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Review article

Magnesium metabolism and perturbations in the elderly

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Abstract

It is generally accepted that magnesium requirements increase in the elderly. Multiple reasons for this exist. In the elderly, magnesium intake tends to be low, intestinal absorption is frequently diminished, and urinary output is often enhanced. As a result, the magnesium status of aging subjects is likely to be marginal, if not frankly deficient. Because magnesium plays important roles in arterial structure and function by maintaining endothelial and platelet integrity, a deficiency can increase progression of arteriosclerosis, hypertension, and cardiac complications, including dysryhthmias. Magnesium inhibits pathological calcification, and a deficiency can contribute to formation of calcium uroliths. The element's role in calcium metabolism (improving utilization) and bone matrix formation (maintaining bone elasticity) might be important in preventing osteoporosis and brittleness of bones. Accordingly, physicians must always consider magnesium status in elderly patients.

Introduction

Magnesium (Mg) influences over 300 enzyme systems, including Na-K ATPase-mediated transport and is essential for calcium homeostasis, nerve conduction, skeletal muscle activity, and maintenance of calcium and potassium homeostasis. Therefore, depletion of this cation can cause a number of abnormal perturbations.

Hypomagnesemia and magnesium depletion are currently receiving more attention from the medical community than in the past because of evidence that deficiency contributes to atrial and ventricular ectopy with and without occurrence of acute myocardial infarction and sudden cardiac death [1–15]. In addition, newer means to measure the cation have provided physicians with capability to more readily assess abnormal magnesium status [16, 17], and a promising technic of measuring free ionic magnesium in erythrocytes and serum (the most accurate measure of clinical magnesium status) is being used under experimental conditions [18–20]. Nonetheless, there are gaps in our knowledge of the precise role of magnesium in health and disease. This is especially apparent in geriatric patients, whose magnesium intake tends to be low, whose intestinal absorption may be diminished, and whose urinary output may be increased. To make matters worse, many medications taken by the elderly and the stress they often endure also tend to cause magnesium loss with further lowering of tissue magnesium levels. Accordingly, it is generally accepted that magnesium requirements are elevated in the elderly.

Normal physiology and biochemistry

Magnesium is the fourth most abundant cation in humans; and, next to potassium, is the most abundant intracellular cation. Roughly, 98–99% resides in either bone or cells [21–23]. Much difficulty arises in determining excesses and deficiencies, for various compartments such as bone, muscle, and circulation may differ independently. It is no wonder that the 1% present in extracellular space does not necessarily reflect the general situation. In fact, no present laboratory test will unequivocally identify magnesium deficiency. The individual with a moderate deficiency is most difficult to diagnose, because as many as one half may have serum concentrations considered normal. Therefore, it is apparent that circulating levels will not necessarily reflect total body stores.

To obtain better evidence of body magnesium status, bone, muscle, erythrocyte, lymphocyte, and mononuclear white blood cell magnesium levels have been determined (Table 1). Nevertheless, with the exception of erythrocytes, there are difficulties in obtaining cellular samples for analysis. Also, white blood cell separation is complex and normal values for various tissues are still uncertain. Therefore, serum magnesium concentration is most commonly used for assessment despite its shortcomings. Even with serum samples, there is no consensus concerning normal values. The range of 1.5–2.5 mEq/L that has been considered normal [24] is incorrect. Experts in magnesium metabolism agree that limits of normal magnesium range are narrow, deviating from mean by no more than 10–20% [11, 16, 22, 23, 25–30]. Normal means have been reported at between 1.70–2.16 mEq/L. To convert these values to mg/dl, multiply by 1.2, which places the normal means reported by different laboratories at 2.0–2.6 mg/dl. Among the explanations for value variability are: diversity of instruments and procedures and loss of magnesium on storage of diluted samples [29]. Spuriously high serum values are obtained when difficulty in venipuncture leads to local cyanosis – hypoxia being associated with egress of cellular magnesium [31, 32].

Table 1. Clinical laboratory assessment of magnesium status

1.	Serum, Plasma
2.	Bone
3.	Muscle
4.	Red Blood Cells
5.	Mononuclear White Blood Cells
6.	Magnesium Loading

Thus, each laboratory should establish its own normal values, carefully selecting controls who are healthy, and preferably matched by age and gender.

To overcome some difficulties in assessment, magnesium loading tests have been used. Although a crude estimate, a magnesium deficiency is probable if more than 40% of an intravenously administered load (0.2 mEq/kg) is retained as assessed by urinary excretion. On the other hand, one can determine adequate correction of a deficit through magnesium supplementation if less than 20% of an administered load is retained [11, 16, 33, 34]. The difficulty in precise laboratory evaluation has raised the question whether empiric magnesium supplementation is justifiable to prevent adverse consequences of occult magnesium deficiency. Risks were first indicated by cardiovascular and renal tubular lesions caused by sustained magnesium deficiency not severe enough to cause convulsions and sudden death. Epidemiological correlations of a higher prevalence of cardiovascular and kidney stone disease in low versus high magnesium areas (i.e., hard versus soft water regions) provided suggestive human confirmation. Finally, oral magnesium supplementation in management of patients with uroliths, and pharmacological doses given parenterally to patients with or at risk of arrhythmias (i.e., post acute myocardial infarction) has proven beneficial and even life-saving [5–11, 13–16, 25, 35–39].

Analysis of metabolic balance data in healthy young adults discloses that magnesium intakes of less than 5 mg/kg/day (or 300 mg for a 60 kg [132 lb] person) are unlikely to maintain magnesium equilibrium [40]. Surveys of dietary intakes

Table 2. Principle dietary sources of magnesium

1.	Green Vegetables
2.	Legumes
3.	Seafoods
4.	Whole Grains

of college students and other presumably healthy free-living young adults have shown that relatively few attain even that level; and in the case of larger subjects, requirements are likely to be greater than 300 mg daily. It is proposed that at least 6 mg/kg/day is a preferable intake, allowing for the greater needs that may be associated with stresses of normal life. Those under considerable physical and/or emotional stress may need considerably more – possibly as much as 7–10 mg/kg/day [11, 12, 41, 42]. Studies of usual dietary intakes of Americans [43–46] have revealed that magnesium is likely to be ingested in amounts below 5 mg/kg/day, even below the lesser amount cited as the american recommended dietary allowance [47] in the 1980 issue, which has unfortunately been further lowered without scientific justification in the current (10th) edition [48].

The foods richest in magnesium are green vegetables, legumes, whole grains, and seafoods (Table 2). Since many components of the Western diet often consumed in excess (fat, sugar, phosphate, vitamin D and calcium) increase need for magnesium and soft water provides little magnesium, as compared with that supplied in most hard drinking waters [11, 39, 40], inadequacy may be more common than realized [11, 12, 25, 40–45]. Over the past several years, dietary intake of calcium has risen, while that of magnesium has remained constant, intensifying the relative magnesium deficiency [38]. However, significance of magnesium as a contributory factor to a variety of disorders of cardiovascular, renal, gastrointestinal, neuromuscular, and skeletal systems [9, 11, 12, 14–16, 21, 25, 40–51] is gaining increased attention.

Approximately one third of dietary magnesium is absorbed from the intestines, primarily in the jejunum and ileum [15, 33, 52]. Passive diffusion accounts for about 10% of absorption [47]. Facilitated diffusion from intestinal lumen to cells and then into blood by an energy dependent mechanism is a saturable process that may function to partially compensate for differences in magnesium intake [53]. Absorption varies directly with intake and is influenced by other dietary components [15, 54–57]. Vitamin D deficiency [55, 56] or its abnormal metabolism in renal disease [57], interferes not only with calcium but also with magnesium absorption. Fiber-rich diets and excess intakes of calcium and phosphate can interfere with intestinal absorption of magnesium [41, 58–62]. Diets that enhance parathyroid or calcitonin secretion, and possibly insulin secretion may improve absorption of magnesium [25, 63, 64]. Any disorder interfering with small intestinal absorption or causing diarrhea can produce magnesium deficiency. Small fecal losses are obligatory. Familial selective magnesium malabsorption identified in infants and young children with convulsive hypomagnesemic hypocalcemia [11, 65–69] might be a contributory factor to familial renal magnesium wasting of later childhood and adult life [11, 70]. Calcemic treatment of the hypocalcemic convulsions when associated with magnesium deficiency has been associated with intraluminal calcareous deposits in Henle's loop – the portion of the nephron where most tubular magnesium reabsorption occurs.

The major control of magnesium balance is via renal handling [71]. The diffusible 80% of circulating magnesium is filtered at the glomerulus, with the majority then being reabsorbed along the tubules. Approximately 25% is reabsorbed by proximal tubules. Sixty-five per cent is reabsorbed by the thick ascending sites. The remaining 5% is excreted. There is a maximal tubular reabsorptive capacity (Tm) for magnesium. The Tm Mg is 2–3 mEq/L [71]. Obviously, high filter loads can lead to marked magnesiuria, while low levels result in almost no excretion.

Magnesium excretion can be increased by factors known to augment sodium excretion. Among these conditions and factors are extracellular fluid volume expansion, high sodium intake, osmotic

diuresis, elevated blood glucose concentrations, diuretic agents, diuretic phase of acute tubular necrosis, and post obstructive diuresis. In addition, hypermagnesiuria can be created by excess glucocorticoids and mineralocorticoids, renal vasodilation, cardiac glycosides, hypercalcemia, growth hormone, thyroid hormone, calcitonin, alcoholism, and inappropriate ADH [72]. A major cause of excess urinary loss of magnesium is the use of aminoglycosides, i.e., gentamicin, anti-neoplastic agents, and immunosuppressants to improve acceptance of bone marrow and other tissue transplants [73–76].

Bone and skeletal magnesium comprise most of magnesium available to compensate for extracellular deficiency in the adult [77]. The amount of bone magnesium loss (mobilized) reported has ranged from insignificant amounts [78] to 14–35% [79, 80], which approaches the theoretical values of 30% from in vitro elution studies [65]. In the human, roughly 15% of total body magnesium can be drawn from bone and skeletal muscle during hypomagnesemia. However, there may also be smaller, but potentially damaging losses from vital organs: heart, kidney and brain [77]. Evidence indicates that it is unsafe to rely wholly on body reserve to protect the extracellular pool [77]. Supplementation is necessary when hypomagnesemia develops, but it is preferable to maintain optimal intake of magnesium to prevent development of deficiency.

Magnesium requirements of the elderly have not been systematically investigated. Thus, it is unlikely that evidence accrued from healthy young adults to develop Recommended Dietary Allowances [46, 47] is applicable to aged individuals. Their dietary intake is apt to be poor. Also, the elderly are subject to diminished intestinal absorption and increased urinary output of magnesium [21, 35, 81, 82] as a result of many factors including emotional stress, illness, and medications that increase magnesium requirements and interfere with utilization [21]. In fact, it is possible that the RDAs may be below an optimal amount even for the young [11, 12, 41, 49].

Pathophysiology

Magnesium is a key intracellular cation involved in many biochemical roles: it activates over 300 enzymes; maintains conformation of nucleic acids; and participates in regulation of many other important biological processes including energy metabolism and maintenance of appropriate intracellular/extracellular potassium/sodium gradients [22]. Magnesium is intimately coupled to phosphate as an activator and energy source, because it activates many of the enzymes involved in phosphate metabolism. This element binds the phosphate of creatine kinase and forms a metal-protein complex of pyruvate kinase [22, 25]. Adenylate cyclase, alkaline phosphatases, thiokinases, and enzymes involved in protein synthesis and glucose metabolism require magnesium, as do adenosine triphosphatases and nucleic acid polymerases [22, 25, 83]. Magnesium is a cofactor in many enzyme systems requiring vitamins B1, B6, B12, C, D and E [12]. Through its activation of lecithin-cholesterol-acyl-transferase (LCAT) and insulin-dependent lipoprotein lipase, magnesium plays important roles in triglyceride clearance, cholesterol esterification, and in increasing the high density lipoprotein/low density lipoprotein ratio [84, 85]. Interrelationship with insulin activity leads to increased synthesis of certain proteins and augments influx of potassium and magnesium into cells [86].

Comprehension of physiological relationships associated with magnesium are paramount toward understanding the pathophysiological consequences of inadequate magnesium levels, including its role in calcium metabolism, improving its utilization and inhibiting pathological calcification [11, 87–89]. Magnesium maintains normal renal structure – inhibiting development of glomerulosclerosis, calcinosis, and calcific urolithiasis [35–37, 88, 89]. It maintains normal arterial structure and function directly and indirectly, both serving to inhibit intravascular coagulation and arterial constriction [1, 50, 88, 90–93]. Its direct effects are by antagonism of humoral and calcium-induced vasoconstriction, and by counteracting the pro-coagulant effect of

calcium on the coagulation cascade. Its indirect effects, via stabilization of endothelial and platelet membranes, enhance release of vasodilating and anticoagulating cytokines. Magnesium also protects against cholesterol deposition in arteries by favorably affecting lipid metabolism [84, 85]. The many activities of magnesium provide insight into how magnesium deficiency can increase progression of arteriosclerosis, as well as hypertensive and cardiovascular complications, and its antiarrhythmic pharmacological effects. The observation of hypomagnesemia in patients with acute myocardial infarction, and in others at risk of ectopic rhythms implicates magnesium deficiency in their pathogenesis, and suggests that the therapeutic effects of pharmacological doses may be partially due to repletion of a deficit [1–11, 13, 25, 32–34, 88, 93–95]. The participation of magnesium in neuromuscular activity and transmission [96–99] may explain conditions associated with marginal deficit, such as latent tetany and possibly the fatigue and pre-menstrual syndromes [25, 51, 98–102], as well as the convulsions of severe depletion [96, 97]. Magnesium also participates in mechanisms involved in host defenses, from temperature control, wound healing, and immunocompetence [25, 54, 83, 103–105].

Flink [106] categorized clinical manifestations of magnesium deficiency as: (1) neuromuscular hyperactivity, (2) psychiatric disturbances, (3) cardiac effects, and (4) electrolyte perturbations (Table 3). Neuromuscular signs of magnesium deficiency include tremors, grimaces, ataxia, coma, and convulsions depending on the degree of deficiency. Less severe manifestations of chronic magnesium inadequacy are latent (normocalcemic) tetany. This is considered by Durlach [25] as the most commonly seen perturbation of magnesium deficiency. This syndrome is characterized by a variety of manifestations: anxiety, hyperemotivity, apathy, depression, nervousness, pharyngeal and/or laryngeal paresthesia, tremors, morning asthenia, episodes of fatigue, headaches, neck pain, vertigo, insomnia, swooning, cardiac palpitations, precordial discomfort, and skeletal and intestinal cramps. Such manifestations of marginal magnesium deficiency have been reported much more frequently in latino populations than in individuals of northern European derivation [100]; however, many in East Germany have been described with this disorder [51]. The delirium, hallucinations, combativeness, and psychosis seen with overt hypomagnesemia are manifestations of severe deficiency.

Table 3. Common clinical manifestations of hypomagnesemia

Neuromuscular
Weakness
Tremor
Muscle Fasciculations
Muscle Spasticity
Ataxia
Nystagmus
Tetany
Hyperreflexia
Seizures
Coma
Chvostek and Trousseau Signs
Psychiatric
Apathy
Depression
Agitation
Hallucinations
Psychosis
Cardiac
Arrhythmias
Coronary Atherosclerosis
Coronary Vasospasm
Ischemic Heart Disease
Cardiomyopathies
Congestive Heart Failure
Myocardial Infarction

It is noteworthy that two conditions that were early implicated as causes of severe hypomagnesemia are chronic alcoholism [107] and decompensated diabetes mellitus [108] – both diseases that are associated with microangiopathic cardiomyopathy comparable to that produced by chronic magnesium deficiency [11]. The cardiac dysrhythmic effects of alcohol withdrawal, digitalis intoxication, post-cardiotomy, post gastrointestinal surgery, and after acute myocardial infarction that respond to parenteral magnesium therapy

include otherwise intractable ventricular tachycardia and fibrillation with and without hypomagnesemia, *torsades de pointes*, ventricular tachyarrhythmia, paroxysmal atrial tachycardia, flutter and fibrillation, and multifocal atrial tachycardia [2, 4–11, 13, 16, 92–96]. The increased incidence of myocardial infarction and sudden unexpected cardiac death, noted in patients under diuretic treatment for congestive heart failure and in large scale anti-hypertension studies is increasingly being recognized as associated with magnesium loss [9, 11, 95, 107–111]. In addition, chronic magnesium deficiency can result in congestive heart failure [112].

Because magnesium deficiency causes abnormalities in intra- and extracellular levels of potassium and calcium, changes in the electrocardiogram often reflect combined electrolyte perturbations and differ depending on the extent of magnesium deficiency and resultant potassium and calcium changes [9–11]. Since magnesium depletion leads to hypokalemia and hypocalcemia [3, 22, 33, 51, 113, 114], the status of magnesium should be investigated in all patients with refractory potassium or calcium deficiencies. Whang lists the occurrence of hypomagnesemia associated with other electrolyte disturbances as follows: hypokalemia 45/106 (42%), hypocalcemia 49/223 (22%), hyponatremia 121/516 (23%), and hypophosphatemia 34/127 (29%) [114].

A major unanswered question is whether magnesium inadequacy contributes to aging and/or diseases common in the aged. Could magnesium supplementation ameliorate certain aspects of the aging process? Various findings suggest this may be the case. Many cardiovascular events are influenced by magnesium status. For example, transient ischemic attacks (TIA) may be affected by magnesium deficiency. Patients who added magnesium to their diets were less likely to suffer ischemic events [115–119]. One of us has presented evidence that low magnesium might be a factor in the osteoporosis process, because magnesium participates in normal matrix osteoporosis formation (necessary to maintain bone elasticity) and is necessary for normal calcium utilization [1, 11, 21, 50, 88]. Finally, the fact that experimental magnesium deficiency has long been known to cause histamine release [116] is finding classical application in it adjunctive use in emergency treatment of bronchial asthma [117–119].

Common causes of magnesium deficiency in the elderly

Seelig lists three major categories or factors affecting magnesium requirements, particularly in the aged: (1) dietary, (2) host and (3) environmental [16] (Table 4). In addition to poor nutrient intake and decreased gastrointestinal absorption, other interrelationships with nutritional status are present in the elderly.

There is no doubt that the proportion of macronutrients in the diet can influence magnesium absorption and utilization. The average diet of an elderly individual generally contains more carbohydrates and less proteins and fats than the younger counterpart. Sugar excess is associated with magnesiuria [120], and fiber can decrease gastrointestinal absorption of magnesium [42, 58–61]. Low protein ingestion often correlates with negative magnesium balance [121]. Perturbations of thiamine (B1), pyridoxine (B6), Vitamins E and D have been associated with alterations in magnesium homeostasis [12, 83].

Aging is also associated with a high frequency of clinical situations associated with hypomagnesemia. Older patients, because of their proclivity for cardiovascular disorders, are more apt to be taking digitalis and diuretic preparations. Unfortunately, urinary magnesium excretion increases 25 to 400% following digitalis and diuretic therapy [32]. Stress, alcoholism., diabetes, and gastrointestinal disorders, all common in the aged, frequently have a role in magnesium depletion. Finally, medications to treat infections (aminoglycosides) and constipation (purgatives) can lead to negative magnesium balance.

Table 4. Factors influencing geriatric magnesium balance

Dietary Factors
Poor Intake
Refined Processed Food
Increased Ca, P, Na
Decreased K, Cl
Fiber Excess
Sugar Excess
Levels of Protein Ingestion
Vitamin B1, B2, E, D
Host Factors
Anabolism or Catabolism
Ischemia
Disease
Decreased Intestinal Absorption
Increased Renal Excretion
Hormonal, Enzyme, Vitamin Imbalance
Alcohol Excess
Environmental Factors
Medications (Cardiac, Diuretics, Antibiotics, Purgatives)
Stress (Disease Provoked, Psychological)

Adapted from Seelig [16].

Prevention and treatment of magnesium deficiency

Although magnesium depletion is rarely seen among those with normal renal and gastrointestinal function who consume normal diets, marginal or occult magnesium deficiency, difficult to detect, is not uncommon. It can usually be prevented by inclusion of magnesium-rich foods in the diet (Table 1). Among the elderly, especially those under psychological or physical stress or undergoing normal anabolism (as during convalescence), magnesium supplementation of 100–300 mg/day of elemental magnesium (starting with divided low doses and increasing as tolerated without diarrhea) can be recommended. Those with magnesium-specific or general malabsorption, or with idiopathic or iatrogenic renal wasting, might require four or five times the normal daily intake. Acute and chronic disorders may result from failure to repair magnesium deficiency. Accordingly, inclusion of serum magnesium among the tests ordered, especially in the elderly receiving enteral or parenteral tube feeding and/or magnesium-wasting medications, should become routine. Substitution of magnesium-sparing diuretics, which are also potassium-sparing, or their addition to stronger "loop" diuretics may be indicated for elderly patients needing diuretic treatment [122].

Certainly, prevention is desired over repletion. With moderate deficiencies, perhaps increasing consumption of natural foods loaded with magnesium may suffice (Table 1). If not sufficient, pharmacological treatment may be given; because persistent magnesium deficiency is rarely reversed by diet alone. Patients with malabsorption or renal wasting generally require four to five times the normal daily intake.

Regarding oral supplementation, there is little risk of hypermagnesemia in individuals with normal renal function. Magnesium chloride, given in enteric coated form, is a desirable means of therapy as it repairs both magnesium and chloride deficits. There are 64 mg of elemental magnesium in each pill. The usual replacement dose is 2–4 tablets per day. In alkalosis, and in patients with depressed hydrochloric acid production such as in elderly and those taking H-2 receptor antagonists, magnesium chloride is the preferred agent for replacement. It is worthy to note that 35% of older patients have achlorhydria. Other supplements include oxides and citrates, which are claimed to be better utilized than the organic salts of magnesium [123]. Although magnesium salts can induce diarrhea, supplementary doses are generally below cathartic levels (>120 mEq).

Parenteral magnesium is generally reserved for symptomatic hypomagnesemia unresponsive to oral supplementation. Replacement is by sulfate salt which contains 4 mEq/ml. The usual IM dose is 16 mEq every 2–4 hours [124]. When given by IV route, the amount should not exceed 50 mEq within an 8 hour period. As a rule, one should not attempt to replace more than 50% of deficit over the first 24 hours. The remainder of replacement can be achieved over the next 3 to 4 days. In patients with renal insufficiency, doses should be reduced 25% or 50% depending on the extent

of renal impairment. Side effects of parenteral replacement are sweating, flushing, sensation of heat, and T wave changes in the EKG. A magnesium concentration above 6 mEq/l can create a curare-like effect causing anesthesia, paralysis, respiratory depression, and even death. Suffice it to say, serum magnesium and patellar reflexes should be checked frequently during replacement.

In many patients displaying hypomagnesemia and hypocalcemia, the serum calcium returns to normal after 4–5 days of magnesium therapy. In the case of hypomagnesemia-hypokalemia, both ions should be replaced to prevent deleterious symptoms from the ion not replaced.

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