deNovo Medica

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Magnesium – when is supplementation warranted?

Introduction

Magnesium is essential for all living cells; it is required for DNA and RNA synthesis, is a co-factor for more than three hundred enzymatic reactions and is integral to adenosine triphosphate (ATP) metabolism.

Interest in the role of magnesium in health and disease has been sustained over the past thirty years, particularly as dietary surveys still reveal that intake of magnesium is less than the recommended daily allowance (RDA).

In the United States in 2015, the Dietary Guidelines Advisory Committee found that 48% of the US population consume less than the daily requirement of magnesium, partly due to increased processing of food and a lower consumption of magnesium-rich whole grains, fruit and vegetables. This shortfall is of public health concern as hypomagnesaemia is associated with chronic diseases such as insulin resistance and type 2 diabetes (T2DM), hypertension, cardiovascular disease, migraine headaches and depression.

KEY MESSAGES

- Magnesium deficiency is more prevalent than generally thought and is particularly associated with common disorders such as diabetes, hypertension, cardiovascular disease and depression
- Hypomagnesaemia occurs together with other electrolyte abnormalities such as hypokalaemia and hypocalcaemia
- Magnesium and zinc deficiency are particularly associated with depression and evidence supports supplementation to reduce depressive symptoms
- Hypomagnesaemia may result from use of certain medications, including loop and thiazide diuretics, digoxin and long-term use of proton pump inhibitors (PPIs).

Functions of magnesium

Magnesium is a co-factor in more than 300 enzyme systems that regulate protein synthesis, muscle and nerve transmission, neuromuscular conduction, blood glucose and blood pressure (Table 1).

Table 1. Main functions of magnesium

Function	Mechanism
Energy production	Essential for ATP production (MgATP) responsible for intermediate metabolism of carbohydrates, proteins and fats
Enzyme activation	Na^+/K^+-ATPase, creatine kinase, tyrosine kinase activity of the insulin receptor
Acts as calcium antagonist	Control of calcium influx into cells, maintenance and stabilisation of membrane physiology, muscle contraction
Cardiovascular system – economisation of cardiac pump action	Regulates potassium movement in myocardial cells, protection against stress, vasodilation of coronary and peripheral arteries, reduction of platelet aggregation
Structural role	Is a component of mineralised bone (structure, microarchitecture)
Nutrient metabolism	Metabolic activation of vitamin D, B vitamins (e.g. thiamine and glutathione)

This report was made possible by an unrestricted educational grant from **Cipla**. *The content of the report is independent of the sponsor.*

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Magnesium is stored mainly in bone (50-60%), skeletal muscles and non-muscular soft tissue. Age has an influence on magnesium storage, with decreased magnesium content held in bone hydroxyapatite. Intracellular magnesium is ionised and bound to proteins, negatively charged particles and ATP. Extracellular magnesium, primarily found in serum and red blood cells, accounts for about 13% of total body magnesium.

Understanding and interpreting serum total magnesium concentration (STMC)

STMC is the predominant test used by healthcare providers to assess magnesium status, although assessing overall magnesium status is difficult because most magnesium is stored in the cells or in bone.

The normal reference range for magnesium in blood serum is 0.76-1.15mmol/ℓ. However, it is important to look at the populations used to determine this reference level. Arising from the National Health and Nutrition Examination Survey (NHANES) 1 study of healthy individuals during the course of 1971-1974, a reference interval of 0.75-0.95mmol/ℓ was set.

A more recent European study has related the serum total magnesium concentration to clinically-determined symptoms of magnesium deficiency – these results are summarised in Table 2.

The risk ratio for the development of T2DM was raised when the serum magnesium level was <0.85mmol/ℓ

Table 2: Serum total magnesium levels and clinical magnesium deficiency

Serum magnesium level	% with clinical symptoms
0.70mmol/ℓ	90%
0.75mmol/ℓ	50%
0.80mmol/ℓ	10%
0.90mmol/ℓ	1%

A study following a cohort of the initial NHANES 1 participants for eighteen years has found that the risk ratio for the development of T2DM was raised when the serum magnesium level was <0.85mmol/ℓ.

There are now efforts to establish a revised serum magnesium reference interval but in the interim, laboratory test results need to be interpreted together with a clinical assessment of magnesium deficit symptoms.

Signs and symptoms of magnesium deficiency

Early signs of magnesium deficiency are non-specific and include loss of appetite, lethargy, weakness, fatigue, nausea and vomiting. More pronounced deficiency signs and symptoms are summarised in Table 3.

Table 3: Signs and symptoms of magnesium deficiency

General	Anxiety, lethargy, weakness, depression, headache, loss of appetite, nausea, impaired athletic performance
Muscular system	Muscle spasm, cramps in the soles of the feet, leg cramps, back aches, urinary spasms
Nervous system/CNS	Nervousness, increased sensitivity to excitatory neurotransmitters, migraine, poor memory, seizures (severe hypomagnesaemia), tremor
Cardiovascular system	Risk of arrhythmia, hypertension, coronary spasm, digitalis sensitivity
Electrolytes	Hypokalaemia, hypocalcaemia, retention of sodium
Metabolism	Dyslipoproteinaemia – increased triglycerides, cholesterol, decreased glucose tolerance, insulin resistance, disturbances of bone and vitamin D metabolism.

Magnesium supplementation can be considered in patients who are overweight and with the metabolic syndrome and therefore at high risk of developing T2DM

Who may benefit from magnesium supplementation?

Patients at high risk of diabetes or with T2DM

While international and South African diabetes guidelines do not recommend universal mineral supplementation, recommended dietary approaches emphasise magnesium-rich foods such as whole grains, beans, nuts and green leafy vegetables. The RDA for magnesium from dietary sources is 350mg/day in adults.

The incidence of hypomagnesaemia in patients with T2DM varies widely from 13-47%. Magnesium depletion is of pathogenic significance in the development of diabetic complications (Figure 1).

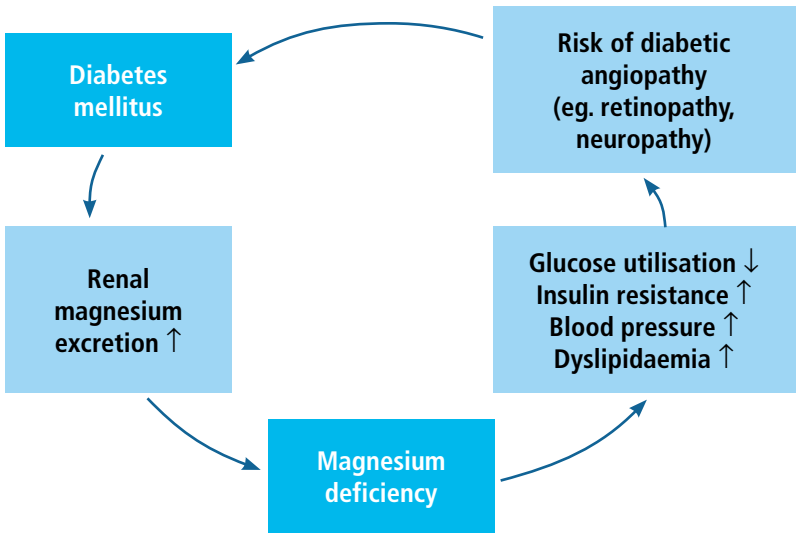

Figure 1. Magnesium deficiency and diabetes[7]

Magnesium supplementation can be considered in patients who are overweight and with the metabolic syndrome and therefore at high risk of developing T2DM, as there is evidence of benefit in these patients.

Patients at risk of cardiovascular disease

The Prospective Urban Rural Epidemiology (PURE) study was conducted in more than 130 000 individuals aged 35-70 years, without cardiovascular disease, from 613 communities in 18 low-income, middle-income and high-income countries across seven continents, and including a South African cohort. The association between cardiovascular disease and the intake of fruits, vegetables and legumes (including beans, black beans, lentils, peas, chickpeas and black-eyed peas) was assessed. Legumes are magnesium-rich vegetables with, for example, 1 cup of black beans containing 120mg of magnesium. Legumes are also high in potassium and iron. The PURE study showed that higher legume consumption (60g/day) was associated with a lower risk of major cardiovascular disease, cardiovascular mortality and total mortality. Vegetable intake reduced risk minimally while the highest fruit intake category (three to four servings per day) also lowered cardiovascular risk.

Magnesium can be beneficial in the prevention and treatment of cardiovascular disease based on its antihypertensive, antidysrhythmic and anti-inflammatory actions.

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Patients with depression

Micronutrient deficiencies are thought to play a role in the development of depression; consequently, numerous studies have explored the benefits of micronutrient supplementation as an additional therapy to traditional antidepressants. In particular, studies have examined how zinc and magnesium may influence depression and

This CPD accredited programme was written for *deNovo Medica* by
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reduce symptoms thereof.

Intervention studies have shown that increasing intake of dietary zinc or adding supplemental zinc can have a mood-enhancing effect. The addition of zinc therapy in patients using antidepressants has shown that zinc increases the effectiveness of antidepressants, likely due to zinc ions improving synaptic transmission.

Magnesium has an equivocal effect on depression as zinc, and has been shown in a recent double-blind placebo-controlled trial to improve mood in patients who have hypomagnesaemia.

Age-related loss of muscle mass and strength

A recent systematic review of the role of minerals in preventing and treating age-related loss of muscle mass, muscle strength and physical performance has shown that magnesium, selenium, iron and zinc improve physical performance in older patients. Decreased magnesium intake has also been found to be related to increased risk of sarcopenia.

What are the recommendations for use of magnesium supplements?

Magnesium supplements are available as magnesium oxide, magnesium chloride, magnesium citrate, as well as other amino acid chelates. Experts recommend that the ideal magnesium intake should be based on body weight (4-6mg/kg/day).

Magnesium is generally well tolerated, but it does cause gastrointestinal symptoms. Attention and caution are required if treating patients with renal insufficiency (CrCl <30mℓ/min) and in patients being treated with aminoglycosides, bisphosphonates, calcium channel blockers, tetracycline and skeletal muscle relaxants.

The combination of magnesium and zinc offers useful synergies when treating patients with symptoms of hypomagnesaemia, particularly in older patients who frequently have associated zinc deficiency. This combination also offers useful synergies for pregnant and lactating women, those with heavy alcohol use or on weight loss diets, sportspeople, heavy bleeders and users of diuretics.

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Reg: 2012/216456/07
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