



Investigative algorithms for disorders affecting plasma magnesium: a narrative review

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Background and Objective: The following article is a part of a special series to aid the reader in diagnosing the cause of various electrolyte imbalances. By the end of the article, the reader will be able to order and interpret appropriate investigations when faced with a patient with low or high magnesium.

Methods: A narrative, focused literature review was performed using PubMed, OMIM and Google during September 2021 to January 2022 to identify references published from database inception to January 2022. Reference lists from identified articles were also used. Language was restricted to English.

Key Content and Findings: Magnesium is primarily intracellular with homeostasis tightly controlled via regulated gastrointestinal and renal absorption. It should be noted that in acutely ill people, hypomagnesaemia is more likely to be an epiphenomenon rather than representing a true magnesium deficiency—which takes months to years to develop (with plasma concentration maintained). If hypomagnesaemia is identified screen for gastrointestinal diseases or problem drinking and consider a 24-h urine collection to establish renal handling. For hypermagnesaemia consider drugs and tissue lysis.

Conclusions: Diagnostic schema will be presented and the limitations of the laboratory tests discussed. The following schema, by focusing on the investigation of hypomagnesaemia and hypermagnesaemia, should support healthcare professionals to efficiently and systematically approach people with these electrolyte abnormalities.

Keywords: Magnesium; hypomagnesaemia; hypermagnesaemia; deficiency; algorithm

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Introduction

Magnesium is an abundant intracellular cation and is an essential cofactor for multiple enzymes. Most importantly, magnesium helps in the transfer of inorganic phosphate in many metabolic reactions such as in glycolysis, gluconeogenesis, citric acid cycle and ATP synthesis (1). Only 1% of total body magnesium resides in the extracellular space, 50–65% is complexed in bone and acts as a buffer pool to maintain magnesium homeostasis,

and the remainder is found in the intracellular space (*Figure 1*) (2). Of the total extracellular magnesium, just over half circulates as a free divalent cation, 30% is bound to plasma proteins (particularly albumin), and 15% is complexed with anions (carbonate, phosphate, citrates, hydroxide and chloride). Therefore, changes in protein binding or anion quantity will influence serum magnesium concentration if measuring total magnesium (the most commonly used analytical method to quantitate magnesium in the UK) (1,3).

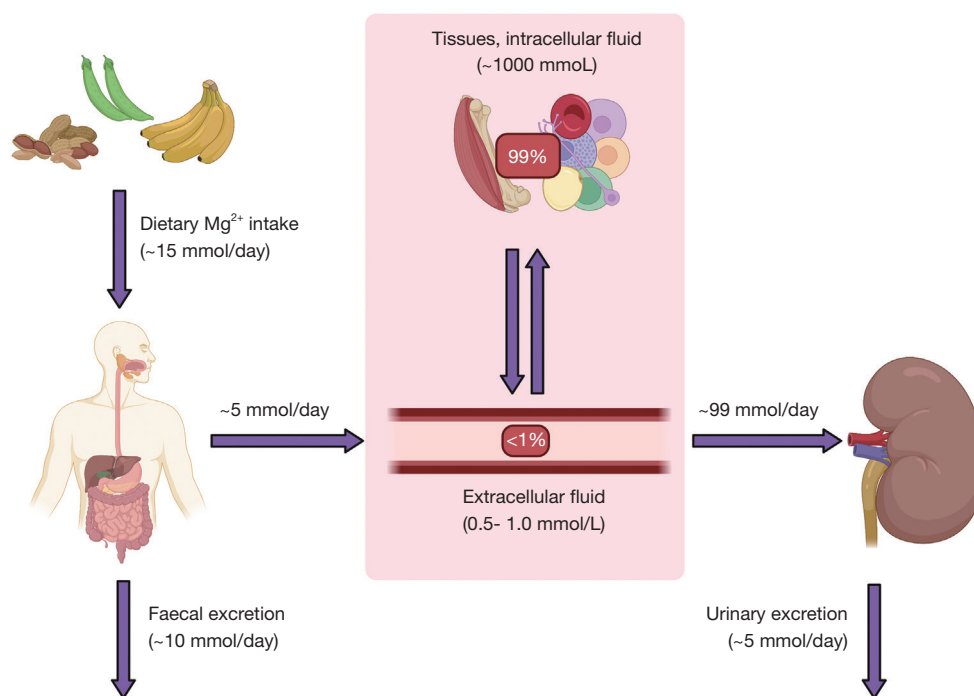


Figure 1 A basic overview of the distribution and homeostasis of magnesium in humans.

Serum magnesium has a concentration of 0.7–1.0 mmol/L, although this will be method and population dependent, and is not always a reliable indicator of the status of total body magnesium (3). The following algorithms aim to provide a rough guide on using laboratory diagnostics to evaluate the causes of magnesium disturbances. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://jlp.m.amegroups.com/article/view/10.21037/jlp.m-22-6/rc>).

Methods

The narrative literature review was undertaken with review of Medline, Google Scholar, OMIM and seminal texts. The search was performed from September 2021 to January 2022 from database inception. Language was restricted to English. Diagnostic algorithms were created from synthesis of the information obtained from literature review. More information is found in the supplementary information (Table 1).

Metabolism and regulation

Magnesium is found in a variety of foodstuffs including green vegetables, legumes, whole grains, nuts, seeds,

rice and fruits. Bodily magnesium levels are regulated by intestinal absorption (mainly in the colon and distal small intestine), hormonal control of stores in the bone, and renal reabsorption, specifically at the ascending limb of the loop of Henle (Figure 1). Only 30–50% of dietary magnesium is normally absorbed by the gastrointestinal tract, increasing to around 80% in hypomagnesaemia (2). Magnesium is absorbed in the gastrointestinal tract using luminal membrane transporters, namely Transient Receptor Potential Melastatin type 6 and 7 (TRPM-6 and -7), and paracellularly as tight junction claudins are limited (Figure 2) (2). TRPM-6 and -7 have close homology. TRPM-7 is ubiquitously expressed whereas TRPM-6 is mainly localised to the apical surface of the colon and renal epithelia. Following TRPM absorption, magnesium enters the bloodstream through the solute carrier family 41 member 1 (SLC41A1), a basolateral membrane sodium-magnesium exchanger (2,4).

The kidneys reabsorb 90–95% of filtered magnesium—10–20% in the proximal convoluted tubule (PCT), 50–70% in the thick ascending loop of Henle (TAL) and 5–10% in the distal convoluted tubule (DCT) (2,5). Paracellular absorption occurs in the PCT and TAL, and fine-tuning transcellular absorption in the DCT using TRPM-6 and SLC41A1 channels as described above (Figure 2) (4).

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	September 2021 to January 2022
Databases and other sources searched	Medline, Google Scholar, OMIM
Search terms used (including MeSH and free text search terms and filters). Examples include:	Hypermagnesaemia (hypermagnesaemia), Hypomagnesaemia (hypomagnesaemia), Magnesium, Diagnosis, Investigation, Causes, Aetiology, Paediatrics, Pregnancy, Human
Timeframe	From database inception to January 2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	All papers and reviews were included restricted to English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	C Darragh-Hickey, S Kaur and KE. Shipman conducted initial search, with refinement by all other authors to obtain consensus and agreement
Any additional considerations, if applicable	Seminal texts were also searched and the references of important articles and texts were obtained and checked for relevance

Hypomagnesaemia and hypocalcaemia stimulate parathyroid hormone (PTH) secretion, which in turn regulates calcium homeostasis. PTH facilitates bone resorption which can cause release of calcium and magnesium ions into the circulation. PTH also causes vitamin D activation which causes renal reabsorption of both calcium and magnesium (1). This therefore means that hypermagnesaemia and hypercalcaemia can coincide in hyperparathyroidism. In the kidney, both the PTH receptor type 1 and the calcium-sensing receptor (CASR) activate the Na-K-Cl cotransporter (NKCC2) in the TAL promoting reabsorption of magnesium (6). Outside of hyperparathyroidism, hypercalcaemia can cause hypomagnesaemia by competing for protein binding in the circulation and for renal uptake resulting in hypermagnesaemia.

Importantly, total magnesium assays may be misleading. Adjustment formulae which use albumin concentration exist, but unlike calcium, they have been shown to have little clinical relevance (3,7). Globally, ionised magnesium assays are in use, and it is worth understanding if the reported value is adjusted for pH and calcium concentration. Such adjustments may not be valid at extremes of pH for example, and the adjusted value may also not represent the true *in vivo* status. Therefore, no single test is easily considered gold standard. Theoretically, ionised magnesium may be the most likely candidate. However, there is a lack of evidence on what the reference range should be, how to treat abnormalities and what a treatment target should be, what the relationship is with total magnesium (which

will remain complicated by the variables that affect ionised magnesium such as calcium concentration, pH, temperature and dilution), and if treatment based on ionised magnesium targets will make a clinically significant improvement to patient outcomes (8). More research is required before we can be more confident on which test to use and how this relates to management protocols.

Hypomagnesaemia

Due to large magnesium stores in bone, it can take months/years for magnesium deficiency to manifest biochemically and clinically. To complicate the diagnosis, it is possible to have a total body deficiency but with a normal serum total magnesium concentration (9). A magnesium loading test can be useful to confirm deficiency in patients with normomagnesaemia and normal renal function. The test involves administration of magnesium as sulphate or chloride intravenously and monitoring the urinary magnesium excretion over 24 h. Patients with latent magnesium deficiency tend to retain more and excrete less of the load than those who are magnesium replete. However, the magnesium loading test is usually reserved for cases where there is a strong clinical suspicion of magnesium deficiency, despite normal serum/plasma magnesium concentration. The loading test is not routinely performed due to its many contraindications and the uncertainty around its clinical usefulness (10-12).

On the other hand, a low serum magnesium concentration can be misleading if there are substantial changes to protein

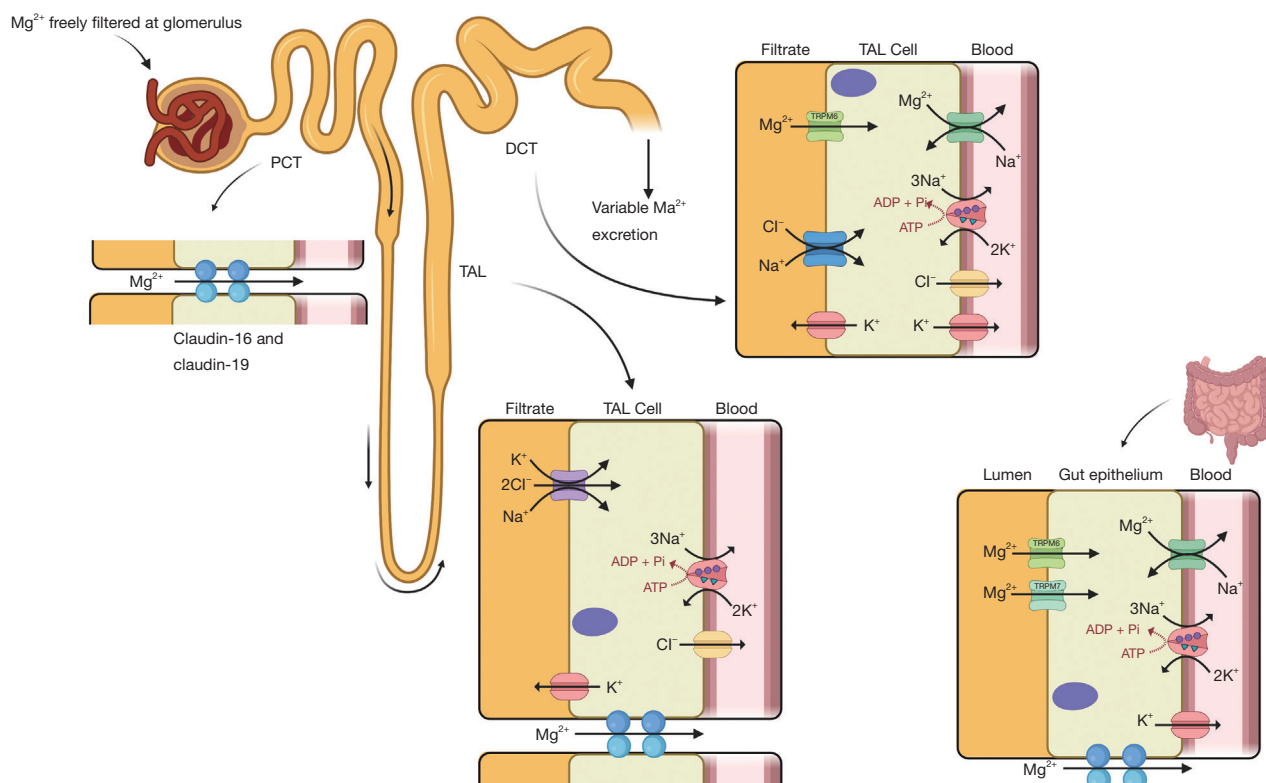


Figure 2 Magnesium reabsorption in the human kidney and absorption in the gastrointestinal tract. Passive reabsorption in the PCT and TAL via the tight junctions, through claudin-16 and claudin 19, is driven by positive luminal potential difference. Magnesium flux is further stimulated by salt reabsorption in the TAL, via apical NKCC2 and ROMK transporters and basolateral sodium pump and CLC-Kb channels. Transcellular transport and fine regulation of magnesium reabsorption occurs in the DCT (and colon) by TRPM6 and TRPM7 transporters with a gradient thought to be produced by the SLC41A1 sodium-magnesium exchanger at the basolateral membrane. In the gut, paracellular transport also occurs due to lack of tightening claudins. ADP; adenosine diphosphate, ATP; adenosine triphosphate, DCT, distal convoluted tubule; PCT, proximal convoluted tubule; Pi; inorganic phosphate, TAL, thick ascending limb, TRPM6/7; Transient Receptor Potential Melastatin type 6 and 7.

levels or acid-base status (3,10). This infers that some low serum magnesium concentrations may not be clinically relevant or indicative of total body magnesium deficiency, since serum magnesium concentration can drop quickly and stores are usually slow to respond. In these cases, total body magnesium is replete and supplementing magnesium will not benefit the patient (3).

Once hypomagnesaemia is confirmed, we present an algorithm from a laboratory investigatory approach to diagnosis (Figure 3). Initially the focus of the algorithm is on establishing if the hypomagnesaemia is real via consideration of albumin adjustment, albumin concentration also being a useful marker of acute severe illness, and calcium concentration as a marker of possible contamination of the specimen by cation chelators found in

types of specimen tubes as well as intracellular shift. Low calcium due to cation chelators can be subtle. However, in moderate contamination, the calcium concentration will be unexpectedly low, e.g., no evidence of disease in history or bloods and may be out of keeping with normal physiology, e.g., normal renal function and potassium concentration >10 mmol/L and calcium concentration <1 mmol/L in ethylenediaminetetraacetic acid (EDTA contamination) (13). If earlier results are available, then rapid shifts in selected analytes can be indicative. Citrate, EDTA and oxalate are common tube additives that chelate cations; primarily designed to chelate calcium to inhibit clotting to produce plasma specimens. Refeeding syndrome, hungry bone disease and treatment of diabetic ketoacidosis can cause magnesium redistribution to the

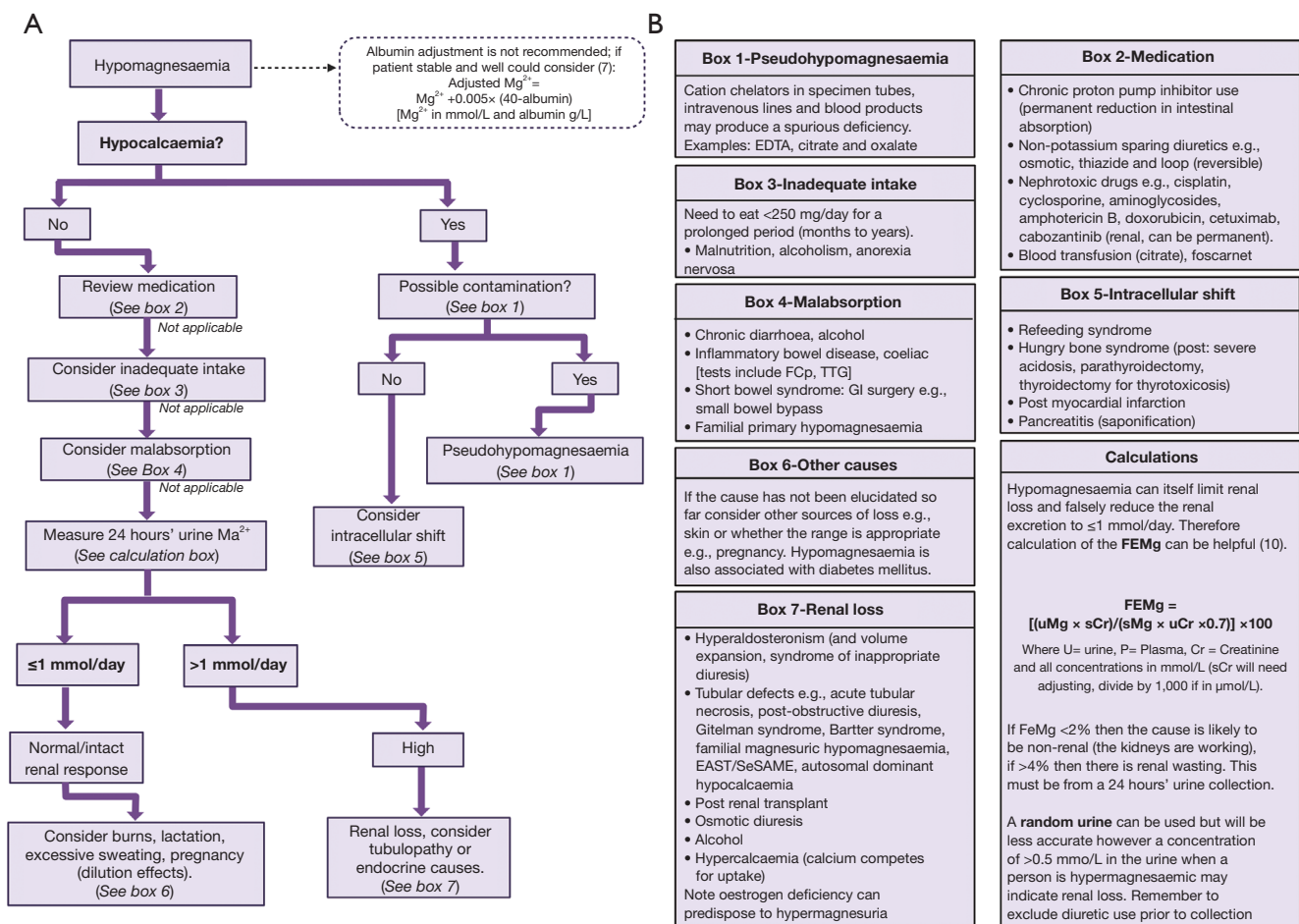


Figure 3 Diagnostic laboratory algorithm for hypomagnesaemia in humans with supportive information. (A) Diagnostic laboratory algorithm for hypomagnesaemia in humans; (B) boxes providing supportive information for diagnostic algorithm. EDTA, ethylenediaminetetraacetic acid; FCp, faecal calprotectin; TTG, serum tissue transglutaminase; GI, gastrointestinal; EAST, epilepsy, ataxia, sensorineural deafness and tubulopathy syndrome; SESAME, seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance syndrome; FEMg, fractional magnesium excretion.

intracellular space and should be evident from history and clinical assessment (multiple biochemical abnormalities, e.g., acidosis, hypocalcaemia, hypokalaemia as well as administration of medications and past medical history).

Having established the hypomagnesaemia is real and not due to acute illness or changes in binding or tissue compartment, then risk factors for deficiency should be sought in the history. Medication, dietary intake and history of gastrointestinal disorders therefore form the next steps of establishing the cause. Gastrointestinal diseases (e.g., inflammatory bowel disease), surgery (e.g., colectomy) or chronic alcoholism can also predispose individuals to hypomagnesaemia (1,14). At this point, assessment for possible renal wasting is recommended

with a 24-h urine collection for magnesium concentration. Chronic hypomagnesaemia can occur in the elderly due to a combination of reduced dietary intake and urinary magnesium wasting (1).

Establishing if renal loss is the cause of hypomagnesaemia can also be complicated by the fact that magnesium concentration affects renal reabsorption. For example, if magnesium is low due to renal loss, the deficiency itself reduces the amount of magnesium excreted, which may mean the urine magnesium concentration is spuriously low appearing to rule out hypermagnesaemia (15). Conversely, if a magnesium infusion has been given, the high plasma magnesium concentration will stimulate renal magnesium wasting with an estimated 50% of an intravenous

magnesium load being lost in the urine (10). Therefore, although a 24-h urine magnesium collection combined with fractional excretion calculation may be the most useful tests to estimate renal loss, the results can be unreliable due to treatments administered and the low magnesium itself (10).

Primary renal disease can lead to renal magnesium wasting, e.g., tubulopathy. Tubulopathies can be evident by loss of other electrolytes, e.g., potassium and phosphate, and presence of protein and glucose in the urine. Chronic kidney disease patients though often have hypomagnesaemia as a result of a reduced vitamin $1,25(\text{OH})_2\text{D}_3$ concentration, which causes renal losses as magnesium reabsorption is stimulated by $1,25(\text{OH})_2\text{D}_3$ (2). Persistently low eGFR and high parathyroid hormone concentration can indicate a chronic kidney condition as can hyperkalaemia, acidosis, and hyperuricemia. Magnesium is a cofactor for 25-hydroxylase and $1-\alpha$ -hydroxylase; hence, hypomagnesaemia can exacerbate its own deficiency and cause a magnesium dependent vitamin D resistant rickets (1). Similarly, as previously mentioned, magnesium is needed for PTH secretion. Therefore, extremely low concentrations of magnesium results in PTH suppression, which will also exacerbate the deficiency (1). Renal wasting of magnesium can therefore indicate either primary renal disease, endocrine disorders as mentioned above and hyperaldosteronism, drugs, e.g., alcohol or competition from calcium in hypercalcaemia.

If renal wasting is not identified, noting the difficulties with interpretation of urine magnesium concentration, then consider loss from skin, e.g., burns, breast milk during lactation or dilutional effects such as in pregnancy. Multiple other related electrolyte (hypokalaemia, hypocalcaemia, hypophosphataemia) and acid base disorders (respiratory/metabolic alkalosis or mixed disorders) can occur with hypomagnesaemia, depending on the underlying cause. Please refer to companion articles in the series to aid with diagnosis if another abnormality is particularly marked. Note disorders of potassium do not primarily cause magnesium disorders but commonly coexist, i.e., causes of gastrointestinal and renal losses or tissue translocation will affect both analytes (and calcium). However, magnesium concentration does directly control potassium concentration by affecting the function of potassium pumps, channels and membrane charge and permeability (16).

Hypermagnesaemia

Hypermagnesaemia is significantly rarer than

hypomagnesaemia (17). A diagnostic algorithm is presented to aid determination of the aetiology (*Figure 4*). Hypermagnesaemia is primarily due to ingestion of magnesium containing drugs, e.g., laxatives such as Epsom salts, combined with unregulated absorption due to gastrointestinal pathology, or lack of excretion from renal failure (18-20). Increased intake via intravenous infusion, ingestion of magnesium rich sea water and milk alkali syndrome, can all rarely lead to hypermagnesaemia. Therefore, drug and past medical history form an essential start to the diagnostic approach. Note lithium therapy increases the renal reabsorption of magnesium, as does hypothyroidism [defined by low thyroxine (T_4) and triiodothyronine (T_3)], adrenal insufficiency (hypocortisolaemia particularly after stimulation with synthetic adrenocorticotrophic hormone which can be associated with postural hypotension, skin pigmentation, and hyponatraemia with hyperkalaemia) and hyperparathyroidism (hypercalcaemia with normal or high PTH concentration). It is worth noting that hypercalcaemia can cause hypomagnesaemia due to PTH suppression, but hypercalcaemia due to hyperparathyroidism (or the very rare familial hypocalciuric hypercalcaemia which presents like primary hyperparathyroidism except there is no history or normocalcaemia on previous blood tests and calcium:creatinine clearance ratio is <0.01) is associated with hypermagnesaemia (21).

To approach the diagnosis therefore the next step, after excluding a likely cause from the history, is to focus on the results of laboratory investigations. Initially, intracellular shifts caused by acidosis or tissue lysis and hypercalcaemia should be ruled out, followed by primary renal disease (renal failure potentially also contributing to the hypermagnesaemia associated with acidosis and tissue lysis syndromes). Tissue lysis conditions will also be associated with other blood test abnormalities including raised creatinine kinase, aspartate aminotransferase and potassium for example. Finally endocrine causes such as adrenal insufficiency and hypothyroidism should be ruled out. The order being dictated by order of patient clerking, those most obvious on clinical assessment (for example tumour lysis or rhabdomyolysis should be detected in the history) and clinical severity.

Pregnancy and paediatrics

Pregnancy is associated with multiple metabolic changes; perhaps most notable is significant haemodilution.

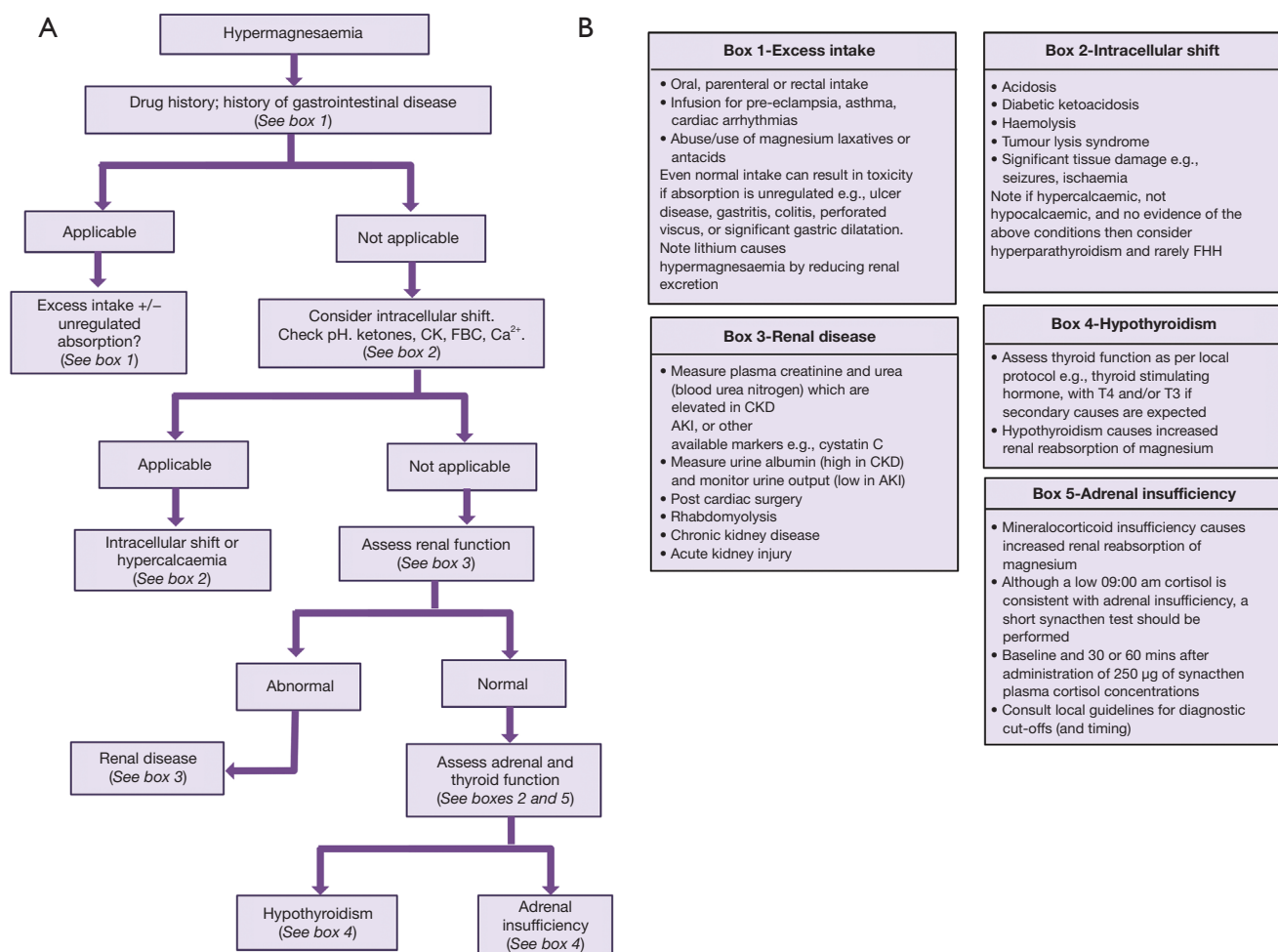


Figure 4 Diagnostic laboratory algorithm for hypermagnesaemia in humans with supportive information. (A) Diagnostic laboratory algorithm for hypermagnesaemia in humans; (B) boxes providing supportive information for diagnostic algorithm. CK, creatinine kinase; FBC, full blood count; FHH, familial hypocalciuric hypercalcaemia; CKD, chronic kidney disease; AKI, acute kidney injury.

Magnesium concentration is significantly affected, with approximately a 0.1 mmol/L reduction at both lower and upper ends of the reference interval. However, this is most marked at the lower limit (up to 0.4 mmol/L lower, i.e., a 30% reduction) at 34–38 weeks gestation (22–24). Interestingly, ionised and intracellular magnesium concentrations also fall in pregnancy, and urine excretion increases by 25% (19). A small study suggested that there might be benefit in magnesium supplementation during pregnancy, but it was underpowered for the number of comparisons (25). It is also worth noting that oestrogen acts to stimulate TRPM6 expression. Therefore, menopause may be a risk factor hypermagnesaemia, which in turn can induce hypomagnesaemia (2,26).

The upper limit of the reference interval for magnesium is higher in children, particularly in the first 15 days of life, but more subtly until 1 year of age where the range equates well to adult ranges. However, this could represent the influence of venesection technique and haematocrit (27). Breast milk contains between 15–64 mg/L of magnesium, and infants must supplement their micronutrients to satisfy their needs while growing. Formula powder has 42 mg/100 g magnesium for the infancy period. It is often seen in the developing world that babies are nutrient deficient, although fed sufficiently (1). Conversely, lactation acts as a source of magnesium excretion and can precipitate maternal magnesium depletion if an excess volume of milk is produced (28).

Table 2 Examples of rare congenital conditions associated with excess renal wasting or reabsorption of magnesium

Condition	Mutations
Renal magnesium wasting condition	
Familial primary hypomagnesaemia (and familial primary hypomagnesaemia with secondary hypocalcaemia)	<i>CLDN16</i> , <i>CLDN19</i> , <i>FXD2</i> , <i>HNF1B</i> , <i>CNNM2</i> , <i>EGF</i> , <i>KCNA1</i> (Kv1.1), <i>TRPM6</i>
Bartter syndrome (type I, II, III and V)	<i>SLC12A1</i> (NKCC2), <i>KCNJ1</i> (ROMK), <i>BSND</i> (CIC-Kb), <i>CASR</i>
Gitelman syndrome	<i>SLC12A3</i> (NCC)
EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy)/ SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)	<i>KCNJ10</i> (Kir4.1)
Renal cysts and diabetes syndrome	<i>HNF1-B</i>
Autosomal dominant hypocalcaemia	<i>CASR</i> , <i>GNA11</i>
Increased renal magnesium absorption	
Familial hypocalciuric hypercalcaemia	<i>CASR</i> , <i>GNA11</i> , <i>AP2S1</i>

Rare conditions

Understanding the functioning of regulatory magnesium proteins can help clarify how congenital conditions can develop due to an imbalance in both isolated magnesium conditions and with salt wasting tubulopathies (Table 2). Mutations in the *TRPM6* genes have been identified in an autosomal recessive disorder called hypomagnesaemia with secondary hypocalcaemia which can present from infancy to adulthood depending on the severity of mutation (6,29). Autosomal dominant *KCNA1* gene mutations result in Kv1.1 K⁺ channel defects. Isolated dominant hypomagnesaemia with hypocalciuria (IDH) is caused by mutations in the *FXD2* gene, leading to a mutant γ -subunit of the Na⁺-K⁺-ATPase protein (30). Patients present from young ages with these syndromes with severe hypomagnesaemia, tetany, muscle weakness, cramps and tremor (2).

The seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance syndrome, or SESAME (also known as EAST, for epilepsy, ataxia, sensorineural deafness and tubulopathy) syndrome, is a hypomagnesaemia disorder caused by mutations in *KCNJ10* gene expressing the Kir4.1 K⁺ channel. Patients experience electrolyte abnormalities and hypomagnesaemic symptoms, as well as deafness, neurological manifestations, seizures and ataxia (2).

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis result from mutations in the claudin-16 and -19 genes (31,32). Renal failure, nephrocalcinosis, polyuria and polydipsia are some of the features described.

Thiazide diuretics inhibit the Na⁺-Cl⁻ cotransporter (NCC/SLC12A3) which prevents sodium and magnesium reabsorption in the DCT, a process mimicked by Gitelman syndrome caused by a mutant NCC protein (2). Similarly, Bartter syndrome occurs with mutations in the NKCC2 and ROMK/KCNJ1 transport proteins, preventing magnesium reabsorption. These tubulopathies cause hypokalaemic metabolic alkalosis and can present from young ages including with failure to thrive and short stature.

CASR regulates PTH secretion based on the blood ionised calcium concentration. Autosomal dominant hypoparathyroidism (ADH), or familial hypocalciuric hypercalcaemia with hypomagnesaemia, occurs when there are activating mutations in the *CASR*. Conversely, inactivating *CASR* mutations cause familial hypocalciuric hypercalcaemia, and patients experience hypermagnesaemia. In neonatal severe hyperparathyroidism (NSHPT) with inactivating *CASR* mutations, patients often require a total parathyroidectomy to control for the severe hypercalcaemia with hypermagnesaemia (23).

Epidermal growth factor (EGF) is needed for the absorption of magnesium in the DCT. Colon cancer patients treated with an anti-EGF antibody cetuximab have been shown to develop hypomagnesaemia from renal magnesium wasting (2).

Conclusions

Confirming the presence of hypomagnesaemia in particular

can be challenging with multiple factors affecting magnesium concentration but not necessarily total body status. Diagnostic algorithms have been presented that are hoped to support users by providing an approach to diagnosing the cause of hypomagnesaemia and hypermagnesaemia. It is worth noting that magnesium may not be affected in isolation and use of related algorithms may further support the diagnosis (e.g., see acid base and potassium algorithms within this series). These algorithms cannot replace specialist knowledge, experience, and local guidelines but aim to support systematic investigation.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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