Hypomagnesaemia: clinical relevance and management

Hypomagnesaemia is a relatively common yet frequently under-diagnosed and poorly managed electrolyte disorder. Untreated hypomagnesaemia could result in severe life-threatening neurological and cardiac complications. This review discusses the clinical relevance, commonly encountered causes and management of hypomagnesaemia.

Hypomagnesaemia is one of the most commonly encountered electrolyte disorders in clinical practice. It has a particularly high prevalence among patients admitted to acute and intensive care units. Mild hypomagnesaemia is by and large asymptomatic but more severe forms of magnesium deficiency could present with potentially serious neuromuscular, neurological and cardiac manifestations. A meticulous clinical assessment including a detailed drug history is often sufficient to identify the cause of hypomagnesaemia. Treatment of hypomagnesaemia should focus on both correcting the underlying cause and replacing the magnesium deficit.

There is a general lack of awareness among physicians about the clinical significance of hypomagnesaemia and its management. This review provides a rational approach to the diagnosis, investigation and management of hypomagnesaemia, using a case scenario to illustrate key points.

Magnesium homeostasis

Magnesium is one of the most common and essential elements in all living cells. It is the fourth most abundant cation and the second most common intracellular cation after potassium. The average adult body contains 25 g (1000 mmol) of magnesium and the bulk of this (99%) is found in the intracellular compartment. Bone tissue accounts for 60% of the intracellular magnesium store while the remaining 40% is distributed in muscles and other soft tissues. Intracellular magnesium plays a vital role as a cofactor in a variety of essential physiological processes including energy metabolism via oxidative phosphorylation of adenosine triphosphate (ATP), DNA transcription, protein synthesis, neuromuscular function and secretion of parathyroid hormone (al-Ghamdi et al, 1994; Whang et al, 1994).

Normal serum magnesium concentration ranges from 0.75–0.95 mmol/litre. About 70% of serum magnesium is found in the physiologically active ionized (free) form whereas 30% is bound to albumin. Although a low serum magnesium level strongly correlates with depleted total body magnesium stores, a normal serum magnesium level does not rule out total body magnesium deficiency (Agus, 1999). Magnesium homeostasis is tightly regulated by the interplay between small bowel absorption and renal excretion. Bone magnesium, a third of which is readily exchangeable, also plays a role in magnesium homeostasis when there is depletion of magnesium stores (al-Ghamdi et al, 1994; Whang et al, 1994; Agus, 1999).

A balanced diet is often sufficient to meet the daily body magnesium requirement. The recommended dietary magnesium intake is 300 mg/day but higher consumption is required in special circumstances such as pregnancy and patients taking loop diuretics. Green leafy vegetables, legumes, chocolate, nuts, wholegrain cereals and animal protein are food sources that are rich in magnesium. Only 40–50% of the dietary magnesium intake is absorbed, mostly in the jejunum and ileum. The amount of magnesium absorbed from the small intestine is inversely proportional to the dietary intake. The kidney filters approximately 70% of the plasma magnesium but excretes only 5% of the filtered magnesium load. The thick ascending loop of Henle is the main site of renal magnesium handling where 60% of the filtered magnesium gets reabsorbed. The remaining 20–30% is reabsorbed in the proximal tubule (al-Ghamdi et al, 1994; Topf and Murray, 2003).

Hypomagnesaemia

Prevalence

The reported prevalence of hypomagnesaemia varies from 2.5% to 15% in the general population to as high as 65% among patients admitted to intensive care units (Reinhart and Desbiens, 1985; Ryzen et al, 1985b; Topf and Murray, 2003). Despite its high prevalence, hypomagnesaemia remains one of the most under-diagnosed electrolyte disorders in clinical practice (Croker and Walmsley, 1986; Whang, 1987). In a study involving 1000 blood samples sent for measurement of electrolyte concentrations, Whang and Ryder (1990) demonstrated that physician-initiated testing detected only 10% of patients with hypomagnesaemia. These data highlight the importance of a more regular approach to checking serum magnesium concentration.

Dr Yared N Demssie *is Consultant Physician,* **Dr Leena Patel** *is Foundation Year 2 Trainee and* **Dr Mohit Kumar** *is Specialist Trainee in the Department of Endocrinology, Royal Blackburn Hospital, Blackburn BB2 3HH, and* **Dr Akheel A Syed** *is Consultant Physician in the Department of Endocrinology, Salford Royal NHS Foundation Trust, Salford and The University of Manchester, Manchester*

Correspondence to: Dr YN Demssie (Yared.Demssie@elht.nhs.uk)

Causes

Gastrointestinal absorption and renal excretion are the two most important mechanisms for regulating magnesium homeostasis. Malabsorption and renal magnesium wasting are therefore the two most common causes of hypomagnesaemia. Other less common causes include poor dietary intake, medications and endocrine disorders (*Table 1*) (al-Ghamdi et al, 1994; Whang et al, 1994; Agus, 1999; Topf and Murray, 2003). In some patients, such as the patient discussed in the *case study*, the aetiology of hypomagnesaemia could be multifactorial.

Gastrointestinal causes

Chronic diarrhoea, short bowel syndrome and intestinal bypass, nasogastric suction and acute pancreatitis are common gastrointestinal causes of hypomagnesaemia. Hypomagnesaemia is also commonly encountered in patients with eating disorders and malnutrition. A third of alcoholic patients have hypomagnesaemia as a result of a combination of poor nutrition, increased magnesium loss through vomiting, diarrhoea, malabsorption and renal magnesium wasting (De Marchi et al, 1993).

Table 1. Causes of hypomagnesaemia

Dietary	Malnutrition
	Eating disorder
	Alcoholism
	Total parenteral nutrition
Redistribution	Correction of metabolic acidosis
	Hungry bone syndrome
	Refeeding syndrome
	Acute pancreatitis
Gastrointestinal loss	Vomiting and diarrhoea
	Malabsorption
	Short bowel syndrome
	Intestinal bypass surgery
	Nasogastric suction
	Laxative abuse
Miscellaneous	Proton pump inhibitors
	Hypercalcaemia
	Hyperaldosteronism
	Burns
	Excessive sweating
	Primary infantile hypomagnesaemia
	Familial isolated hypomagnesaemia
Renal magnesium wasting	Gitelman syndrome
	Bartter syndrome
	Diuretics
	Antimicrobials
	Chemotherapeutic agents

Renal causes

Renal magnesium wasting is commonly related to the use of drugs which interfere with the tubular reabsorption of magnesium. These include loop and thiazide diuretics, antibiotics such as ticarcillin, carbenicillin and gentamicin, and chemotherapeutic agents such as cisplatin (Shah and Kirschenbaum, 1991). Gitelman and Bartter syndromes are autosomal recessive inherited tubular disorders characterized by hypokalaemic metabolic alkalosis, hyperreninaemia and hypomagnesaemia (Kurtz, 1998).

Endocrine causes

Hungry bone syndrome is a postoperative complication of parathyroidectomy and thyroidectomy for hyperparathyroidism and hyperthyroidism respectively. This condition is characterized by an acute postoperative drop in both serum calcium and magnesium levels as a result of rapid remineralization of bone upon abrupt withdrawal of high levels of parathyroid and thyroid hormones (Frisch and Mimouni, 1993).

Hypomagnesaemia is also prevalent among patients with diabetes mellitus. Up to a third of patients with insulin-treated diabetes have been found to have low serum magnesium level and the prevalence appears to correlate with the degree of hyperglycaemia (White and Campbell, 1993). Glycosuria-related renal magnesium wasting is the proposed mechanism for the high prevalence of hypomagnesaemia among diabetic patients (Sjogren et al, 1986). Studies have also shown an inverse correlation between dietary magnesium intake and risk of type 2 diabetes (Kao et al, 1999; Larsson and Wolk, 2007).

Diabetic ketoacidosis is strongly associated with hypomagnesaemia through combined mechanisms of intracellular shift and increased urinary magnesium loss. Other endocrine causes of renal magnesium wasting include hyperaldosteronism, hypercalcaemia and hyperthyroidism.

Miscellaneous causes

The chronic use of proton pump inhibitor drugs is associated with hypomagnesaemia through the presumed mechanism of impaired intestinal absorption of magnesium (Furlanetto and Faulhaber, 2011; Hess et al, 2012). This association is stronger in patients who are concurrently taking diuretic drugs. In a large cohort study of 11 490 patients admitted to an intensive care unit, the prevalence of hypomagnesaemia was higher in patients with concurrent use of proton pump inhibitors and diuretics than in those who only used diuretics (Cundy and Dissanayake, 2008).

Major surgery is known to cause hypomagnesaemia through catecholamine-induced intracellular magnesium shift and increased binding to free fatty acids.

Redistribution of magnesium to the intracellular compartment in refeeding syndrome and following correction of metabolic acidosis could also cause a significant drop in serum magnesium level. Severe burns, excessive sweating and lactation could all result in clinically significant hypomagnesaemia.

Clinical manifestations

Hypomagnesaemia is mostly asymptomatic but its nonspecific symptoms such as lethargy, apathy and anorexia could also be overshadowed by coexisting clinical conditions. The severity of magnesium deficiency and the rate at which the deficiency develops determine the clinical manifestations of hypomagnesaemia. Most symptoms and signs of hypomagnesaemia become evident when the serum magnesium level drops to <0.5 mmol/litre (Agus, 1999). Neuromuscular symptoms and signs are the most common clinical manifestations of hypomagnesaemia (*Table 2*). These include muscle cramps, fasciculations, tremors and tetany. Chvostek's sign (twitching of facial muscles on tapping the ipsilateral facial nerve) and Trousseau's sign (induction of carpopedal spasm by inflation of the sphygmomanometer above the systolic blood pressure) could be elicited. The neuromuscular manifestations of hypomagnesaemia could be partly related to concurrent hypocalcaemia secondary to impaired secretion of parathyroid hormone and resistance to its action at target tissues (Rude et al, 1976; Allgrove et al, 1984). Hypokalaemia, which is often refractory to potassium replacement, is also found in patients with hypomagnesaemia as a result of increased urinary potassium loss (Whang et al, 1985).

Neurological manifestations of hypomagnesaemia include vertigo, nystagmus, choreoathetosis, hemiparesis, aphasia and convulsions. Hypomagnesaemia has also been associated with a variety of cardiac arrhythmias such as torsade de pointes, ventricular and supraventricular arrhythmias. Hypomagnesaemia is one of the most common electrolyte disorders associated with digitalis toxicity (Young et al, 1991). There is some evidence to suggest that hypomagnesaemia increases the risk of coronary artery disease (Gartside and Glueck, 1995; Liao et al, 1998).

Investigations

Measurement of serum magnesium level should be routinely undertaken in patients admitted to acute and intensive care units. In addition, patients at risk of low magnesium level such as those suffering from alcoholism, chronic diarrhoea or malabsorption, patients taking diuretics and those manifesting signs and symptoms of hypomagnesaemia should have their serum magnesium level measured. Investigation of hypomagnesaemia should include a full biochemical profile including serum calcium, potassium, glucose, glycated haemoglobin, bicarbonate, 25-hydroxyvitamin D, parathyroid hormone and thyroid hormone levels. A 12-lead electrocardiogram should also be routinely performed to detect abnormal rhythms. Other electrocardiogram abnormalities include flattened T waves, U waves, wide QRS com-

Case Study

A 58-year-old woman presented to hospital with a history of generalized muscle cramps of 5 days' duration, and diarrhoea of 2 weeks' duration. Her background medical history included hypertension, hypercholesterolaemia and dyspepsia for which she was taking bendroflumethiazide, simvastatin and omeprazole tablets. General physical examination was unremarkable except for muscle fasciculation, and positive Chvostek's and Trousseau's signs. Her investigations confirmed low adjusted serum calcium level of 1.22 mmol/litre (reference range 2.15–2.65 mmol/litre) along with low serum magnesium level of 0.14 mmol/litre. Her parathyroid hormone level was marginally raised at 8.3 pmol/litre (1.5–7.6 pmol/litre). Electrocardiogram showed normal sinus rhythm with borderline corrected QT prolongation at 450 ms.

She was treated with intravenous 100 ml 10% calcium gluconate and 16 mmol magnesium sulphate infusion. Her symptoms resolved with this treatment and both her serum calcium and magnesium levels returned to normal. She continued to have diarrhoea and further investigation with colonoscopy confirmed colitis. Despite ongoing diarrhoea, the patient was discharged from hospital without any maintenance oral calcium or magnesium supplements. She was also maintained on both bendroflumethiazide and omeprazole which further predisposed her to recurrent hypomagnesaemia.

Not surprisingly, the patient was readmitted 2 weeks later with recurrence of neuromuscular symptoms along with profoundly low serum calcium and magnesium levels of 1.4 mmol/litre and 0.15 mmol/litre respectively. She was once again treated with both calcium and magnesium infusions until her serum levels returned to normal. She was also maintained on oral magnesium glycerophosphate at a dose of 24 mmol/day in three divided doses. Her bendroflumethiazide was stopped to reduce renal magnesium wasting and omeprazole was replaced with ranitidine. She has remained asymptomatic since and both her serum calcium and magnesium levels have stayed normal.

Table 2. Clinical manifestations of hypomagnesaemia

Neuromuscular or neurological	Muscle cramp and/or weakness
	Carpopedal spasm
	Chvostek and Trousseau signs
	Nystagmus
	Vertigo
	Choreoathetoid movements
	Aphasia
	Hemiparesis
	Delirium
	Apathy and/or depression
Cardiac	Ventricular arrhythmias
	Torsade de pointes
	Supraventricular arrhythmias
	Increased digoxin sensitivity
Electrolyte abnormalities	Hypocalcaemia
	Hypokalaemia

plexes and prolongation of the QT segment which could all be secondary to concomitant hypokalaemia.

In most cases, a thorough history including dietary review, alcohol intake, gastrointestinal symptoms and the use of medications such as diuretics could identify the cause of hypomagnesaemia. However, clinical assessment alone may sometimes prove inconclusive as to the cause of magnesium deficiency. In such scenarios, measurement of urinary magnesium excretion could be a useful tool to differentiate between renal and non-renal magnesium loss. Measurement of urinary magnesium excretion can be undertaken either on a 24-hour urine sample or alternatively on a spot urine sample by calculating fractional excretion of magnesium using the formula shown in *Figure 1*. A fractional magnesium excretion >2% suggests renal magnesium wasting (Elisaf et al, 1997).

A magnesium loading test, which involves infusing a magnesium load followed by measurement of the urinary magnesium excretion rate over a 24-hour period, can be used as a measure of intracellular magnesium store in patients suspected to have normomagnesaemic magnesium depletion (Ryzen et al, 1985a). However, the use of this test in routine clinical practice is limited by its cumbersome nature and high false positive rate.

Treatment

The mode of treatment of hypomagnesaemia depends on the degree of hypomagnesaemia and the severity of its clinical manifestations. A serum magnesium level below 0.4 mmol/litre and the presence of neuromuscular, neurological or cardiac manifestations warrants more aggressive parenteral replacement therapy (Weisinger and Bellorin-Font, 1998; Agus, 1999). Patients presenting with cardiac arrhythmia, seizure and tetany should receive immediate intravenous magnesium sulphate infusion of 4–8 mmol in 100 ml 5% dextrose over 5–10 minutes. This should be supplemented by a further slow infusion of 16–32 mmol of magnesium sulphate in 1 litre of 5% dextrose solution over 12–24 hours. This could be repeated as necessary aiming to keep serum magnesium level above 0.4 mmol/litre. Patients suspected to have normomagnesaemic magnesium depletion with refractory hypocalcaemia and hypokalaemia require repeated doses of slow magnesium infusion over 3–5 days. Patients with severe renal insufficiency should receive a reduced dose of magnesium infusion to prevent hypermagnesaemia (Topf and Murray, 2003).

The main limitation of intravenous magnesium infusion therapy lies in the loss of up to 50% of the infused magnesium through enhanced renal excretion (al-Ghamdi et al, 1994; Agus, 1999; Topf and Murray, 2003). This is because the rate of magnesium reabsorption from the ascending loop of Henle is dictated by the serum magnesium concentration. It is important to keep this in consideration when deciding the dose and duration of intravenous magnesium replacement therapy.

The use of oral magnesium replacement therapy is adequate in asymptomatic patients and those with serum magnesium level above 0.4 mmol/litre. A number of magnesium salt preparations with variable magnesium content and tolerability are available for oral replacement therapy. These include glycerophosphate, gluconate, lactate, chloride, aspartate, phosphate, citrate and hydroxide salts of magnesium. The usual replacement dose is 10–40 mmol/day in 2–4 divided doses. Sustained release preparations are preferred to reduce renal wasting. The major side effect of oral magnesium preparations is diarrhoea and this could affect both the bioavailability and compliance with treatment. A regular parenteral magnesium infusion therapy should be considered if oral therapy is not tolerated.

Patients with renal magnesium wasting including those on chronic diuretic therapy may respond to the addition of the potassium-sparing diuretic amiloride to their replacement therapy (al-Ghamdi et al, 1994; Agus, 1999; Martin et al, 2009). Correction of the underlying cause, including withdrawing drugs which are known to cause hypomagnesaemia, is of utmost importance to prevent recurrent hypomagnesaemia.

Figure 1. Formula for calculating fractional excretion of magnesium. FEMg = fractional magnesium excretion, u = urinary; s = serum; Cr = creatinine; Mg = magnesium. The 0.7 in the denominator refers to the proportion of magnesium that is free (unbound) and filtered by the kidneys.

$$FEMg = \frac{(uMg \times sCr)}{(sMg \times uCr \times 0.7)} \times 100$$

KEY POINTS

- Serum magnesium level should be routinely checked in patients admitted to both acute and intensive care units, those with predisposing factors for hypomagnesaemia and patients with suggestive neuromuscular, neurological and cardiac manifestations.
- Normomagnesaemic magnesium depletion should be suspected in patients with treatment-refractory hypocalcaemia and hypokalaemia.
- The cause of hypomagnesaemia is often apparent from clinical assessment but measurement of urinary magnesium excretion could be a useful test when no obvious cause is identified.
- Patients at risk of recurrent hypomagnesaemia should receive long term oral magnesium replacement therapy.
- Treating the underlying cause of hypomagnesaemia, including withdrawal of drugs which cause magnesium wasting, is essential to prevent recurrent hypomagnesaemia.

Conclusions

Hypomagnesaemia is a common electrolyte disorder that all physicians should actively identify through targeted screening of high risk patient groups and those with suggestive symptoms. An accurate diagnosis of the cause of

hypomagnesaemia is a crucial step in its management. Addressing reversible causes of hypomagnesaemia, such as withdrawing offending drugs, is of paramount importance to prevent treatment refractory cases. **BJHM**

Conflict of interest: none.

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