MAGNESIUM

Introduction

Magnesium is a metal, the eighth most abundant element in the universe. It is used industrially to make lightweight alloys and has structural properties similar to those of aluminium. But since the metal is flammable (at temperatures equivalent to that of burning petrol) its applications in this respect are somewhat limited. Magnesium is widely distributed in the plant world, acting as the light-capturing molecule of chlorophyll; it is thought that approximately one third (or 120 mg) of the dietary magnesium typically ingested as chlorophyll is absorbed into the blood from the intestine. Homeostasis of magnesium is by urinary elimination, with faecal magnesium representing the unabsorbed magnesium from the diet. No single factor plays a dominant role in magnesium absorption from the gut [1].

After potassium, magnesium is the second most abundant cation within mammalian cells and the fourth most abundant cation in the extracellular water after sodium, potassium and calcium. However, 60% of the human total body magnesium is found in bone, with a further 30% in muscle. In all, less than 1% of the total body magnesium is extracellular, so measurements of extracellular (i.e. serum or plasma) magnesium are of limited value in nutritional studies. It is for this reason that red cell magnesium measurement is preferred for the investigation of possible deficiency states [2,3].

Food sources of magnesium

Green vegetables are sources of magnesium primarily because of their chlorophyll content. Some legumes, nuts and seeds, and whole, unrefined grains are also good sources of magnesium. Refined grains are generally low in magnesium [4,5] since the magnesium-rich germ and bran are removed in the refining process. Tap water can be a source of magnesium, but the amount varies according to the water supply, with "hard" water containing more magnesium than "soft" water.

The daily requirement for magnesium in man is from 400 - 800 mg per day (equivalent to 2 – 5 gm of magnesium sulphate) [6] and the average UK diet provides somewhat less than this figure (336 mg for men, 250 mg for women). Many authors have made the point that a sustained diet which is somewhat deficient in magnesium will produce a gross deficiency over a long period of time [6].

Physiology of magnesium

Magnesium has various important physiological functions; it is a cofactor for DNA and protein synthesis, for oxidative phosphorylation and for many enzymes, it is a co-factor for more than 300 different metabolic reactions, particularly those involved in energy use and storage. Magnesium also functions as a calcium antagonist and is required for neuromuscular excitability, as well as, for example, regulation of parathyroid hormone (PTH) secretion [7].

Of the less than 1% of total body magnesium that is in the extracellular space, c. 70% of the serum magnesium is present in an ionized form, which is the physiologically active fraction for neuromuscular transmission and cardiovascular function [8,9]. Serum magnesium concentrations are regulated by the balance between renal excretion and intestinal absorption, which takes place in the small intestine, via both a saturatable transcellular pathway (which is active and responds to magnesium deficiency) and a nonsaturatable paracellular passive pathway (which responds solely to the amount of magnesium available for absorption) [10]. In the kidney, around 95% of magnesium in the formed urine is usually reabsorbed along the nephron. It is thought that this trans-epithelial magnesium transport is regulated via the transient receptor protein channel *TRPM6* [1,2]. With these mechanisms in place, overdose of magnesium from food or oral ingestion of supplements appears to be unlikely, even in subjects with mild renal impairment.

Interaction between magnesium and vitamin B6

Magnesium is a co-factor for two of the critical enzymes of vitamin B6 metabolism, a) alkaline phosphatase (which is required for the uptake of pyridoxal phosphate by cells) and b) pyridoxine kinase (the action of which is to convert pyridoxal to pyridoxal phosphate, the biologically active form of B6). It has also been known for many years that vitamin B6 alters the rate of Mg uptake by tissues [11]. Mg deficiency thus impairs vitamin B6 status through the depletion of intracellular Mg, which in turn reduces the activity of alkaline phosphatase and pyridoxine kinase [12]. The accepted wisdom is that a combination of vitamin B6 and magnesium should be used in the treatment of magnesium deficiency syndromes. However, studies on the effectiveness of this combination have not, in general, been very credible, for example using doses of vitamin B6 sufficiently high to cause significant neuropathies.

Both magnesium and vitamin B6 are required for energy production in cells and the signs and symptoms of magnesium and vitamin B6 deficiency and toxicity are very similar, so a conclusion that there is some link between the two is unavoidable, even though its exact nature remains to be elucidated [13].

Magnesium deficiency

It is well recognized that magnesium intake among westernized populations is inadequate [14]. In experimental studies of animals, magnesium deficiency was shown to accelerate atherosclerosis and magnesium supplementation suppressed its development [15,16]. Epidemiological observations have also associated low intake of magnesium with various adverse health outcomes, including insulin resistance, the metabolic syndrome, type 2 diabetes, hypertension, and cardiovascular disease [17]. Several mechanisms have been proposed for the potential cardiac benefits of enhanced magnesium intake, including improvement of glucose and insulin homeostasis; antihypertensive, antiarrhythmic, anti-inflammatory, anticoagulant, or antiplatelet effects; improved lipid metabolism; reduced vascular contractility; and increased endothelium-dependent vasodilation [18].

Marked Mg deficiency results in muscle cramps, constipation, disturbances of heart rhythm, weakness, pre-menstrual syndrome, etc. Marginal hypomagnesaemia is relatively common, and most patients have less well defined symptoms. Causes can include inadequate magnesium intake, increased gastrointestinal or renal losses as well as drugs, such as proton pump inhibitors (PPIs) and loop diuretics. Such patients frequently are found to have other electrolyte disturbances which are resistant to treatment until the hypomagnesaemia has been corrected [19]. PPIs cause hypomagnesaemia by reducing intestinal absorption; the underlying mechanism is thought to involve alteration in the active transport pathway via disruption of *TRPM6* channel function. PPI-induced hypomagnesaemia is increasingly reported in the literature [20,21].

Neuromuscular and cardiac effects of magnesium depletion

Neuromuscular symptoms include muscular weakness, apathy, tremors, paraesthesia, tetany, nystagmus (involuntary eye movements) and positive Chvostek and Trousseau signs [22,23]. Although many of these features could be attributed to coexisting metabolic abnormalities, similar findings have been demonstrated when isolated magnesium depletion was induced in volunteers [24]. Severe effects such as seizures, drowsiness, confusion and coma occur at magnesium concentrations <0·4 mM [25].

The mechanism for the cardiovascular manifestations of intracellular magnesium deficiency impairs the Na^+/K^+-ATPase membrane pump, resulting in a decrease in intracellular potassium. This leads to the disturbance of the resting membrane potential and repolarization phase of the myocardial cells [26]. Electrocardiographic changes seen with hypomagnesaemia include flattened T-waves, U-waves, prolonged QT interval and widened QRS complexes [23]. Hypomagnesaemia has been associated with both atrial and ventricular arrhythmias, although the underlying mechanism is unknown and it is unclear whether this association exists in subjects without underlying cardiac disease [27]. The most life-threatening cardiovascular manifestation of hypomagnesaemia is ventricular arrhythmia.

Hypokalaemia is associated with hypomagnesaemia in up to 60% of all cases [28]. This is partly due to the underlying common aetiologies that cause magnesium and potassium losses and partly due to a specific disorder of renal potassium wasting as a result of hypomagnesaemia [23].

Hypocalcaemia is also commonly associated with hypomagnesaemia; hypomagnesaemia suppresses the release of PTH and also induces end-organ resistance to PTH [29]. Hypocalcaemia associated with hypomagnesaemia is therefore refractory to treatment until the magnesium deficit has been corrected.

Magnesium administration produces relaxation of smooth muscle [30,31] and reverses the adverse symptoms described above.

Magnesium and osteoporosis

Magnesium is required for bone formation and influences the activities of both the osteoblasts and the osteoclasts [32]. Magnesium also affects the concentrations of both parathyroid hormone and the active form of vitamin D, which are major regulators of bone homeostasis. Several population-based studies have found positive associations between magnesium intake and bone mineral density in both men and women [33]. Other research has found that women with osteoporosis have lower serum magnesium levels than women with osteopenia and those who do not have osteoporosis or osteopenia [34]. These and other findings suggest that magnesium deficiency is a risk factor for osteoporosis [32].

Although limited in number, studies suggest that increasing magnesium intakes from food or supplements might increase bone mineral density in postmenopausal and elderly women [1]. For example, one short-term study found that 290 mg/day elemental magnesium (as magnesium citrate) for 30 days in 20 postmenopausal women with osteoporosis suppressed bone turnover compared with placebo, suggesting that bone loss decreased with magnesium supplementation in these patients [35].

Diets that provide recommended levels of magnesium enhance bone health, but further research is needed to elucidate the role of magnesium in the prevention and management of osteoporosis.

Problems in determining magnesium status

Despite the importance in so many enzyme systems and in the function and structure of vital organs and bones, magnesium is usually one of the last clinical parameters to be explored. In addition, when magnesium levels are requested, the results are often misleading since less than 1% of the total body Mg is in the serum. In spite of magnesium being an intracellular cation, second in concentration only to potassium, it is serum magnesium concentrations that are explored. Unfortunately, the serum magnesium values are not a reliable index of body levels, and also very wide “normal” levels are accepted.

Each possible method of evaluation has its limitations, and in order to determine whether a patient is truly magnesium deficient (unless the deficiency is so profound as to cause unquestioned hypomagnesaemia), a combination of approaches may be necessary [36, 37]. Serum or plasma levels are the easiest to obtain but provide the least reliable index. Red blood cells are in our experience the most practicable cellular sample for assessing magnesium status, but the standardization of the technique used is important when comparing the results to a reference interval [38]. Study of percentage retention of an intramuscular load of magnesium (the magnesium retention test) appears to be the most reliable index and sensitive index of total body Mg [39,40], although this isn’t a routinely available method.

Methodology

Magnesium determinations are carried out by inductively coupled plasma-mass spectrometry (ICPMS) and by atomic absorption spectroscopy.

Interpretation of results

The reference interval for red cell magnesium is 2.08 – 3.00 mmol/L; for whole blood magnesium it is 1.25 – 2.00 mmol/L.

The reference interval for plasma Mg is 0.70 – 1.20 mmol/L: disturbances of plasma magnesium are much less common than losses of intracellular magnesium.

The reference interval for urine Mg is 0.50 – 0.85 mol Mg/mol creatinine, based on an early morning, second void urine sample. Mg is actively conserved, so low levels in the urine may reflect its systemic deficiency; however, a normal early morning urine magnesium does not exclude Mg deficiency.

The reference interval for hair Mg is 60 – 160 µg per gram of hair; hair Mg values are not affected by age or sex.

There is no established statutory maximum permitted level for magnesium in drinking water.

Magnesium deficiencies should be interpreted together blood with B vitamin levels. Magnesium is required for vitamin B1 metabolism and vitamin B6 is required for tissue magnesium uptake. Deficiencies of thiamine and pyridoxine should therefore be considered if a patient's red cell magnesium level fails to respond to oral supplementation.

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