Assessing magnesium forms for optimal clinical outcomes

KEY LEARNINGS

Magnesium sufficiency

- Whilst the typical western diet may provide enough magnesium to avoid a frank deficiency, it is unlikely to provide the levels required to maintain optimal magnesium levels
- There is a growing body of literature which suggests that subclinical magnesium deficiency is one of the leading causes of chronic diseases and should now be considered a public health crisis

Identifying magnesium deficiency

- Magnesium deficiency is an increasing concern, with pharmaceutical, agricultural, industrial, diet, lifestyle and pathological causes
- Diagnosis of magnesium deficiency is challenging in clinical practice due to the numerous factors which impact magnesium status
- Laboratory testing should not be relied upon for diagnosis of magnesium deficiency, with dietary risk factors, medications, disease states and clinical signs and symptoms taking priority in assessing magnesium status

Magnesium forms and bioavailability

- The compound form of magnesium is an important factor that affects the efficiency of absorption
- Inorganic forms of magnesium found as salts, metals, minerals and other carbon-free forms (such as chloride, oxide and sulphate) are generally more poorly absorbed in the gastrointestinal tract when compared to organic forms such as magnesium citrate and magnesium glycinate
- Experimental studies demonstrate that magnesium citrate has a much greater dissolution and solubility under a wide variety of gastrointestinal pH conditions, making it suitable for those with impaired gastric acid production

Magnesium sufficiency and deficiency

Maintenance of magnesium sufficiency requires a dietary intake of 320mg for women and 420mg for men. Numerous studies from around the world have found that many individuals do not reach these recommended intakes, often only reaching two-thirds of this minimum target.[1]

Whilst the typical western diet may provide enough magnesium to avoid a frank deficiency, it is unlikely to provide the levels required to maintain optimal magnesium levels. Recent evidence suggests that the current recommended daily allowance (between 300 and 420mg/day) is insufficient to provide optimal health and longevity and that many individuals require an additional 300mg per day in order to lower their risk of chronic disease, which may require the use of additional supplements.[1]

There is a growing body of literature which suggests that subclinical magnesium deficiency is one of the leading causes of chronic diseases and should now be considered a public health crisis.[1]

Magnesium function

Magnesium is an essential cofactor required for hundreds of enzymatic reactions regulating diverse biochemical processes.[2,3] It is the second most abundant intracellular cation and it is essential for the proper functioning of over 300 enzymes.[1]

Subclinical deficiencies result in negative health consequences often without easily identifiable symptoms. Numerous studies have demonstrated that serum levels on the low end of the 'normal' range is suggestive of magnesium depletion. It is theorised that magnesium depletion may be the most underdiagnosed serum electrolyte abnormality in clinical practice today.[1]

Given the role of magnesium in calcium and potassium transport, cell signaling, energy metabolism, genome stability, DNA repair and replication, it is not surprising that hypomagnesaemia is now associated with many diseases including hypertension, coronary heart disease, diabetes, osteoporosis, and several neurological disorders.[4]

BioMedica Nutraceuticals **P** 1300 884 702 **P** +61 2 8339 0539 **E** info@biomedica.com.au
www.biomedica.com.au or www.biomedica.uk.com
This technical sheet (V.07/20) is intended for the further education of practitioners. Any statements made do not intend to claim a cure for any condition mentioned.

BioMedica NUTRACEUTICALS THE PRACTITIONER COMPANY

Why is magnesium deficiency under-recognised?

Despite its importance to human health, magnesium remains one of the least investigated macro minerals, and while it is getting more attention, this still pales in comparison to the level of investigation into other macronutrients such as calcium or iron. The root cause of this oversight likely lies in the fact that iron and calcium deficiency can be diagnosed through a variety of clinically well recognised associated signs and symptoms, and readily supported by commonly used, and clinically validated, diagnostic assays available for verification. However, this is not the case for magnesium, where deficiency does not present with unique and identifiable clinical manifestations. Furthermore, even if clinical signs and symptoms are present, they are overshadowed by or taken to be the result of common co-morbidities such as diabetes and cardiovascular disease. In addition, the lack of a standardised laboratory test that accurately describes the status of magnesium remains one of the most vexing challenges associated with magnesium research.[4]

Agricultural causes

- Soils which are acidic, light and sandy are usually depleted in magnesium[2]
- Widespread use of potassium and ammonium fertilisers leads to magnesium depletion in crops[2]
- In the U.S, research suggests that crop magnesium levels have redued by 80-90% over the last 100 years[4]

Food preparation causes

- Boiling leads to a large loss of magnesium[2]
- Use of purified or filtered tap water and fluoridated water can reduce available magnesium thorugh filtration or complexation of the metal[4]

Magnesium deficiency is an increasing concern with a variety of underlying causes

Diet and lifestyle causes

- Excessive consumption of sodium, calcium, protein and caffeine, increases urinary magnesium excretion[2]
- Refined foods are lower in magnesium[1]
- Certain medications which increase magnesium wasting[1]

Pathological causes

- Malabsorption, ileal resection or other GIT conditions resulting in reduced dietary absorption of magnesium[1]
- Other chronic diseases which increase magnesium demand or losses[1]

Magnesium homeostasis

The human body contains 0.4g/kg of magnesium found in the bones (60%), muscles (20%), other soft tissues (19%) and the extracellular fluid (<1%).

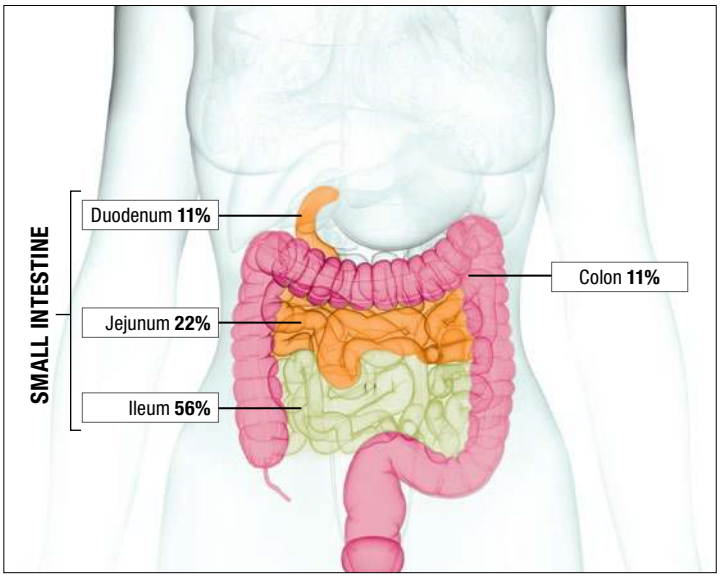
Magnesium homeostasis is efficiently maintained by [2]

Intestines	Absorption
Bones, muscle, soft tissue	Storage
Kidneys	Excretion

Absorption occurs primarily in the distal small intestine and the colon.[2] Approximately 30% of ingested magnesium is absorbed across the intestines, however absorption is upregulated in cases of magnesium deficiency.[3] Magnesium absorption is enhanced by factors that contribute to water flow across the intestinal mucosal membrane, such as simple sugars and urea. Therefore, meals containing carbohydrates and medium chain fatty acids will increase magnesium uptake but will also increase the demand since magnesium is critical to glucose breakdown and insulin release. Solid meals, by prolonging GI transit time, can also enhance magnesium absorption.[4]

Magnesium homeostasis is further regulated through the secretion and reabsorption in the kidneys, where about 95% of filtered magnesium is reabsorbed. However transfer of magnesium from serum into urine begins immediately when magnesium pools are saturated.[3]

Figure 1: GI tract absorption of Mg^{2+} (%)



Interpreting magnesium test results

Due to the efficiency of magnesium homeostasis, magnesium can be pulled from the bone, muscles and internal organs in order to maintain serum levels during times of low intake. Therefore, typical blood and urine analytics may not provide an accurate picture of magnesium status which may mislead the practitioner.[4]

Blood Levels

The current 'normal' magnesium reference range interval of 0.7 – 1.0 mmol/L can be affected by dietary intake but can also be affected by short term changes, affecting day-to-day and hour-to-hour readings. The tight control of magnesium serum levels, representing only 0.8% of total body stores therefore serves as a poor proxy for the 99.2% of magnesium in other tissues that constitutes the body's true magnesium status. Red blood cells' magnesium levels are often cited as preferable to serum or plasma levels due to their higher magnesium content, however methodological flaws in the available studies limit the reliability of drawing such conclusions.[4]

Urine Levels

Due to the large amount of magnesium filtered and the variable degree of reabsorption and secretion, magnesium levels in the urine do not correlate with the magnesium status in the body.[4]

A more complicated method of determining magnesium status relies on intravenous magnesium loading followed by a 24h urine collection, to measure what percentage of administered dose is retained, from which an assessment of magnesium status can be derived. However, this test is costly, more suitable for research units and impractical in most clinical settings.[4]

Other testing methods

To date, numerous other testing methodologies such as sublingual cell magnesium levels, salivary concentrations, faecal excretion, and magnesium isotopes have all been explored however each has significant limitations.[4]

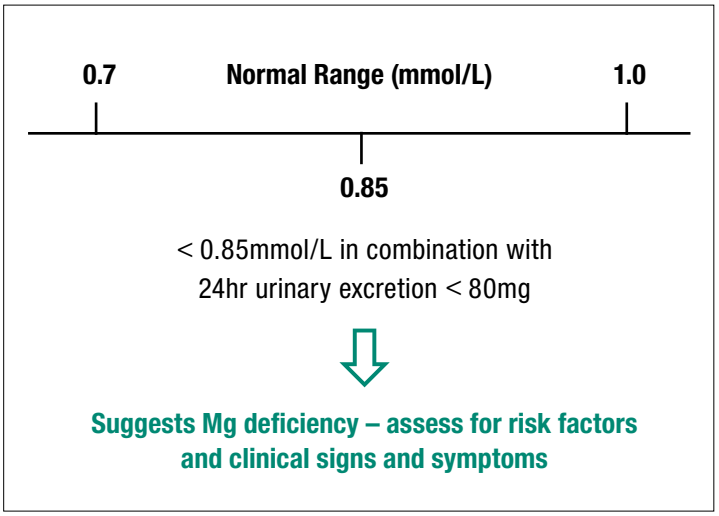
Key clinical considerations

The multiple factors affecting magnesium status (e.g., dietary intake, luminal concentration, gastrointestinal pH, weight and gender) in conjunction with the high degree of inter- and intra-variability of intestinal, renal, and tissue handling make an individual diagnosis somewhat challenging for the clinician.[4]

Until a commercially viable and unambiguous magnesium deficiency biomarker is identified and validated, it is worth exploring an alternative approach to diagnosing magnesium deficiency in the clinical setting.[4]

Whilst clinican's may take into account the results from widely available testing methodologies (see figure 2), pertinent risk factors and the patients symptoms are likely to guide clinical decision making. For example, a patient with dietary risk factors (e.g., high soft drink, coffee, and processed food ingestion); using medications known to affect magnesium (e.g., diuretics, antacids, oral contraceptives); with disease states (e.g., ischemic heart disease, diabetes, and osteoporosis); and clinical signs and symptoms (e.g., leg cramps, sleep disorder, and chronic fatigue); should prompt the practitioner to consider the likely need for magnesium replenishment, even in the presence of 'normal' laboratory readings.[4]

Figure 2: Assessing magnesium status



Choosing superior magnesium forms for optimising magnesium status

The compound form of magnesium is an important factor that affects the efficiency of absorption. Magnesium can be chemically classed as either organic or inorganic magnesium.

Although consensus has yet to be reached, numerous clinical studies have found that the organic forms of magnesium show the highest rate of bioaccessibility (dissolution and availability of the active drug in the digestive tract), and bioavailability (proportion of the active drug that reaches systemic circulation), compared with inorganic magnesium salts.[3]

Inorganic forms of magnesium found as salts, metals, minerals and other carbon-free forms (such as chloride, oxide and sulphate) are generally more poorly absorbed across the gastrointestinal tract when compared to organic forms such as magnesium citrate and magnesium glycinate.[2]

Clinical studies

Urinary magnesium excretion immediately following supplementation is thought to represent a reliable clinical marker of magnesium bioavailability where increased urinary excretion likely represents increased intestinal absorption and systemic bioavailability. In a randomised, double-blind study, both magnesium citrate and magnesium amino acid chelate were found to be more bioavailable than magnesium oxide, exhibiting significantly greater 24hr urinary magnesium excretion. In addition, magnesium citrate significantly increased salivary magnesium concentration whereas no change was observed with magnesium oxide supplementation.[5] These findings have been confirmed by more recent studies which have found that magnesium citrate increases both serum levels and urinary excretion of magnesium over a 24 hour period, compared to magnesium oxide.[6]

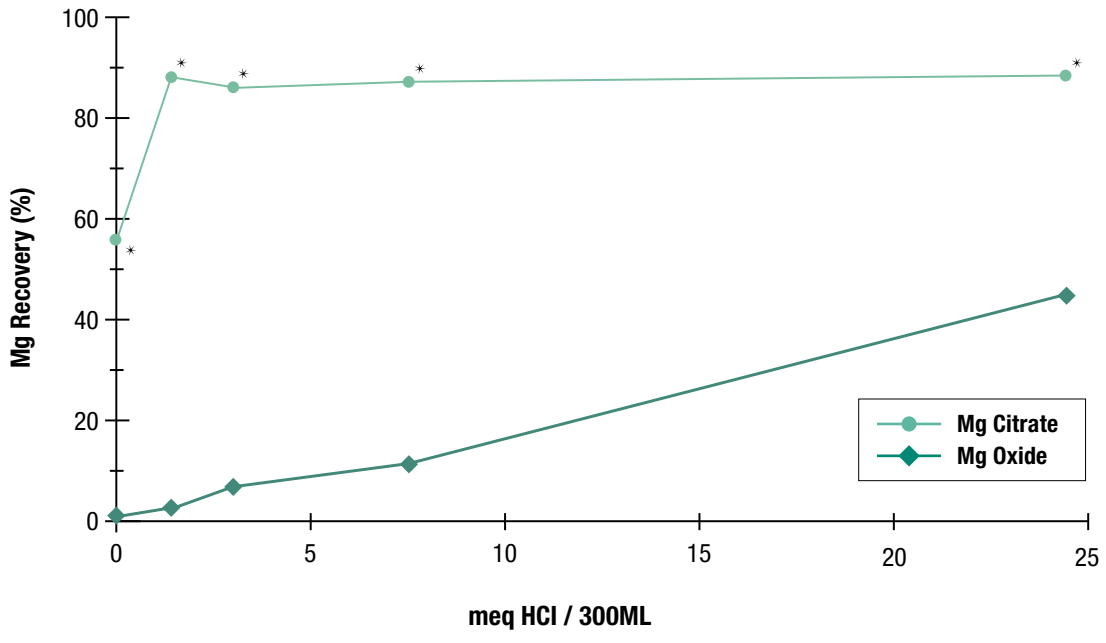
In another clinical study, magnesium citrate was found to equally increase plasma magnesium levels when compared to magnesium oxide, however intracellular ionic magnesium was significantly higher in leukocytes of the individuals supplemented with magnesium citrate.[7,8]

Recent preclinical research also suggests that magnesium citrate is able to dose-dependently increase blood, brain and muscle tissue magnesium concentrations, with magnesium glycinate effectively increasing brain and blood magnesium concentrations.[2]

Gastric acid secretion and magnesium absorption

Experimental studies demonstrate that magnesium citrate has a much greater dissolution and solubility under a wide variety of gastrointestinal conditions. In a simulation of various concentrations of gastric acid secretion, magnesium citrate was found to have a significantly greater solubility compared with magnesium oxide at all concentrations (see figure 3). Importantly, at a concentration of complete acid inhibition (resembling a state of achlorhydria), whilst magnesium oxide was virtually insoluble (0.8% magnesium recovery), magnesium citrate was still highly soluble (55% magnesium recovery).[9] This finding may be of significance for individuals with impaired gastric acid secretion (such as the eldery, anxious or medicated patient) as most magnesium is thought to be absorbed as an ion (Mg^{2+}) through the GIT. Therefore the solubility of the compound form of magnesium appears to be an important precondition for absorption, with increased solubility correlating with increased absorption.[4,10]

Fig. 3: Solubility of magnesium salts (after 60 minutes of incubation) in solutions containing varying amounts of hydrochloric acid. An asterisk indicates a significant difference ($p < 0.05$) between the two magnesium salts at the same hydrochloric acid concentration.[9]



©BioMedica Nutraceuticals. BioMedica is dedicated to providing high-quality and unbiased technical and education materials for healthcare practitioners. The content of these materials remains the Intellectual Property of BioMedica Nutraceuticals.

*This brochure is intended for the further education of healthcare practitioners only.

BioMedica
NUTRACEUTICALS
THE PRACTITIONER COMPANY