Magnesium Disorders

Magnesium (Mg) is involved in a wide range of functions in human physiology. It is essential for all enzyme processes involving adenosine triphosphate (ATP) and many enzymes involved in nucleic acid metabolism. It is a cofactor for DNA, RNA and protein synthesis. It is involved in neuromuscular excitability, cell permeability, regulation of calcium and potassium ion channels, mitochondrial function, cellular proliferation, apoptosis, regulation of parathyroid hormone secretion, muscle contraction, vasomotor tone, blood pressure, cardiac excitability, glucose metabolism and a host of other physiological functions. Changes in normal levels can thus have sweeping effects on body function.

Mg is the fourth most abundant extracellular cation found in the body, and the second most abundant intracellular cation. Most is sequestered in bone and soft tissue cells, with only about 1% in the extracellular fluid. Normal plasma Mg concentration ranges from 0.70 to 1.05 mmol/L.

Plasma concentration is a reflection of the dietary intake of Mg and of the ability of the kidneys and gastrointestinal tract to retain it. Because most Mg is found intracellularly, the relationship between total body deficiency and plasma concentration is poor. However, in cases of severe deficiency, a reduction in plasma concentration can be seen.

Dietary sources of Mg include whole grains, legumes, spinach, potatoes and nuts.[1]

Because of the widespread role of Mg in the body, it has been extensively investigated with regard to therapeutic use. It is an ingredient in a number of laxatives and antacids. There is evidence for its efficacy in eclampsia, pre-eclampsia, asthma, migraine and arrhythmia, and possible efficacy for lowering the risk of metabolic syndrome, improving glucose and insulin metabolism, prevention and management of osteoporosis, alleviating leg cramps in pregnant women, and relieving symptoms of dysmenorrhea. [2] Studies have been done to consider its potential use in disease prevention; reducing atherosclerosis and blood pressure, and in reducing the risk of dementia and stroke. [1] It must be used with caution due to the risk of excess, especially in those with poor renal function.

Hypomagnesaemia

This is variably defined, but usually taken as a level less than 0.7 mmol/L.[3]

Aetiology[4]

It may be caused by:

- Malabsorption syndromes, including:
  - Coeliac disease.[5]
  - Crohn’s disease and ulcerative colitis.
  - Chronic diarrhoea.
  - Steatorrhoea.
  - Short bowel syndrome.
  - Prolonged nasogastric suction.

- Protein-calorie malnutrition. Dietary deficiency causing symptomatic hypomagnesaemia in otherwise healthy individuals is uncommon. Anorexia nervosa may be a cause.
- Disorders of the parathyroid gland.
- Chronic alcoholism - Mg depletion occurs via a number of mechanisms in this condition. It has also been found in those with non alcoholic fatty liver. [6]
- Patients on long-term proton pump inhibitors (PPIs). There is emerging recognition that long-term PPIs can cause hypomagnesaemia, but debate about how to monitor or prevent this. It is a rare side-effect, is associated with all PPIs, and is often accompanied by low potassium and calcium levels. [7] Levels recover quickly when medication is stopped, but drop again when restarted, even with a different PPI. H2 receptor antagonists do not have the same effect. [8]
- Other medications. [9] These include diuretics, digoxin, calcineurin inhibitors, theophylline, cisplatin and some aminoglycosides. These mostly have the result of reducing reabsorption of Mg within the kidney via a variety of mechanisms.
- Renal disorders causing reduced Mg resorption - acute tubular necrosis, post-obstructive diuresis, renal tubular acidosis, post-kidney transplantation.
- Diabetes (due to glucose-induced diuresis secondary to poor glucose control).
- Acute pancreatitis.
- Re-feeding syndrome. [9]
- Genetic causes. Inherited forms exist. [10]
- Severe burns.

Epidemiology[11]

Hypomagnesaemia is thought to have a prevalence of around 2.5-15% in the general population. Symptomatic hypomagnesaemia is less common, as symptoms and signs do not usually present until the level drops below 0.5 mmol/L. Prevalence increases in diabetes clinics, and in hospital patients, and is significantly higher in those who are critically ill or on intensive care units.
Presentation of hypomagnesaemia[11, 12]

Most cases are asymptomatic until levels of Mg drop below 0.5 mmol/L. It is commonly associated with other metabolic abnormalities such as hypokalaemia, hypocalcaemia and metabolic acidosis, making it difficult to distinguish the symptoms of hypomagnesaemia itself. Features may include:

- Neuromuscular symptoms:
  - Weakness and apathy.
  - Tremor.
  - Paraesthesia.
  - Tetany.
  - Muscle fasciculations.
  - Seizures, drowsiness, confusion and coma when very low levels of Mg are reached.

- Cardiovascular features:
  - Arrhythmias.
  - ECG signs may include wide QRS complexes, a prolonged QT interval, flattened T waves and the presence of U waves.

- Associated metabolic abnormalities as above.

Investigations for hypomagnesaemia[11]

- Serum Mg level should be tested. It should be borne in mind, however, that the level may be normal in early mild deficiency because only a small amount of total body Mg is extracellular. An ionised Mg level may give a more accurate picture.
- Protein loss may affect the reading, as the majority of extracellular Mg is protein-bound.
- Mg deficiency may be associated with hypocalcaemia, hypophosphataemia and hypokalaemia, so calcium, phosphate and potassium levels should all be checked.
- Glucose level should be checked due to the association with diabetes.
- ECG.
- In determining the cause, the following tests are sometimes used:
  - 24-hour Mg excretion. High levels in the urine indicate renal wasting.
  - Fractional excretion of Mg. This is a ratio used to help determine if the cause is renal or extra-renal.
  - Mg infusion test. Mg retention is measured after acute loading. There are often false positives, so may not be reliable.
Hypomagnesaemia management

- Identify the cause and treat where possible. Stop causative medication where possible to do so.
- Oral replacement therapy may be used for asymptomatic people with biochemical hypomagnesaemia, or for prevention of recurrence. Absorption is poor compared to parenteral administration. A number of magnesium salts are available, including citrate, hydroxide and glycerophosphate. To prevent recurrence, Mg may be given in doses of up to 24 mmol per day in divided doses for adults. There are no medicines licensed in the UK for this purpose. Their use, however, supported by the British National Formulary (BNF). There is lack of evidence to recommend any particular salt over any other, so choice should depend on local availability, patient tolerability and price. The most frequent side effect of magnesium salts is diarrhoea.
- Severe depletion will require intravenous (IV) replacement, usually with magnesium sulphate. Magnesium sulphate injection is available as 10%, 20% and 50% preparations; for IV use, it should be diluted with 0.9% sodium chloride or 5% glucose to a concentration of 20% Mg or less. No trials have been carried out to determine the optimal regimen for Mg replacement, but it is usually recommended for adults that 8-12 g of magnesium sulphate be given in the first 24 hours followed by 4-6 g per day for three or four days. Maximum infusion rate should not exceed 2 g/hour. Local guidelines should be followed.
- 24-hour urinary Mg excretion may be monitored to ensure response to treatment.

Hypermagnesaemia

This is much less common than hypomagnesaemia. It is most frequently encountered in patients with end-stage kidney disease, those taking medication containing Mg (particularly laxatives, antacids and rectal enemas) and those on parenteral nutrition. In healthy individuals, excess intake is excreted by the kidneys. Other causes of mildly raised Mg levels include lithium therapy, dialysis, hypercalcaemia, hypothyroidism and Addison's disease. It may also occur in neonates born to mothers receiving IV Mg therapy for pre-eclampsia.

There are no reliable figures for prevalence.

Presentation of hypermagnesaemia

Features include:
- Nausea and vomiting.
- Facial flushing.
- Hypotension.
- Paralytic ileus (due to smooth muscle paralysis).
- Weakness, followed by flaccid muscle paralysis.
- Disappearance of deep tendon reflexes.
- Respiratory depression.
- Bradycardia
- Complete heart block or cardiac arrest (at levels >6.0-7.5 mmol/L).

Investigations for hypermagnesaemia

- Serum magnesium level.
- Hypocalcaemia is often present and these levels should also be checked.
- TFTs and an early morning cortisol test should be performed if hypermagnesaemia is unexplained, recalcitrant or recurrent.
- ECG.

Hypermagnesaemia management

- Usually withdrawal of the cause, if excessive intake, will solve the problem.
- It should be preventable by monitoring if Mg-containing medication is being used, especially in those with poor renal function.
- Hypermagnesaemia can be corrected using IV calcium. The patient should be treated in an intensive care unit with regular ECG and serum monitoring.
- If the patient has a normal urine output and renal function, Mg loss can be enhanced using IV saline infusions and furosemide diuresis.
- Dialysis may be occasionally be required for patients with:
  - Renal insufficiency.
  - Severe hypermagnesaemia (>4 mmol/L).
  - Serious cardiovascular or neuromuscular symptoms irrespective of serum Mg level.
- On discharge, the patient's ongoing medication regime should be reviewed to ensure that it does not include Mg-containing laxatives or antacids.

Further reading & references

- Fact Sheet for Health Professionals, Magnesium; National Institutes of Health, November 2013
10. Hypomagnesemia 3, Renal, HOMG3 (Familial Hypomagnesemia); Online Mendelian Inheritance in Man (OMIM).
13. British National Formulary
14. Preventing recurrent hypomagnesaemia: oral magnesium glycerophosphate, NICE advice, January 2013

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