

Hypomagnesemia

An Evidence-Based Approach to Clinical Cases

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Hypomagnesemia is defined as a serum magnesium level less than 1.8 mg/dL (< 0.74 mmol/L). Hypomagnesemia may result from inadequate magnesium intake, increased gastrointestinal or renal losses, or redistribution from extracellular to intracellular space. Increased renal magnesium loss can result from genetic or acquired renal disorders. Most patients with hypomagnesemia are asymptomatic and symptoms usually do not arise until the serum magnesium concentration falls below 1.2 mg/dL. One of the most life-threatening effects of hypomagnesemia is ventricular arrhythmia. The first step to determine the likely cause of the hypomagnesemia is to measure fractional excretion of magnesium and urinary calcium-creatinine ratio. The renal response to magnesium deficiency due to increased gastrointestinal loss is to lower fractional excretion of magnesium to less than 2%. A fractional excretion above 2% in a subject with normal kidney function indicates renal magnesium wasting. Bartter syndrome and loop diuretics which inhibit sodium chloride transport in the ascending loop of Henle are associated with hypokalemia, metabolic alkalosis, renal magnesium wasting, hypomagnesemia, and hypercalciuria. Gitelman syndrome and thiazide diuretics which inhibit sodium chloride cotransporter in the distal convoluted tubule are associated with hypokalemia, metabolic alkalosis, renal magnesium wasting, hypomagnesemia, and hypocalciuria. Familial renal magnesium wasting is associated with hypercalciuria, nephrocalcinosis, and nephrolithiasis. Asymptomatic patients should be treated with oral magnesium supplements. Parenteral magnesium should be reserved for symptomatic patients with severe magnesium deficiency (< 1.2 mg/dL). Establishment of adequate renal function is required before administering any magnesium supplementation.

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INTRODUCTION

Magnesium plays a major role in overall cell functions, including DNA and protein synthesis, glucose and fat metabolism, oxidative phosphorylation, neuromuscular excitability, and enzyme activity.¹ Magnesium is primarily distributed in 2 major compartments. Approximately, 99% of total body magnesium is intracellular (bone, 85%;

soft tissue and liver, 14%), with only 1% present in the extracellular space. Up to 70% of total plasma magnesium is ionized and is freely filterable by glomerular function, while 30% is protein bound.^{2,3} The kidney is a major regulator of total body magnesium homeostasis. Approximately, 95% of the filtered magnesium is reabsorbed by the nephron (60% to 70% in the thick ascending loop

of Henle, 15% to 25% in the proximal tubule, and 5% to 10% in the distal convoluted tubule).⁴ The kidneys can lower magnesium excretion to as little as 0.5% of the filtered load in the presence of decreased intake, redistribution from extracellular to intracellular space, or increased intestinal loss.⁴

Since magnesium is predominantly distributed intercellular and in the bone, serum concentrations do not accurately reflect total body magnesium stores. The normal range for serum magnesium is 1.8 mg/dL to 2.3 mg/dL (0.74 mmol/L to 0.94 mmol/L).^{2,3} Hypomagnesemia is defined as a serum magnesium concentration of less than 1.8 mg/dL (< 0.74 mmol/L).³ Hypomagnesemia may result from inadequate intake, intracellular shift (treatment of diabetic ketoacidosis, refeeding syndrome, and hungry bone syndrome), increased gastrointestinal loss (chronic diarrhea, malabsorption syndrome, Steatorrhea, vomiting, and nasogastric suction), or most common, increased losses in urine.^{5,6} Renal magnesium wasting can result from genetic or acquired kidney disorders.⁷⁻⁹ Acquired renal magnesium wasting can result from inhibition of magnesium reabsorption in the thick ascending loop of Henle or distal convoluted tubule following extracellular fluid volume expansion, loop and thiazide diuretics, aminoglycoside antibiotics, tacrolimus, carboplatin, or proton-pump inhibitors administration.⁹⁻¹⁴

Several inherited renal tubular disorders are associated with excessive urinary loss of magnesium.¹⁵⁻¹⁷ Gitelman syndrome is an autosomal recessive disorder caused mainly by mutations of the *SLC12A3* gene that encodes the thiazide-sensitive sodium chloride cotransporter in the distal convoluted tubule.^{16,17} Patients with Gitelman syndrome often present with symptoms of hypomagnesemia, hypokalemia, metabolic alkalosis, hypocalciuria, and urinary magnesium wasting.¹⁸ Bartter syndrome can cause mild hypomagnesemia in a manner similar to that of loop diuretics.¹⁹ Classic Bartter syndrome (type III) is caused by mutations of the chloride gene, *CLCNB*.²⁰ The infantile forms of Bartter syndrome (Type I and type II) are life threatening, and they share similar clinical and biochemical findings.^{19,21} The antenatal form of type I Bartter syndrome is caused by mutations in the *SLC12A1* gene that encodes the Na-K-2Cl cotransporter,¹⁹ and type II mutation in potassium channel *ROMK1* gene.²¹ Type IV Bartter

syndrome is the combination of the infantile variant of Bartter syndrome and sensorineural deafness, which is caused by mutation of the *BSND* gene.²² Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is an autosomal recessive disorder of renal magnesium wasting.²³ Individuals who are affected often present with growth failure, polyuria, muscle weakness, renal magnesium and calcium wasting, nephrocalcinosis, nephrolithiasis, recurrent urinary tract infections, and progressive kidney failure.²⁴ Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is caused by a mutation in the gene *CLDN16*, which encodes paracellin-1 (claudin-16), a tight junction protein which is expressed in the thick ascending loop of Henle and in the distal convoluted tubule, where reabsorption of magnesium occurs.²⁵

Autosomal dominant hypocalcemia with hypercalciuria is another hereditary renal magnesium wasting characterized by hypocalcemia, hypercalciuria, hypomagnesemia, and a low level of plasma parathyroid hormone level, which is caused by mutations of the calcium-sensing receptor located in the thick ascending loop of Henle.²⁶ Isolated dominant renal magnesium wasting with hypocalciuria has also been reported in 2 families due to a mutation in the gene *FXYD2*, which encodes for gamma subunit of the sodium-potassium adenine triphosphatase in the distal convoluted tubule.^{2,27} Isolated recessive hypomagnesemia with normocalciuria is a rare hereditary disorder of renal magnesium wasting due to a mutation of the epidermal growth factor which is expressed in the distal convoluted tubule.²⁸ The isolated recessive hypomagnesemias is distinguished from autosomal dominant hypocalcemia by demonstration of renal magnesium wasting in the presence of normal calcium excretion.^{27,28}

SYMPTOMS

Most patients with hypomagnesemia are asymptomatic. Symptoms usually do not manifest until the serum magnesium concentration is below 1.2 mg/dL (0.49 mmol/L).³ Hypomagnesemia often coexist with other metabolic disorders, such as hypocalcemia or hypokalemia. This copresentation makes it difficult to distinguish the clinical manifestations related to the magnesium deficiency.²⁹ Both hypermagnesemia and hypomagnesemia can result in decreased

parathyroid hormone secretion.³⁰ In the case of hypermagnesemia, elevated magnesium levels result in stimulation of calcium-sensing receptors on the pituitary. This, in turn, attenuates parathyroid hormone secretion. In the case of hypomagnesemia, there is a diminution of parathyroid hormone secretion and a resistance to hormone activity.³⁰

The prominent organ systems associated with magnesium deficiency are the cardiovascular and neuromuscular.³¹ Manifestations of hypomagnesemia may include muscle weakness, positive Chevestek sign and Trousseau sign, tetany, and generalized seizures as may be seen with hypocalcemia.³² The most life-threatening cardiovascular effect of hypomagnesemia is ventricular arrhythmia.³¹

TREATMENT

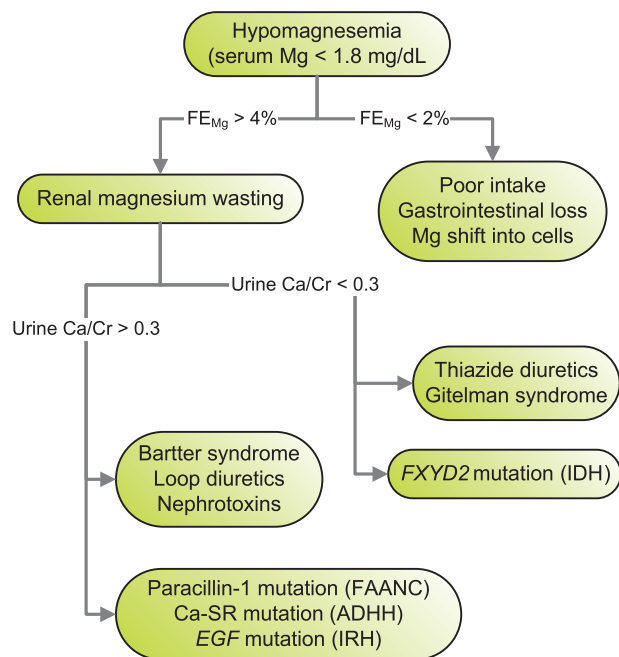
Patients with mild to moderate deficiency (1.2 mg/dL to 1.7 mg/dL) should be treated with diet or oral magnesium supplements.³ Symptomatic patients should receive 3 g to 4 g (24 mEq to 32 mEq) of intravenous magnesium sulfate slowly over 12 to 24 hours.³ This dose can be repeated as necessary to maintain serum magnesium level above 1.2 mg/dL. Rapid intravenous push administration raises the serum magnesium concentration above physiologic levels, causing a large percent of magnesium to be excreted in the urine. Establishment of adequate kidney function is required before administering any magnesium supplementation. Patients with renal insufficiency should receive 25% to 50% of the initial dose recommended for patients with normal kidney function.

DIAGNOSTIC APPROACH

The first step to define the likely cause of the hypomagnesemia is to measure fractional excretion of magnesium (FE_{Mg}) and urinary calcium-creatinine ratio on a random urine sample (Figure). The formula used to calculate the FE_{Mg} is the same as that for fractional excretion of sodium³⁵:

$$FE_{Mg} = (\text{urine magnesium} \times \text{serum creatinine}) / [0.7 (\text{serum magnesium} \times \text{urine creatinine})] \times 100$$

The serum magnesium level is multiplied by 0.7, because up to 70% of blood circulating magnesium is ionized and is freely filterable by glomerular function. A calculated FE_{Mg} less than 2% suggests



Diagnostic algorithm for evaluation of hypomagnesemia. Mg indicates magnesium; FE_{Mg} , fractional excretion of magnesium; Ca/Cr, calcium-creatinine ratio; FDDNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (paracillin-1 mutation); ADHH, autosomal dominant hypocalcemia with hypercalciuria (Ca-SR mutation); Ca-SR, calcium-sensing receptor; IRH, isolated recessive hypomagnesemia with normocalciuria (EGF mutation); and IDH, isolated dominant hypomagnesemia with hypocalciuria.

poor intake, gastrointestinal losses, or a shift of magnesium into cells.³³ An FE_{Mg} above 4% in a subject with normal kidney function indicates renal magnesium wasting.³³ Bartter syndrome, loop diuretics, and familial hypomagnesemia with hypercalciuria and nephrocalcinosis, which inhibit sodium reabsorption in the loop of Henle, are associated with renal magnesium wasting and hypercalciuria (calcium-creatinine ratio > 0.22).³⁴ Gitelman syndrome and thiazide diuretics which inhibit sodium chloride cotransporter in the distal convoluted tubule are associated with renal magnesium wasting and hypocalciuria (calcium-creatinine ratio < 0.22).³⁴

CLINICAL QUIZ

The following clinical quiz was first published by the author in a book entitled *Clinical Decisions in Pediatric Nephrology: A Problem-Solving Approach to Clinical Cases*,³⁵ and hereby is presented with some modification with the written permission of the publisher.

Case 1

You are asked to evaluate a family with a high incidence of hypercalciuria and nephrolithiasis, and you find that 2 children born to a sibling with hypercalciuria and nephrolithiasis died in early childhood of kidney failure and had nephrocalcinosis. An extensive workup reveals that the family members affected with hypercalciuria also demonstrated hypomagnesemia and hypermagnesuria.

Question. Which one of the following is the most likely basis for this disorder?

- (a). Isolated recessive hypomagnesemia
- (b). Familial hypomagnesemia secondary to mutations in paracellin-1 gene
- (c). Familial defect in calcium-sensing receptor
- (d). Hypomagnesemia with secondary hypercalciuria associated with a defect in tubular transport of phosphate
- (e). Abnormal proximal tubular oxalate transporter

The answer is *b*. Paracellin-1, a tight-junction protein-mediating paracellular transport, is mutated in the familial hypomagnesemia, complicated by hypercalciuria and nephrolithiasis.²⁵ Isolated recessive hypomagnesemia is not associated with hypercalciuria, and defects in the calcium-sensing receptor are not associated with nephrolithiasis or kidney failure in this fashion. Defects in the tubular reabsorption of phosphate are associated with hypocalcemia. An abnormality in oxalate transport would not produce hypercalciuria.

Case 2

A 16-year-old girl complained of easy fatigability and generalized muscle weakness. Her history was otherwise unrevealing, and she denied vomiting or the use of any medications. Physical examination revealed a thin anxious girl with a normal blood pressure. Her examination was otherwise unremarkable. Her serum sodium was 141 mEq/L; potassium, 2.1 mEq/L; chloride, 85 mEq/L; bicarbonate, 45 mEq/L; calcium, 9.5 mg/dL (reference range, 8.5 mg/dL to 10.3 mg/dL); phosphate, 3.2 mg/dL (reference range, 2.8 mg/dL to 4.5 mg/dL); magnesium, 1.2 mg/dL (reference range, 1.8 mg/dL to 2.3 mg/dL); and albumin, 4.6 g/dL (reference range, 3.5 g/dL to 5.0 g/dL).

Question 1. Which of the following statements is true (select all that apply)?

- (a). Hypokalemia can alter the renal handling of magnesium and cause hypomagnesemia.
- (b). Hypomagnesemia can alter the renal handling of potassium and cause hypokalemia.
- (c). Both statements are true.
- (d). Neither statement is true.

The answer is *b*. Magnesium is required for adequate renal handling of potassium. Hypomagnesemia can cause hypokalemia because of the increased urinary loss of potassium, likely by opening potassium channels in the thick ascending loop of Henle.²⁹ This may become apparent when hypokalemia persists despite potassium supplementation.

Question 2. Which of the following studies would be the best initial laboratory to determine the cause of the hypomagnesemia in this patient (select all that apply)?

- (a). Urine diuretic screen
- (b). Plasma renin and aldosterone levels
- (c). Plasma cortisol level
- (d). Twenty-four-hour urine for sodium, potassium, and aldosterone levels
- (e). Twenty-four-hour urine for magnesium, calcium, chloride, and creatinine levels

The answers are *a* and *e*. The findings of hypokalemia, metabolic alkalosis, and a normal blood pressure suggest the diagnosis of secondary hyperaldosteronism caused by surreptitious vomiting, diuretic abuse, Bartter syndrome, or Gitelman syndrome. Measurement of urinary chloride, calcium, and magnesium is useful in the differentiation between these disorders. The urinary chloride concentration is typically less than 15 mEq/L in hypovolemia due to surreptitious vomiting. In contrast, a urinary chloride greater than 15 mEq/L suggests diuretic abuse, Bartter syndrome, or Gitelman syndrome. Measurement of the urine calcium will help to distinguish between Bartter syndrome and Gitelman syndrome.³⁴ Screening urine for diuretics is indicated if surreptitious ingestion is suspected. Measurement of the urinary magnesium will help to distinguish between gastrointestinal and renal losses as the major contributor.³³

Question 3. The fractional excretion of magnesium was 6.5%, the urine chloride was 56 mEq/L, and the urine calcium-creatinine ratio was 3.2 (reference range, < 0.22). What is the most likely diagnosis now (select all that apply)?

- (a). Bartter syndrome

- (b). Primary hyperaldosteronism
- (c). Loop diuretic abuse
- (d). Apparent mineralocorticoid excess
- (e). Liddle syndrome
- (f). Gitelman syndrome

The answers are *a* and *c*. Bartter syndrome can cause hypokalemia, metabolic alkalosis, renal magnesium wasting, and hypomagnesemia without hypertension in a manner similar to that of loop diuretics.²¹ Bartter syndrome is caused by mutations in a furosemide-sensitive ion transport mechanism in the loop of Henle and is associated with hypercalciuria.²¹

Question 4. Which study would you like now to differentiate between Bartter syndrome and diuretic abuse?

- (a). Plasma renin activity and plasma aldosterone level
- (b). Twenty-four-hour urine for calcium, magnesium, and creatinine
- (c). Twenty-four-hour urine for sodium, potassium, and creatinine
- (d). Urine diuretic screen

The answer is *d*. A diuretic screen is the only way to rule out diuretic abuse.^{9,34} The diuretic screen was negative.

Question 5. Suppose the laboratory staff call to tell you that the urinary calcium-creatinine ratio was misreported and the correct value is 0.20, not 3.2. What is the most likely diagnosis now?

- (a). Gitelman syndrome
- (b). Bartter syndrome
- (c). Primary hyperparathyroidism
- (d). Isolated recessive renal magnesium wasting

The answer is *a*. Gitelman syndrome is the only condition among the above which is associated with hypocalciuria.³⁴ Gitelman syndrome is a variant of Bartter syndrome, characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, renal magnesium wasting, and normal blood pressure.^{16,18} Gitelman syndrome is caused by loss-of-function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron and is associated with hypocalciuria. Bartter syndrome and primary hyperparathyroidism are associated with hypercalciuria. Isolated recessive magnesium wasting is characterized by renal magnesium wasting in the absence of hypocalcemia or hypercalciuria.²⁷

Question 6. Which of the following would be

most beneficial therapeutic effects in a patient with Gitelman syndrome (select all that apply)?

- (a). Thiazide diuretics
- (b). Potassium-sparing diuretics
- (c). Low-salt diet
- (d). Oral magnesium and potassium supplementation
- (e). Loop diuretics

The answers are *b* and *d*. Magnesium supplements are typically necessary to increase the serum magnesium and the serum potassium concentrations. Amiloride can be very useful in this condition, because it may help to enhance distal tubular reabsorption of magnesium, as well as inhibit potassium secretion.¹⁸

She was treated with magnesium and potassium supplementation and amiloride. Serum potassium level improved to 3.2 mEq/L and serum magnesium level rose to 2.2 mg/dL. Six months later, she was brought to the emergency department because of shock due to internal bleeding as a result of automobile accident. She received 7 units of blood transfusion and underwent repair of hepatic laceration. She was oliguric postoperation for 4 days. The laboratory data revealed a hemoglobin of 12.6 g/dL; blood urea nitrogen, 55 mg/dL; serum creatinine, 3.9 mg/dL; serum sodium 137, mEq/L; serum chloride, 95 mEq/L; serum potassium, 4.9 mEq/L; serum bicarbonate, 20 mEq/L; serum calcium, 5.5 mg/dL; serum phosphate, 5.5 mg/dL; and serum albumin, 3.9 g/dL. Urinalysis showed trace protein, negative for blood and glucose. The electrocardiography showed significant prolongation of the QT interval.

Question 7. What should be done next to define the likely cause of the hypocalcemia?

- (a). Draw blood for a parathyroid hormone assay.
- (b). Give intravenous magnesium.
- (c). Draw blood for a plasma magnesium level.
- (d). Draw blood for a calcidiol level.
- (e). Draw blood for a calcitriol level.

The answer is *c*. Hypermagnesemia can suppress parathyroid hormone level and can cause hypocalcemia. Checking the plasma magnesium level to look for hypermagnesemia as the cause of hypocalcemia is the best choice in this situation.³⁰

The plasma magnesium level was 5.8 mg/dL. The physician in the emergency department rechecked her medications and realized that no one had

discontinued the supplemental magnesium that she was receiving for Gitleman syndrome. Thus, hypermagnesemia and subsequent hypocalcemia may have ensued when she developed acute kidney failure.³⁰ Hemodialysis was instituted and the magnesium supplements were discontinued. Hypermagnesemia resolved and hemodialysis was discontinued after two treatments. Serum creatinine level slowly returned to normal level over 7 days. She was subsequently returned on magnesium supplements.

Case 3

You are called by the emergency department to see a 36-year-old woman complaining of cramps and tightening in her throat. Past medical history is significant for mild hypertension for which she is being treated with hydrochlorothiazide, 12.5 mg/d. She had a total thyroidectomy for a large toxic, multinodular goiter 6 months earlier and is maintained on 1-thyroxine, 100 µg/d. Bone densitometry was consistent with osteoporosis, and she was started on alendronate, 10 mg/d. Five days prior to admission, she began to note intermittent severe cramps in her hands and feet. On the day of admission, she noted some tightening in her throat and came to the emergency room. She denies the use of any other medications or over-the-counter supplements.

On examination, her blood pressure is 140/86 mm Hg; pulse, 86 beats per minute; respiration, 12 breaths per minute; temperature, 37°C; weight, 52.5 kg; and height, 159 cm. The rest of the physical examination revealed no abnormal sign. Laboratory studies revealed a hemoglobin of 13.0 g/L; leukocyte count, $5.1 \times 10^9/L$; sodium, 138 mEq/L; potassium, 4.1 mEq/L; chloride, 100 mEq/L; bicarbonate, 27 mEq/L; blood urea nitrogen, 6 mg/dL; creatinine, 0.7 mg/dL; calcium, 7.3 mg/dL (reference range, 8.5 mg/dL to 10.3 mg/dL); phosphate, 6.3 mg/dL (reference range, 2.8 mg/dL to 4.5 mg/dL); magnesium, 1.5 mg/dL (reference range, 1.8 mg/dL to 2.3 mg/dL); and albumin, 4.2 g/dL (reference range, 3.5 g/dL to 5.0 g/dL). Urinalysis showed trace protein, and it was negative for glucose and blood. Her electrocardiography showed prolonged QT intervals.

Question 1. What would you do at this point (select all that apply)?

- (a). Draw parathyroid hormone level.

- (b). Draw serum magnesium level.
- (c). Draw calcitriol level.
- (d). Draw calcidiol level.
- (e). Give intravenous magnesium.

The answers are *a*, *b*, and *e*. The combination of hypocalcemia and hypomagnesemia in the absence of kidney failure certainly suggests the presence of hypoparathyroidism. Hypomagnesemia can cause suppression of parathyroid hormone secretion and/or resistance to parathyroid hormone and produce acute hypocalcemia.³⁰ It is appropriate to consider this and draw a serum magnesium level. In the absence of renal insufficiency, magnesium infusion is safe and reasonable while waiting for the results to come back from the laboratory.

She remained symptomatic despite of the intravenous magnesium administration. However, she responded to intravenous calcium and experienced relief of her acute symptoms. Her laboratory studies, which were obtained in the emergency department, returned as follows: parathyroid hormone, 15 ng/mL and serum magnesium, 2.0 mg/dL.

Question 2. What is the primary diagnosis?

- (a). Hypoparathyroidism
- (b). Alendronate toxicity
- (c). Vitamin D deficiency
- (d). Hypomagnesemia
- (e). Pseudohypoparathyroidism

The answer is *a*. She has hypocalcemia and a parathyroid hormone value that is inappropriately in the low-normal range, consistent with hypoparathyroidism.¹⁴ She likely had subclinical hypoparathyroidism that was undiagnosed and that now has been masked by alendronate therapy.

CONFLICT OF INTEREST

None declared

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