Magnesium[1,2]

PO Wester, MD

Introduction

Magnesium, atomic number 12, has an atomic weight of 24.32 and is one of the four *bulk* metals in the human body. It is the most abundant intracellular ion in plants, the second most common divalent ion in the oceans, the third most common on land, and the fourth most abundant metal in living organisms. In man, Mg is the second intracellular cation. In the adult human body there are about 1000 mmol (24 g), ~60% in the skeleton, ~39% in the intracellular space (20% in skeletal muscle), and only 1% occurring extracellularly. There are at least three different Mg pools in the human body: one with a quick turnover, mainly consisting of extracellular Mg; a second with a turnover rate about half that of the first pool, mainly consisting of intracellular Mg; and a third pool containing the skeletal Mg with a very slow turnover rate. The relationship between extra- and intracellular bulk ion is seen in **Figure 1.** The normal serum level of Mg is narrow (0.7 –1.0 mmol/L) and lacks correlation to total body Mg. Although there is no known homeostatic system regulating serum Mg, the values are remarkably constant among individuals. An intracellular Mg deficiency may often occur with normal serum Mg. Intracellular Mg has a good correlation to intracellular K. About 30% of serum Mg is protein bound and most of the remaining fraction is in ionized form and is filtered through the kidney. Mg intracellularly is bound mainly to protein and energy-rich phosphates.

Functions of Mg

Mg has played an important role in the process of biological evolution towards more differentiated organisms with more effective energy utilization. Chlorophyll, which is the base for energy production from sunlight, water, and carbon dioxide, was developed ~3 billion years ago. Mg is a part of the chlorophyll molecule. About 1 billion years later oxidative phosphorylation was developed in which Mg is a necessary ion. The fact that Mg is indispensible to the metabolism of ATP means that it is essential in a great many metabolic processes such as glucose utilization; synthesis of fat, protein, and nucleid acids; muscle contraction; and some membrane transport systems. Overall Mg is important for > 300 different enzyme systems.

Mg absorption

Gastrointestinal net absorption, studied by means of the conventional balance technique, has on average been found to be 35–40% (1). More recently Mg absorption has been studied with Mg^{28} administered orally (2). Within 1 h detectable absorption was observed, which may indicate some absorption as early as in the gastric mucosa (3). Steady-state absorption occurred after 2–3 h, reaching a maximum after 4 h (4) and remaining more or less constant for the next 4–6 h, a time schedule which corresponds fairly well with that for passage through the small intestine and which suggests that Mg is absorbed mainly in the small intestine in both the upper and in the lower parts (5). Only a small amount was absorbed in the period 12–36 h after ingestion. However, the colon may play a role in the absorption of Mg under certain circumstances as has been demonstrated in some case reports on hypermagnesemia after solutions containing Mg were administered by enema. It has been suggested that possibly a compensatory increase in the absorption of Mg from the colon may occur during diseases of the small intestines, eg, inflammatory processes interfering with the Mg absorption (6).

[1] From the Department of Medicine, Umeå University, Umeå, Sweden.
[2] Address reprint requests to Dr PO Wester, MD, Department of Medicine, Umeå University, Umeå S-90185, Sweden.

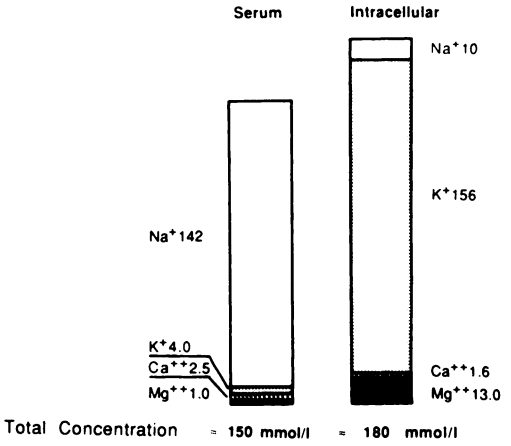

FIG 1. Distribution of different ions in the extra- and intracellular compartments.

There are several factors which influence Mg absorption such as the amount of ingested Mg, the Mg status of the body, and the calcium, phosphate, phytate, protein, etc content of the diet. With a very low dietary intake of Mg (< 1 mmol/d) 75% of the ingested Mg was absorbed while a high intake (25 mmol/d) resulted in a decrease in the absorption to 24% (5).

In animal experiments high calcium intake may precipitate magnesium deficiency and increasing the calcium intake increases the Mg loss. It has further been suggested that in Mg-deficient animals' bone calcium can be mobilized. Hypercalcemia and soft tissue calcinosis, which are found in Mg depleted animals, may be mediated both by enhanced calcium absorption and by mobilization of body stores. In humans the picture is far less clear. Increasing the calcium intake does not seem to have any striking effect on Mg balance in subjects on normal or high Mg intake (6). In subjects on low Mg intake calcium supplementation seems to reduce dietary Mg retention (6). Increasing the Mg intake improves rather than interferes with calcium utilization. In patients with malabsorption administration of Mg corrected the Mg deficiency and also enhanced calcium retention (7). In patients with hypocalcemia due to intestinal surgery the calcium abnormality cannot be corrected without correcting the Mg deficiency that occurs simultaneously (8).

Whether the amount of protein in the diet causes positive or negative Mg balance seems to depend on the relative amounts of each in the diet (9). In subjects on low Mg intake and very low protein intake increasing the protein intake to a marginally adequate level improved the Mg retention but further increase of the protein intake impaired Mg retention. There are also several other dietary factors which may influence Mg balance such as the amount of phosphate, phytate, fat, and others (10).

There is a considerable secretion of Mg into the intestinal tract from bile and pancreatic and intestinal juices. Pancreatic juice contains about 0.05 mmol/L, gastric juice 0.5, and bile 0.7 mmol Mg/L. This secretion is followed by almost complete reabsorption. However, patients with excessive losses of gastrointestinal fluid may develop Mg deficiency (11). Endogenous fecal Mg excretion is normally low. After iv injection of Mg^{28} < 1% could be recovered in the feces (12).

Urinary excretion

The kidney is the major excretory pathway for absorbed Mg. The average excretion of Mg in urine per day on an ordinary diet has been found to vary between 2 and 5 mmol (13, 14) with individual variations but with fairly small variations from day to day in the same individual. Additional Mg given with an ordinary diet increases urinary Mg by only a few percent (5, 7). Most of the Mg administered orally leaves the body with the feces. With a low dietary intake the kidneys are normally able to save Mg very effectively. In experimental Mg deprivation it may take several months to develop a deficiency just because of the kidney's ability to save Mg (14–16). Iv-administered Mg is excreted almost entirely with the urine. The percentage retention of iv-administered Mg may be used as a loading test for Mg deficiency (11, 17). The maximal renal capacity for excretion is not known but is probably quite high (18).

The ionized fraction consisting of ~70% of the serum Mg is filtered in the kidneys. Thus ~75 mmol Mg passes the glomeruli each day but only 3–5% of the filtered Mg is excreted in the urine. About 20–30% of Mg is reabsorbed by the proximal tubule and the reabsorption in this segment is related to sodium transport (19). There is a very active transport mechanism for Mg in the distal nephron. The

thick ascending limb of the loop of Henle is the major site for Mg reabsorption. In this segment ~65% of the filtered Mg is reabsorbed. The reabsorption follows the Tm/GFR model with a lower limit of ~0.6 mmol/L and a less-well-defined upper limit of ~1.00–1.50 mmol (20). One interesting finding is the medullary recycling of Mg, ie, Mg is added to the filtrate in the descending limb of the loop of Henle and then reabsorbed in the ascending limb (21).

A comparatively small increase in serum Mg will result in increased urinary Mg excretion. Available data regarding Mg secretion by the renal tubule are contradictory and if Mg secretion by the nephron exists at all in human beings, it plays only a minor role in the renal handling of Mg (19).

There are many factors influencing tubular reabsorption of Mg. **Table 1** presents factors that decrease and enhance tubular reabsorption of Mg. Extracellular fluid volume expansion decreases Mg reabsorption parallel to that of sodium (21, 22). Osmotic agents such as mannitol and urea and extra supplies of Na, Ca, and Mg inhibit the tubular reabsorption of Mg (19).

Alcohol has been shown to increase urinary excretion of Mg following both acute and chronic ingestion (23). Loop diuretics which act on the thick ascending part of the loop of Henle inhibit the Mg absorption in this segment (24). The thiazide diuretics, which also to some extent increase urinary output of Mg, act at the cortical segment and the distal tubuli where Mg is not reabsorbed. Thus, the effect of the thiazides on urinary Mg excretion probably does not depend on a direct action on the tubules. It may instead depend on secondary hyperaldosteronism aggravated by the thiazides and possibly also on interaction with calcium metabolism. Digitalis, which is often used in combination with diuretics, has also been found to increase urinary Mg excretion due to decreased tubular Mg reabsorption. There are also other drugs, eg, aminoglucosides, which decrease tubular Mg reabsorption.

Increased ingestion of glucose in the diet increases urinary Mg excretion because of a reduction in tubular reabsorption while the intake of fat has no effect on urinary Mg excretion (19).

TABLE 1
Factors influencing tubular Mg reabsorption

Decreasing	Enhancing
Glucose intake	Mg deficiency
Alcohol intake	Low Mg intake
Extra supply of Na, Ca, Mg	PTH in high doses
Extracellular volume expansion	
Osmotic agents	
Diuretics and digitalis	

Influence of hormones and vitamins

A complicated but not yet fully understood system of interactions exists between Mg and various hormones and there is no evidence of a specific Mg-regulating hormone. Parathyroid hormone (PTH) seems not to be essential for the regulation of Mg balance under normal circumstances. PTH in large doses increases both intestinal absorption and the renal reabsorption of Mg while small doses seem to have no effect (25). A mild Mg deficiency results in an increased release of PTH although a severe deficiency leads to a decreased release and also to a decreased peripheral sensitivity to PTH administered exogenously.

Thyroid hormones have been reported to increase renal excretion of Mg and possibly also to increase the transport of Mg from extra- to intracellular compartments. Low serum Mg is also often observed in hyperthyroidism (26).

A long-term excess of mineralo- or glucocorticoids may result in a low serum Mg and also in cellular Mg depletion mainly due to increased urinary Mg excretion. However, short-term infusion of aldosterone has no effect on the urinary elimination of Mg (27). Thus the effect seems not to be a direct hormonal effect but is mediated via extracellular volume expansion due to sodium retention (28). Mg deficiency has in turn been shown to increase aldosterone release, which may result in a vicious circle (29). Catecholamines seem to lower serum Mg and possibly increase intracellular Mg in certain tissues (30, 31).

Insulin causes a shift of Mg from the extracellular to the intracellular compartment resulting in low serum Mg while urinary excretion and gastrointestinal absorption seem to be unaffected (32). In poorly controlled diabetes, urinary excretion of Mg is increased probably due to osmotic diuresis and reduced

tubular reabsorption related to hyperglycemia. Hypomagnesemia has also been reported in many patients with diabetes mellitus (33) and it has been suggested that it is related to the degree of retinopathy (34).

Vitamin D may increase the gastrointestinal absorption of Mg and increase the transport of Mg from extra- to intracellular space (35). However, the picture is complicated by simultaneous changes in calcium and phosphate metabolism.

Mg and thiamine are interrelated. In animal experiments thiamine administered to Mg-deficient animals is not utilized and thiamine deficiency may develop. In addition the administration of thiamine in Mg-deficient states may accentuate symptoms of Mg depletion (36).

Mg-K interaction

It has been demonstrated that Mg influences the balance between extra- and intracellular potassium (37). The reason for this is not clearly understood. An attractive theory is from the observation that Mg is necessary for the function of Na-K ATPase. A Mg deficiency will thus lead to an impaired pumping of sodium out of the cell and of potassium into the cell. It has been shown that potassium supplementation in hypokalemic patients normalizes serum potassium but not muscle potassium if there is a concomitant Mg deficiency (38). Further Mg infusions but not potassium infusions normalized the muscle potassium (39).

Mg-Ca relations

Mg is necessary for the release of parathyroid hormone (PTH) and also for the action of PTH on bone, kidney and gut. Mg deficiency stimulates PTH secretion in vitro but severe Mg deficiency may impair PTH secretion (40, 41). Severe hypomagnesemia blocks the response of the parathyroid glands to hypocalcemia and Mg injections can rapidly stimulate PTH secretion under these circumstances (42). Large doses of Mg block PTH secretion but calcium is three times more effective in this respect (40). Mg is also required for the hepatic 25-hydroxylation of vitamin D. Thus, many steps in calcium homeostasis are dependent on Mg and hypomagnesemia is also very often accompanied by hypocalcemia. Mg is also considered to be a natural calcium antagonist (43, 44) affecting uptake, content, binding, and distribution of calcium in smooth muscle cells (45).

Mg deficiency

Mg deficiency was first observed in cattle (grass staggers) (46). The symptoms (irritability, excitation, exhaustion, fibrillary fasciculations, muscle cramps, tetany, etc) could be relieved by feeding the animals Mg supplements. Autopsy examinations of cows and calves who died revealed severe cardiovascular damage including necroses and calcification. Experimental Mg deficiency in rats produces degenerative changes in skeletal and cardiac muscle and renal tubular changes with nephrocalcinosis (47).

Studies of experimental deficiency in man have been hampered by the constancy of serum Mg due to the large capacity of the kidneys to retain Mg and to easily mobilize depots in the muscle and in the skeleton. Thus, it is difficult to achieve a significant Mg depletion in normal individuals through dietary restrictions. During prolonged fasting a deficit of 20% of total-body Mg may occur but serum Mg remains unchanged (48).

Mg deficiency in man may develop in many disease states (**Table 2**). Symptoms may come from the central nervous system, the skeletal muscles, the gastrointestinal tract, and the cardiovascular system (**Table 3**). The symptoms are often vague and uncharacteristic in mild deficiency.

The question of whether Mg deficiency can develop in the absence of disease remains unsettled. Acute Mg deficiency probably develops only in pathological conditions. However, the possibility that a prolonged dietary insufficiency may contribute to the development of chronic disease cannot be excluded.

Mg deficiency has been discussed as a possible contributory factor in the development of atherosclerosis, myocardial damage, arterial hypertension, cardiac arrhythmias, and kidney stone disease among others (49). Dietary Mg deficiency tends to produce cardiovascular damage in experimental and domestic animals

TABLE 2
Causes of Mg deficiency

Nutritional and gastrointestinal
Inadequate dietary habits (eg, in elderly people)
Prolonged intravenous feeding without adequate Mg supplementation
Long-term gastric drainage or intestinal fistulae
Prolonged diarrhea
Malabsorption
Alcoholic abuse
Renal
Diuretic therapy
Hypercalcemia
Certain kidney diseases
Certain antibodies
Endocrine
Primary and secondary aldosteronism
Diabetes
Hyperthyroidism
Hyperparathyroidism

and hypertension as well as hyperlipidemia has been observed in Mg-deficient animals (50, 51). There is also some evidence from epidemiological data that Mg might be involved in cardiovascular disease.

Coronary death rates in various countries have been observed to correlate with the dietary Ca:Mg ratio (52). The suggestion has been made that the inverse correlation between the hardness of the drinking water and the death rate from cardiovascular disease observed in many countries is more closely correlated to magnesium than to calcium (53) and that magnesium is a cardioprotective factor in hard water (54). In Finland the regional death rates from ischemic heart disease are found to be inversely correlated with the hardness and Mg content of the drinking water and to the content of exchangeable Mg in the soil (55). Mg, among other ions, may be of importance in the development of essential hypertension but its role in this condition is unclear. In some studies the addition of Mg lowered arterial blood pressure (56–58) and in others it did not (59, 60). Clinically, Mg deficiency may in some patients be a responsible factor in the development of various arrhythmias (61) and there are numerous cases published in the literature of successful treatment through the addition of Mg. There are also some recent reports of the beneficial effect of Mg given to patients with acute myocardial infarction with regard to arrhythmias, infarct size, and survival (62).

Mg in food

The daily intake of Mg is usually 10–20 mmol mainly from the intake of cereals; 60–70% is excreted in the feces and 30–40% absorbed and excreted in the urine. The Mg content for different kinds of food is given in **Table 4.** On a weight basis spices, nuts, cereals, and sea foods are rich in Mg and sugars and fats are very poor. On a calorie basis vegetables are very rich in Mg especially green leafy vegetables which are rich in the Mg-containing chlorophyll. Among the beverages coffee, tea, and cocoa are rich in Mg, while hard liquors are very poor.

The amount of Mg in drinking water may vary widely from almost 0 to > 15 μg/mL (18) and in a US survey waterborn Mg provided

TABLE 3
Symptoms of Mg deficiency

Central nervous system
Difficulty remembering things
Decreased ability to concentrate
Apathy and depression
Confusion
Hallucinations
Paranoid ideas
Neuromuscular symptoms
Numbness, tingling, cramps
Muscular weakness
Muscle fasciculations
Tremor
Ataxia
Nystagmus
Tetany

TABLE 4
Mg content in foods and beverages

	μg/g	mg/100 kcal	mg/MJ
Spices	2600	72	171
Nuts	2000	33	79
Cereals	800	24	57
Sea foods	350	37	88
Meat	270	15	36
Vegetables	200	100	238
Daily product	160	18	49
Fruits	80	17	40
Sugars	60	2	4.7
Fats	7	0.1	0.2
Coffee powder	5000	—	—
Cocoa powder	4000	95	226
Milk, beer, and wine	100	15	36
Drinking water	~6	—	—
Hard liquor	1	< 0.1	< 0.2

9–27% of the daily Mg intake (63). In Canada it is reported that waterborn Mg provided ~18% of the daily Mg intake in hard-water regions and only one-tenth as much in soft-water localities (64). Hard water in Great Britain accounts for 3% of the Mg intake (65).

Refining and cooking may diminish the Mg content very substantially (18). The refining of whole wheat to patent flour results in a loss of 80–96% (18, 66) of the Mg content and the polishing of rice may remove > 80%. The refining of sugar removes almost all the Mg (18, 67) and boiling vegetables may cause a Mg loss of > 50% (18). There are observations that the Mg intake of humans has declined very sharply during the past few decades (68). This may be due to the refining and preparing of food but also to the use of fertilizers with no Mg (53).

Mg requirements

From results of balance studies carried out on healthy young adults the National Research Council in the United States has stated that the RDA (Recommended Dietary Allowance) for Mg is 350 mg/d for adult men and 300 mg/d for adult women (69) with an extra 150 mg/d in pregnancy and lactation. These recommendations are followed in many countries including Sweden. The RDA in West Germany of 360 mg/d (70) is close to the US recommendations. However, the RDA in Canada is 240 mg/d for men and 190 mg/d for women (71). There has been a lot of controversy about the daily requirement of Mg in the literature (13, 18, 72, 73). Assuming that the dietary requirements are equal to the obligatory losses through urine and sweat, far lower figures for the RDA than those given above have been suggested as the minimal requirement (18, 72).

On the other hand, Seelig (10) in an extensive review of balance studies presented in the literature, suggested higher values. On the basis of 251 balance periods with an intake of < 4 $mg \cdot kg^{-1} \cdot d^{-1}$, which corresponds to 280 mg (~12 mmol) for an individual of 70 kg, she found that 83% of the periods were negative for men and 73% for women, assuming a sweat loss of 15 mg/d. At an intake of 4–4.9 $mg \cdot kg^{-1} \cdot d^{-1}$ (~12–15 mmol) based on 1941 test days, the overall average daily balance showed a loss of 28 mg for men and 2 mg (0.1 mmol) for women. At an intake of 5–5.9 $mg \cdot kg^{-1} \cdot d^{-1}$ (15–17 mmol) the women were at equilibrium and the men on average slightly negative still assuming a sweat loss of 15 mg/d. At an intake of 6–6.9 $mg \cdot kg^{-1} \cdot d^{-1}$ most balance periods were positive. In general women seemed to maintain equilibrium on a lower intake than men.

From these data Seelig suggested that the daily recommended Mg intake should not be < 6 $mg \cdot kg^{-1} \cdot d^{-1}$. At this level of intake positive balances were reached for at least 75% of the subjects.

There are various dietary factors which influence Mg resorption. Among others excess calcium, vitamin D, phosphate, phytate, and protein seem to increase the Mg requirements (20). Considering these data the RDA in the US does not appear to be too high. With regard to individual differences even higher amounts such as 15 mmol/d might be required to reach an optimal Mg intake.

Current intake of Mg

Compared to the RDA there are indications that Mg intake may be suboptimal in several countries (74) (**Table 5**). Self-selected diets among US males have been estimated to be ~30% lower in Mg then the RDA (75), and one study in the UK and one in West Germany found almost the same situation (67,

TABLE 5
Current Mg intake

		Amount
		mg/d
US		
Brown et al 1970	*n* = 955	♂ 262
Pao et al 1981	*n* = 37 000	♂ 266
		♀ 228
UK		
Hamilton et al 1972/73		♂ ♀ 250
West Germany		
Holtmeier et al 1972	*n* = 1852	♂ ♀ 235
New Foundland		
Fodor et al 1978	*n* = 188	♂189
		♂143
Ireland		
Brown et al 1970	*n* = 1039	♂ 415–472
US hospital diet		
Schroeder et al 1969		~200
Vegetarian diet		
Abdulla et al 1981		542

70). In a recent survey in the US of more than 37 000 individuals only 25% had a dietary intake of Mg that equalled or exceeded the RDA (76). In Newfoundland the diet has been reported to be very low in Mg reaching only 50% of the US RDA (77). Hospital and institutional diets in the US have also been reported to be very low in Mg (18). However, figures from Ireland exceed the US RDA (75). Oriental diet seems to be very rich in Mg (6) as is the diet of vegetarians (78, 79).

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