Magnesium (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Magnesium

1.2 Alternative names
None

1.3 NMLC code
To follow

1.4 Description of analyte
Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation.

1.5 Function of analyte
Magnesium is an essential co-factor in the formation of the substrates (including ATP) of many enzymes and is also an allosteric activator of many enzyme systems. It is important in oxidative phosphorylation, glycolysis, cell replication, nucleotide metabolism and protein biosynthesis. Magnesium has an important role in membrane stabilisation, nerve conduction, ion transport and calcium channel activity.

Magnesium is the second most prevalent intracellular cation; this fraction accounts for approximately 45% of the total body magnesium. Extracellular magnesium accounts for 1% of the total body magnesium content, with the remainder in the skeleton. Approximately 55% of extracellular magnesium is free, 30% is associated with proteins, primarily albumin and 15% is complexed with anions.

2 Sample requirements and precautions

2.1 Medium in which measured
1. Magnesium can measured in serum and heparinised plasma.
2. Magnesium can also be measured in urine. Urine samples should ideally be collected into acid to prevent precipitation of magnesium complexes. The remainder of this article relates to measurements in plasma, serum or whole blood.
3. Free magnesium (non protein-bound or complexed) can be measured in whole blood, plasma or serum.

2.2 Precautions re sampling, handling etc.
1. Heparins containing zinc should be avoided as these increase measured plasma [magnesium]. Anticoagulants containing oxalate, citrate and EDTA should be avoided as these form complexes with magnesium.
2. Haemolysed samples should not be used as erythrocytes contain higher concentrations of magnesium than serum or plasma.
3. Serum or plasma should be separated from the clot or red blood cells as soon as possible to prevent an increase in [magnesium] due to leakage from the red cells.

4. Interference from free calcium has been noted between different analysers when measuring free magnesium. Samples should be handled anaerobically to prevent loss of CO_2 and analysed quickly to prevent changes in $[H^+]$/pH due to metabolism as this alters distribution of magnesium between free, protein bound and complexed forms.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Magnesium is measured in the diagnosis and monitoring of hyper- or hypomagnesaemia (see 6.1 for more detail)

3.2. Limitations

A normal serum [magnesium] does not exclude cellular magnesium deficiency. Measurement of serum or urine [magnesium] cannot provide information as to the cause of either hyper- or hypomagnesaemia

4. Analytical considerations

4.1. Analytical methods

A. Total magnesium is most often measured by photometric methods. A small number of laboratories use atomic absorption spectrometry.

1. Photometric: several metallochromic indicators are used that change colour on selective binding to magnesium at alkaline pH. These include calmagite, xylidyl blue or magon, chlorophosphonazo III and arsenazol. The calcium chelating agent ethylene glycol acetic acid (EGTA) is added to reduce interference by calcium.

2. Formazan dye forms a complex with magnesium at alkaline pH. Thin film reflectance photometry is used to measure the formation of this dye complex.

3. Atomic absorption spectrometry. Samples are diluted with a lanthanum-HCl solution to reduce interference from anions and reduce viscosity. The diluted samples are aspirated into an air-acetylene flame where ground state magnesium ions absorb light from a magnesium hollow cathode lamp. This absorption of light is measured at 282.5 nm and is directly proportional to the number of ground state magnesium ions in the flame.

B. Free magnesium by ion selective electrode (ISE). Calcium ions interfere with magnesium ISEs. To overcome this interference, both ions are measured simultaneously so that free [calcium] is determined simultaneously and the result used to correct the results for [magnesium] according to the known selectivity of the magnesium electrode.

4.2 Reference method

Atomic absorption spectrometry (see 4.1.A.3)

4.3 Reference materials

Magnesium gluconate dehydrate (Standard Reference Material (SRM) 929, National Bureau of Standards, Washington DC, USA)

4.4 Interfering substances

Using thin film reflectance photometry, elevated [calcium] may cause a small overestimation in [magnesium].

4.5 Sources of error

The concentration of free or ionised magnesium in plasma depends on the pH due mainly to the binding of magnesium to albumin, which increases with pH. The pH should also be measured simultaneously to allow adjustment to pH 7.4. The useable pH interval for adjustment is pH 7.0–7.8

5 Reference intervals and variance

5.1.1 Reference interval (adults)

Total magnesium: <60 y: 0.66–1.07 mmol/L;60–90 y: 0.66–0.99 mmol/L
> 90 y: 0.70–0.95 mmol/L
Free magnesium: 0.45–0.60 mmol/L

5.1.2 Reference intervals (others)

Newborn: 0.62–0.91 mmol/L
5 m–6 y: 0.7–0.95 mmol/L; 6–12 y: 0.7–0.86 mmol/L;
12–20 y: 0.7–0.91 mmol/L

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 11.3%
5.1.3.2 Intraindividual CV: 5.6%
5.1.3.3 Index of individuality: 0.5
5.1.3.4 CV of method: typically <2%
5.1.3.5 Critical difference: 16%

5.1.4 Sources of variation

None of significance apart from the slight variations with age and [albumin] (see 6.1.3)]

6 Clinical uses of measurement and interpretation of results

6.1 Indications for measurement

1. Suspected magnesium depletion. This can occur in the following conditions:
   - refeeding
   - treatment of diabetic ketoacidosis
   - long term intravenous fluid replacement
   - malabsorption syndromes
   - chronic diarrhoea
   - post renal transplant
   - renal replacement treatment
   - diuretic treatment
   - hyperparathyroidism, thyrotoxicosis, hyperaldosteronism
   - alcoholism.
2. Suspected magnesium excess. This can occur in:
   - renal failure
   - magnesium replacement treatment (see also 7.1)
   - tumour lysis syndrome
3. Free [magnesium] should be measured in patients who have low total [magnesium] and low [albumin], as they may have normal concentrations of free magnesium.

6.2. Confounding factors

1. Haemolysis can erroneously suggest a high *in vivo* [magnesium] due to release from cells.
2. A normal serum [magnesium] does not exclude cellular magnesium deficiency.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

1. Iatrogenic (i.e. with the use of intravenous magnesium, magnesium-containing cathartics or antacids).
2. Renal failure: plasma [magnesium] is regulated by urinary excretion.
3. Following release from the intracellular space (i.e. tumour lysis syndrome).

7.1.2 Investigation

Magnesium homeostasis depends primarily on balance between intestinal absorption and renal excretion. Patients with renal insufficiency are at most risk of magnesium excess, as are the elderly. Clinical history and determination of renal function should elucidate the cause.

7.2 Low values

7.2.1 Causes

1. Gastrointestinal loss: conditions that cause malabsorption may lead to decreased gastrointestinal absorption of magnesium. Acute or chronic diarrhoea and intestinal fistulae can also cause hypomagnesaemia.
2. Renal loss: chronic parenteral fluid therapy and volume expanded states can result in hypomagnesaemia as renal magnesium reabsorption is related to urine flow. Hypercalcaemia and hypercalciuria decrease renal magnesium reabsorption, so hypomagnesaemia may be observed in hypercalcaemic states such as hyperparathyroidism or malignancy. Osmotic diuresis (e.g. due to diabetes mellitus) is a common cause of hypomagnesaemia. There are two rare congenital magnesium wasting syndromes – Bartter's and Gitleman's syndrome.
3. Drugs: these can cause renal wasting of magnesium by various mechanisms.

7.2.1 Investigation

The cause of hypomagnesaemia can usually be obtained from the history. If gastrointestinal or renal losses cannot be distinguished, measurement of 24 h urine magnesium or fractional excretion may be helpful. Daily excretion of greater than 4 mmol (10 mg) in a patient with normal renal function suggests renal magnesium wasting.

In patients with refractory hypokalaemia or unexplained hypocalcaemia, intracellular hypomagnesiaemia may be the cause (normomagnesaemic magnesium depletion). These patients will have a low urinary magnesium excretion. Hypokalaemia occurs as magnesium is required for proper function of the Na^+/K^+- ATPase pump. Deficiency in magnesium causes an increase in intracellular sodium content and a decrease in potassium. Loss of intracellular potassium also occurs in the renal tubules. This can lead to a hypokalaemia that only responds to magnesium replacement.

Magnesium depletion can cause hypocalcaemia by producing PTH resistance or decreasing PTH secretion in more severe hypomagnesaemia.

7.3 Notes

None

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions
Not applicable

9 Systematic reviews and guidelines

9.1 Systematic reviews
1. Antenatal magnesium sulphate and neurologic outcome in preterm infants: a systematic review. Doyle LW, Crowther CA, Middleton P, Marret S. Obstetrics and Gynecology 2009; 113(6): 1327-1333. *Antenatal magnesium sulphate and neurologic outcome in preterm infants: a systematic review.*
2. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Cochrane Database of Systematic Reviews 2010; Issue 11: CD000025. *Use of magnesium sulphate more than halves the risk of eclampsia and probably reduces maternal death. There is no clear effect on outcome after discharge from hospita).*

9.2 Guidelines
None identified

9.3 Recommendations
1. Intravenous magnesium is indicated in symptomatic patients or if the serum magnesium is <0.5mmol/L. A suitable preparation is magnesium sulphate hexahydrate 20% aqueous solution, which contains 0.8 mmol Mg/mL.
2. In mild hypomagnesaemia (0.5–0.7mmol/L) or to prevent the reoccurrence of hypomagnesaemia in adults, oral magnesium can be given. An appropriate formulation is magnesium glycerophosphate tablets containing 4 mmol Mg per tablet. These are unlicensed but available on a named patient basis.

10. Links

10.1 Related analytes
None

10.2 Related tests
Measurement of urine magnesium can be of value in the investigation of hypomagnesaemia. Measurement of serum creatinine is essential to the investigation of hypermagnesaemia.

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