopathic diet [98, 121, 130].

The essential micronutrients: vitmins B6, B1, E and C, and zinc selenium have also been shown ave protective activities on the rdiovascular system. Charting some of the effects illustrates how several of the nutrients that are commonly taken by those self-supplementing themselves, or that are often prescribed, have effects that conflict with or enhance the beneficial effects of magnesium, and that can increase or decrease its requirements.

Vitamin D Excess or Hyperreactivity, Magnesium Deficiency and the Cardiovascular System

The startling similarities seen in cardiovascular lesions caused by experimental magnesium deficiency or experimental vitamin D toxicity, and those seen in clinical infantile cardiovascular disease (Table II), suggest that hypervitaminosis D, with sub-optimal magnesium, might be contributory to the human disease (Figure 7). Infantile hypercalcemia, with or without the classic constellation of abnormalities of the supravalvular aortic stenosis syndrome, is a genetic disorder caused by hyperreactivity to vitamin D [114]. Lesser degrees of vitamin D excess or hyperreactivity, combined with magnesium inadequacy, contributed to by renal magnesium loss caused by excess D [137], might be factors in the severe disease of infancy and establishment of the roots of the cardiovascular disease that becomes manifest later in life [107].

Magnesium, Vitamin B6 and the Arterial Wall

Comparable activities of magnesium and pyridoxine in protecting against adverse cardiovascular effects of excesses of fats, phosphates, calcium and calcemic agents such as vitamin D are depicted on Figure 8. Deficiency of either magnesium (Review [115, 116]) or pyridoxine [46, 100] causes thickened intima and predominantly medial connective tissue damage. A deficiency of each is important in the pathogenesis of arteriosclerosis [46, 103, 107, 115, 129, 139]. Each protects against cardiovascular damage caused by deficiencies of the other, beneficial effects that are enhanced by potassium and several micronutrients.

Another interaction between magnesium and pyridoxine that might pertain to a pathogenic mechanism in atherogenesis is suggested by the premature atherosclerosis of those with the vitamin B6-dependent disease, homocystinuria [74, 75]. Cystathionine synthetase, a B6 dependent enzyme, that also requires magnesium, converts homocysteine to cystathionine, thereby prevent-

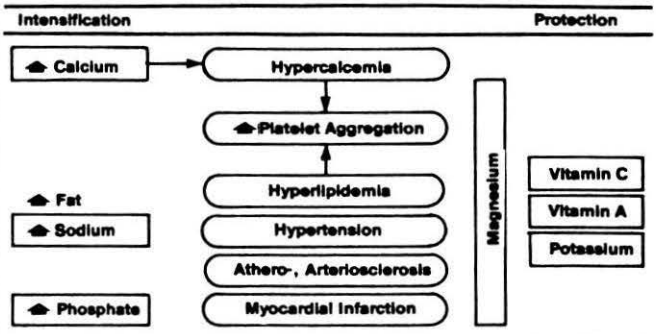


Fig. 7: Vitamin D excess or hyperreactivity in cardiovascular damage — intensifying and protective nutrients

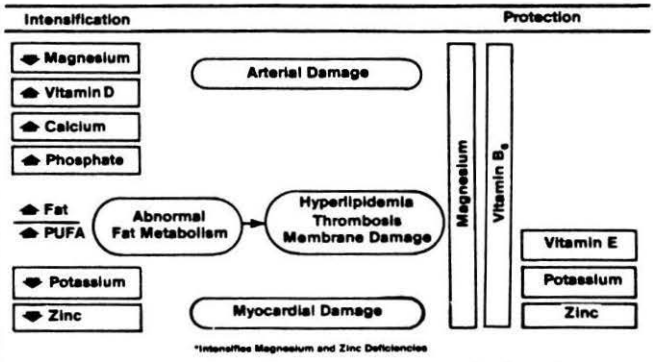


Fig. 8: Cardiovascular effects of vitamin B_6 deficiency*); (magnesium interactions)

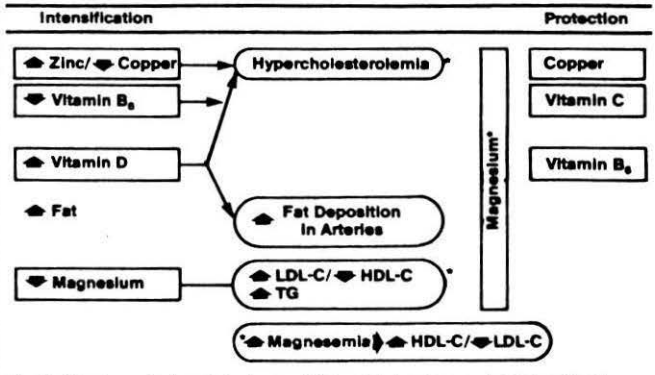


Fig. 9: Vitamins and minerals in abnormal fat metabolism (magnesium interactions)

ing formation of homocystine, which causes intimal damage [74, 129]. That such a mechanism might not be limited only to the rare inborn metabolic error is suggested by the finding that normal subjects fed high protein diets low in pyridoxine excreted homocystine [84].

Vitamins and Minerals that Influence Lipids in Blood and Arteries

Magnesium and Lipids: It was shown, many years ago, that dietary magnesium affects the hyperlipidemia and cardiovascular lipidosis caused by high fat diets [47, 118, 136]. The degree of atherosclerosis was intensified by magnesium deficiency; administration in higher than usual amounts was protective. New findings, that magnesium deficiency favors development of a high LDL/HDL ratio, whereas its administration does the reverse [42, 93–95] provides important new insight into magnesium/fat/arteriosclerosis relations. Thus, dietary imbalances that increase blood triglycerides may well increase magnesium requirements, that when provided protected against atherogenesis (Figure 9). The genetic predisposition to hyperlipidemia, seen in Type A subjects, whose erythrocyte Mg levels are lower than that of Type B subjects [48], is further suggestive evidence that increased Mg intakes (over the RDA) may be protective even in this high risk group.

Vitamin D: Long known to cause arterial calcification secondary to hypercalcemia [Reviews: 51, 114], hypervitaminosis D also causes increased blood lipids [66, 114], and atheromatous as well as calcinotic arterial lesions in children with hyperreactivity to vitamin D [114]. A few studies in adults have shown that even slightly higher than customary supplementation has raised blood cholesterol levels [23, 32, 66].

Vitamin B6: This vitamin has been proposed as a key catalytic agent in lipid metabolism, particularly as it affects the cardiovascular system [140]. Vitamin B6 deficient animals [24, 81] and humans [81] have been reported to develop hypercholesterolemia. Arteriosclerosis seen in B6 deficient animals (supra vide) may be contributed to by the part

B6 plays in conversion of linoleic acid to arachidonic acid [83] — the ability to synthesize which has been correlated with species differences in vulnerability to atherosclerosis [128]. The role of magnesium in lipid metabolism may be not only direct, but also as a cofactor in the B6 apoenzymes, which require magnesium for full activation.

Vitamin B1: Thiamin deficiency, like that of magnesium, results in increased synthesis of triglycerides [56]. Since magnesium deficiency impairs response to B1 and lowers its tissue levels, the effects of the two nutrients on lipid metabolism may be related [56].

Vitamin C: Guinea pigs, which cannot synthesize vitamin C, develop elevated LDL/HDL ratio on diets low in that vitamin [37]. An in vitro study has shown that ascorbate increases LDL receptors in arterial muscle cells [7]. Pharmacologic doses of vitamin C have been used to lower triglyceride levels in humans with hyperlipemia [37, 124]. Vitamin C doses exceeding 1000 mg/day have increased HDL-C levels in a large serres of elderly subjects [57A]; equivocal results in other studies have been attributed to small sample size (Review [57A]). Since there is so much self-medication with high dosage vitamin C, its effect on requirements of other nutrients needs consideration. For example, it has lowered tissue magnesium [59], and has caused urinary B6 wastage [102]. In some subjects high vitamin C dosage has caused increased urinary oxalate excretion [12]. Possibly, since Ca oxalate urolithiasis is inhibited by magnesium therapy [57B] alone or with B6 [36, 57B], those with the oxalate response to vitamin C may have increased B6 and/or magnesium requirements.

Zinc, Copper and Selenium: High zinc/copper ratios have been shown to cause high blood lipids in rats, and have been postulated to contribute to human atherosclerosis [61]. Although, in this role, copper seems to be protective, it has been proposed that the increased copper found in soft water might contribute to the cardiovascular disease in soft water areas, because of its catalysis of lipid oxidation through free radical reactions [45].

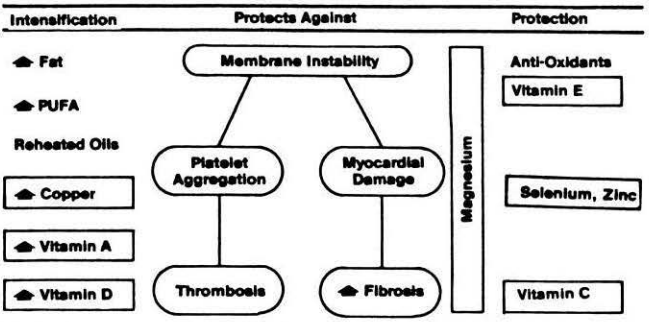


Fig. 10: Anti-oxidants: vitamine E and selenium in cardiovascular disease (magnesium interactions)

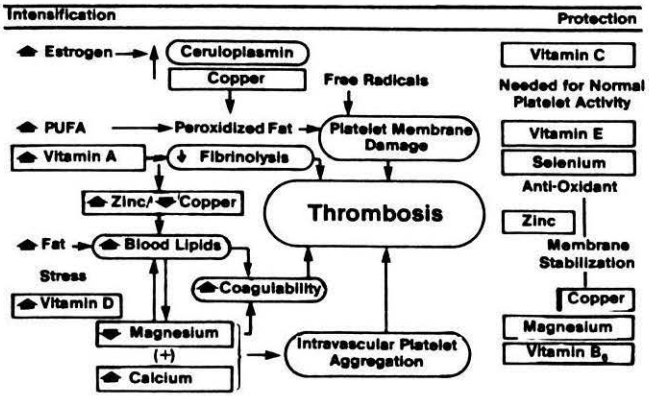


Fig. 11: Vitamins and minerals in thrombogenesis

Polyunsaturated fatty acids, used for many years to protect against harm caused by saturated fats, increase the requirement for antioxidants, such as selenium and vitamin E, to prevent their peroxidation and release of free radicals which pose a threat to stability of membranes: of platelets and of the cardiovascular tissues [68, 131] (Figure 10). Both zinc and magnesium have membrane-stabilizing activities [8, 16, 31].

Magnesium, Vitamins and Trace Minerals in Thrombogenesis

Thrombogenesis — long known as a factor in atherogenesis [25], as well as being the dominant event in myocardial infarction — has even more nutrient interactions in its pathogenesis (Figure 11) than does the hyperlipemic pathway to arterial disease. Magnesium has many activities that have been shown, in vitro, to decrease intra-vascular blood coagulability [27, 31], from counteracting calcium's coagulating effects in many steps of fibrinogenesis to stabilizing platelet membranes. Increased platelet aggregation is favored by decreased magnesium and increased calcium

levels, which inhibit and enhance, respectively, several steps in blood coagulation. The thrombotic events of patients with magnesium deficiency [29], that respond to magnesium repletion, support the premise that magnesium is important, clinically, in inhibiting intravascular coagulation.

Here, too, pyridoxine has activities that enhance those of magnesium. It inhibits platelet aggregation and increases whole blood and thrombin clotting times [134]. Platelet aggregation is also increased by damage to their membranes — against which anti-oxidants such as vitamin E and selenium are operative, and which is intensified by free radicals and peroxidized fats. Vitamin C is included on the chart, because it has been claimed that its use in relatively high dosage has a clinical antithrombotic effect [125], and because contraceptive-induced falls in blood and endothelial levels of vitamin C [101] have been proposed as a factor in intravascular coagulation [18]. It has also been proposed that vitamin C regulates prostaglandin E1 formation, thereby inhibiting platelet aggregation [52]. Noteworthy, here, is the serum magnesium lowering effect of oral contraceptives, which occurs with magnesium shift into bones and soft tissue [39, 117].

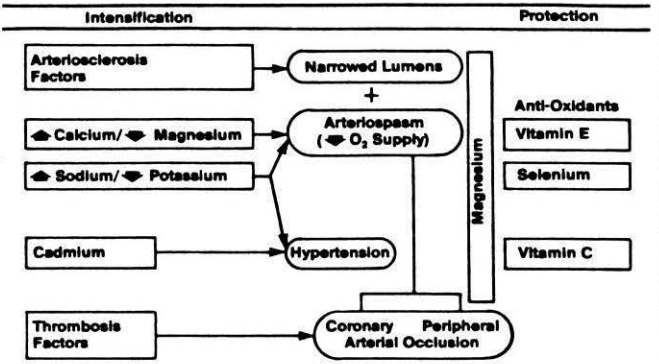


Fig. 12: Vitamin-mineral interactions in arteriospasms, cardiac ischemia causing decreased oxygen supply

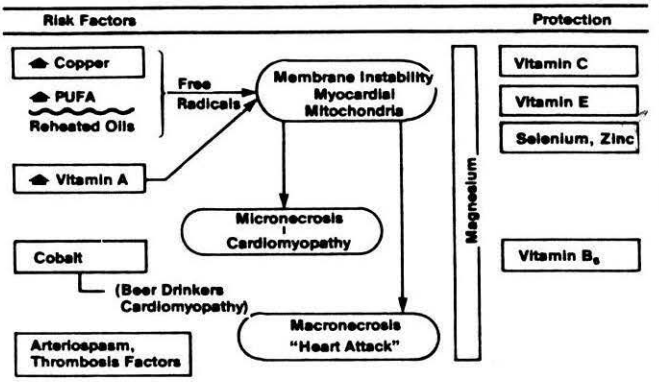


Fig. 13: Vitamins and minerals in myocardial necrosis (magnesium interactions)

Vitamins and Minerals in Arterioconstriction, Hypertension and Myocardial Necrosis

The major nutritional factors in arterioconstrictive disease are increased sodium/potassium ratios and decreased magnesium/calcium ratios [2–4, 30, 43, 44] (Figure 12). Magnesium is important in maintaining adequate potassium levels [30, 119] and in diuretic treatment of hypertension [138]. Direct experimental evidence and epidemiologic data [58] indicate that high magnesium/calcium ratios exert anti-constrictive effects in the arteries and protect the myocardium from many necrosis-inducing challenges, whereas high calcium/magnesium ratios do the reverse.

Agents that cause membrane damage (supra vide) (Figure 13) can give rise to micronecrotic foci, that can be associated with more diffuse cardiomyopathic processes. Nutrients that increase release of free radicals can be implicated in the etiology of this disorder, and anti-oxidant nutrients, magnesium, zinc and pyridoxine are protective. Whether an optimal intake of the protective vitamins and minerals might decrease the need for magnesium — the principal protective nutrient, while high intakes of the risk factors might increase its needs requires further study.

Discussion

The question of nutritional requirements has long been controversial. Ideally, the recommended dietary allowance should be the amount that will maintain health — which has been defined as "physical and mental well being; freedom from disease, pain or defect; normality of physical and mental functions; soundness" [13]. An RDA that merely prevents the clinical syndrome of deficiency does not take into account the changes that im-

pair health and that occur before the development of overt deficency. Studies of biochemical phenomena associated with vitamin depletion of volunteers have disclosed that relying on prevention of such manifestations of deficiency as the definitive index of deficiency would disregard early abnormalities. These include first, reduction of tissue stores, next reduction of enzyme activity due to insufficient cofactors, then evidence of minimal urinary excretion of the nutrient, and then early (prodromal) evidence of physiologic malfunction — all before the classic deficiency syndrome is recognizable [13].

Reliance on prevention of overt signs of magnesium deficiency — such as convulsions — which develop with depletion, risks silent progression of lesions of arteries, heart, kidneys and bone, such as are caused by less profound experimental magnesium deficiency (Review [107]), and that are contributed to by imbalances of other nutrients with which magnesium interacts. Arrhythmia of magnesium deficiency is usually attributed to other causes, and repletion undertaken only on failure of conventional approaches. Less severe neuromuscular manifestations have been recognized and used as clinical parameters of "marginal" magnesium deficiency [28, 29].

Equally unreliable ways to arrive at a recommendation for magnesium intake are to use calculations from the amounts found necessary for induction of depletion or from the amounts required to preserve a "safe" plasma concentration of magnesium — such as have yielded a "requirement" of 100 mg daily [72]. This is less than a third of that necessary to maintain magnesium equilibrium in normal young adults, and would fortunately be difficult to achieve by even poorly balanced diets.

Since it has been repeatedly shown that young adults require at least 5–6 mg magnesium per kg of body weight to remain in equilibrium, at least that amount should be indicated as the RDA (the nutrient needs for maintaining health in otherwise healthy subjects). The panel assigned the task of revising the RDAs prepared a report in which the RDA was to be lowered to an amount essentially equivalent to the MDR [71]. Since this evoked heated controversy among nutritionists, revision of the 1980 RDA book [20] has been delayed. In actuality, it is doubtful if the current RDA is high enough to cover needs of growth and stress [109], or to compensate for the extra requirements caused by the nutritional interrelationships considered here. Most of the metabolic balance data are derived from young adults on controlled dietary intakes, that do not reflect the altered needs caused by dietary indiscretions or customary intakes of foods that increase magnesium needs. Those metabolic studies that indicate lower magnesium requirements than those currently listed as the RDA are with people living in protected environments relatively free of stresses of daily life [109]. The special needs to prevent magnesium loss during stress and illness are rarely considered.

Genetic differences in magnesium requirements might contribute to familial differences in diseases which are characterized by disorders in which magnesium deficiency might play a role. Subnormal intestinal magnesium absorption, its renal wasting, or abnormal membrane transport — extremes of which have been identified as familial disorders [38, 87, 88, Review: 107], each can contribute to individual differences in magnesium requirements.

The concept of biochemical individuality was promulgated to explain differences in requirements for vitamins [140], that is expressed in the extreme form as inborn errors of metabolism classed as vitamin-dependent diseases. The markedly elevated vitamin requirements of such patients are caused by defects in membrane transport, and in conversion of the vitamin into its coenzyme [105]. Since magnesium is involved as a cofactor in many vitamin coenzymes, magnesium deficiency or abnormality in its utilization might be contributory to such diseases. The concept of "vitamin insufficiency" has been suggested to explain the need for higher than customary doses of a vitamin under special conditions — such as the requirement of megadoses of thiamin by those with a genetic variant of transketolase, that becomes clinically manifest as the Wernicke–Korsakoff syndrome only on consumption of large amounts of alcohol [11]. Since transketolase is also magnesium-dependent, and alcohol causes magnesium loss, its deficiency is likely to add to this "vitamin insufficiency" state. Thiamin-dependent alcohol-induced encephalopathies have been shown to respond better to B1 when magnesium is also administered [127, 142]. Other neurologic disorders, in which vitamin B1 and B6 insufficiencies have been implicated [67] include autism and hyperactivity in which there are serotonin abnormalities [10, 19]; autistic children respond better to large B6 doses when magnesium is also given (p. c. *M. Coleman*). The recent elucidation of the effects of magnesium on neurotransmitters in the brain [89] provide additional insight into ways in which magnesium can act conjointly with vitamins that influence brain function.

There may be degrees of vitamin dependence or hyper-reactivity that can affect magnesium requirements, but that are not so severe as to be recognized as typical of the characteristic metabolic disorder. To what extent enzymatic dysfunction caused by both magnesium and a vitamin insufficiency might contribute to disease is worth study.

Most of the emphasis, in this paper, has been on interrelations of magnesium with other nutrients, as they affect the cardiovascular system. To the extent that programs to reduce the intake of fat are successful, the requirement for magnesium will be lowered. "Fortification" of foods with vitamin D continues to supply more of this sterol than needed, especially by those who also take multivitamins and those who are hyperreactive to vitamin D. Active promotion has recently been undertaken in the United States, to increase the intake of calcium substantially. When one considers that the dietary surveys have disclosed a low magnesium/calcium ratio, without such supplements, there should be concern that further imbalancing that ratio might have adverse cardiovascular consequences. Megavitamin consumption might increase magnesium requirements.

Marginal magnesium deficiency is not widely accepted as a factor in a number of diseases that have characteristics such as can be produced by experimental magnesium deficiency. This is partially because it is difficult to diagnose. Also there may be individual and group differences in magnesium requirements, and in clinical expressions of marginal magnesium deficiency. The nutritional dietary constituents, that affect magnesium utilization, and that differ in cultural and geographic settings, might explain some of the enigmas that face investigators in who wish to prove the clinical significance of magnesium deficiency, and the justification of its correction to prevent disease.

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