Abnormalities in Magnesium Metabolism

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Contents

Core Messages

- Magnesium physiology depends on a balance between intestinal absorption and renal excretion.
- Magnesium is the major regulator of its own homeostasis. Hypomagnesemia stimulates and hypermagnesemia inhibits the reabsorption of Mg^{2+} in the loop of Henle.
- Magnesium is a cofactor in all reactions that require adenosine triphosphate (ATP), and it is essential for the activity of Na^{+}–K^{+}–ATPase.
- Symptomatic magnesium depletion needs repletion via oral or parenteral route. Extracellular magnesium does not readily equilibrate with intracellular stores; therefore, fast infusion rapidly increases the plasma concentration but does not correct the total body magnesium.
- Hypermagnesemia usually occurs in two clinical settings: compromised renal function or excessive magnesium intake.
- Hypomagnesemia induces hypocalcemia via multiple mechanisms including both decreased secretion and peripheral resistance to parathyroid hormone (PTH) and Vitamin D; thus, low, normal, or slightly elevated levels of PTH can be seen in the presence of laboratory picture of hypoparathyroidism.
- As soon as the diagnosis of hypomagnesemia is confirmed, treatment with enteral magnesium for at least 7–10 days is necessary for normalization of magnesium stores.

Case Vignette

A 6-day-old baby was admitted to the Pediatric Cardiac ICU after surgery for complex congenital heart disease. During the operation, the patient was on cardiopulmonary bypass for 4 h. The early postoperative admission was complicated by cardiac instability, pulmonary edema, and mild ATN necessitating ionotropic support and daily furosemide administration. The patient was on IV fluids and minimal enteral feeding. Laboratory evaluation on day 6 postoperation showed hypocalcemia (ca. 7.3 mg dL^{-1}, ionized calcium 3.5 mg dL^{-1}, albumin level 3.4 mg dL^{-1}), and treatment with oral calcium and vitamin D supplementation was started. Labs consistently showed hypocalcemia, hyperphosphatemia, and hypercalciuria suggesting hypoparathyroidism. However, serum

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PTH level returned slightly elevated (116 ng L^{-1}; normal range 10–65 ng L^{-1}). 1, 25 VitD level, which was drawn after treatment with vitamin D was initiated, was normal. Despite treatment, calcium levels remained low and furosemide treatment was discontinued. On postoperative day 8, laboratory evaluation showed significant hypomagnesemia (1.1 mg dL^{-1}) treated with intravenous magnesium sulfate. For the next 2 days, magnesium and calcium levels remained low despite repeated daily magnesium infusions and continuous treatment with calcium and vitamin D. Following consultation with Pediatric Nephrology, enteral magnesium replacement was started on day 11 postoperation. After 4 days of enteral magnesium treatment calcium levels normalized, and calcium and magnesium supplementation was subsequently decreased and discontinued.

5.1 Introduction

Magnesium is the second most common intracellular cation after potassium, and the fourth most common cation in the body. Magnesium is a cofactor in more than 300 enzymatic reactions and is involved in multiple processes including hormone receptor binding, calcium channel gating, regulation of adenylate cyclase, muscle contraction, neuronal activity, cardiac excitability, and others [14, 37]. Under physiological conditions, serum magnesium concentration is maintained in a narrow range. Magnesium homeostasis depends on intestinal absorption and renal excretion. Interestingly, magnesium itself is the major regulator of its own homeostasis. Magnesium deficiency can result from low intake, reduced intestinal absorption, and/or renal loss. Magnesium excess is usually a consequence of decreased excretion in acute or chronic renal failure. For the clinician, a complete understanding of the normal magnesium physiology, knowledge of signs and symptoms of magnesium deficiency or excess, and basic principles of therapy are important for the treatment of a critically ill child.

5.2 Units of Measurement and Normal Plasma Concentration

Most laboratories in the United States report the results of body fluid magnesium concentration in units of milliequivalents per liter or milligrams per deciliter, while other countries use also millomoles per liter. The relationship among these units can be expressed by the following equations:

$$1\ \text{mg}\ dL^{-1} = [1\ \text{mmol}\ L^{-1} \times 10]/\text{mol wt.},$$
$$1\ \text{meq}\ L^{-1} = 1\ \text{mmol}\ L^{-1}/\text{valence}$$

Since the molecular weight of magnesium is 24.3 and the valence is +2, 1 meq L^{-1} is equivalent to 0.50 mmol L^{-1} and to 1.2 mg dL^{-1}. The normal range of plasma magnesium concentration of 1.2–1.9 meq L^{-1} is equivalent to 0.60–0.95 mmol L^{-1} and 1.5–2.3 mg dL^{-1}.

5.3 Magnesium Physiology

5.3.1 Overview

Magnesium is predominantly stored in bone (53%), the intracellular compartment of muscle (27%), and soft tissues (19%). Serum magnesium comprises less than 1% of total body magnesium and presents in three states: ionized (62%), protein bound (33%), mainly to albumin, and bound to anions (5%) such as phosphate and citrate [44, 47].

The average daily dietary intake of magnesium is about 300–400 mg in adults and about 5–10 mg kg^{-1} in children. The main sources of magnesium are green vegetables, soybeans, seafood, and whole grain cereals [27, 49]. Thirty percent to fifty percent of the dietary magnesium is absorbed, but this can vary from 10–20% in a high-magnesium diet to 65–75% in a low-magnesium diet. Absorption of magnesium in the GI tract occurs mainly in the small intestine via two different mechanisms: a saturable active transcellular transport and a nonsaturable paracellular passive transport [16, 19, 23]. At low intraluminal concentrations, magnesium is absorbed primarily via the active transcellular route, whereas at higher concentrations, paracellular passive route becomes significant (Fig. 5.1). The major identified epithelial transcellular magnesium transporter (TRPM6) belongs to the transient receptor potential family of cation channels and accounts for both intestinal absorption and renal tubular transcellular reabsorption of magnesium [38, 45].

About 70% of serum magnesium (not protein bound) is freely filtered at the glomerulus to the Bowman space [23, 47]. In contrast to other ions, only a small fraction of filtered magnesium (15–20%) is reabsorbed in the proximal tubule (Fig. 5.2). In immature animals, the proximal tubule accounts for 60–70% of magnesium ions (Mg^{2+}) reabsorption [26]. The mechanism of this phenomenon remains unknown. The majority

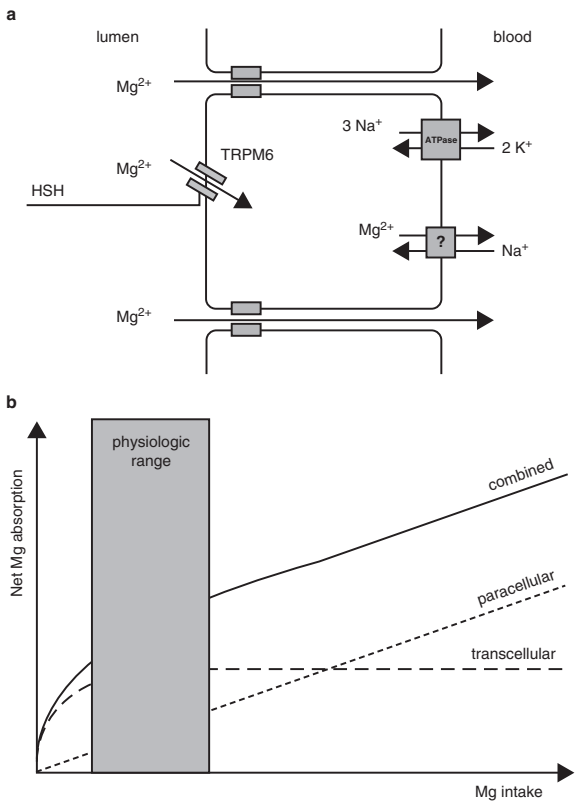

Fig. 5.1 **a** Schematic model of intestinal magnesium absorption via two independent pathways: passive absorption via the paracellular pathway and active, transcellular transport consisting of an apical entry through a putative magnesium channel and a basolateral exit mediated by a putative sodium-coupled exchange. **b** Kinetics of human intestinal magnesium absorption. Paracellular transport lineary rising with intraluminal concentrations (*dotted line*) and saturable active transcellular transport (*dashed line*) together yield a curvilinear function for net magnesium absorption (*solid line*). HSH hypomagnesemia with secondary hypocalcemia, TRPM6 epithelial transcellular magnesium transporter (from [39], with permission)

of magnesium (70%) is reabsorbed in the loop of Henle, especially in the cortical thick ascending limb (TAL) [23, 36]. Transport in this segment appears to be passive and paracellular, driven by the favorable electrical gradient resulting from the reabsorption of sodium chloride (Fig. 5.3a). Paracellular magnesium reabsorption is facilitated by the tight junction protein paracellin-1, which also serves as a main route for calcium reabsorption in this segment. The remaining 5–10% of the filtered magnesium is reabsorbed in the distal convoluted tubule (DCT). Magnesium transport in the DCT is active and transcellular [23]. The proposed model of magnesium absorption in DCT includes apical entry via TRPM6 and extrusion via unidentified sodium–magnesium exchanger (Fig. 5.3b).

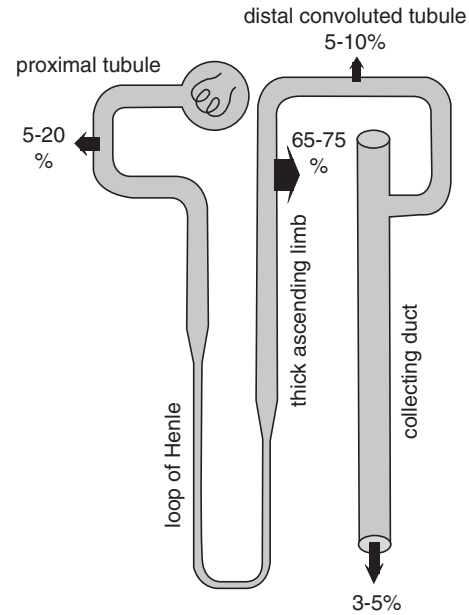

Fig. 5.2 Magnesium reabsorption along the nephron (from [39], with permission)

5.3.2 Regulation of Renal Magnesium Handling

In contrast to other body cations, no single hormone has been identified as an important regulator of magnesium intestinal absorption or kidney excretion [36]. Serum magnesium concentration appears to be the major factor determining renal magnesium handling. Most of the filtered Mg^{2+} ions are reabsorbed passively in the TAL (Fig. 5.3a). Mg^{2+} reabsorption in the TAL is driven by a transepithelial voltage generated by apical Na^+–K^+–$2Cl^-$ cotransporter (NKCC2) concominant with apical K^+ recycling via potassium channel ROMK (rat outer medulla K^+ channel), basolateral Cl^- exit through the chloride channel, and basolateral Na^+ exit via Na^+–K^+–ATPase. The resulting lumen positive (under normal circumstances) voltage is expected to drive the Mg^{2+} reabsorption even against the concentration gradient. Factors controlling Mg^{2+} reabsorption in the TAL include transepithelial voltage and permeability of the paracellular pathway. Factors diminishing the voltage will decrease Mg^{2+} transport in the TAL. For example, loop diuretics inhibit Na^+–K^+–$2Cl^-$ cotransporter NKCC2 and prevent establishment of transepithelial voltage gradient in TAL, thus reducing Mg^{2+} reabsorption [36, 47]. Volume expansion results in decreased Na^+ and Cl^- reabsorption in TAL and subsequent reduction of Mg^{2+} reabsorption. Permeability of the

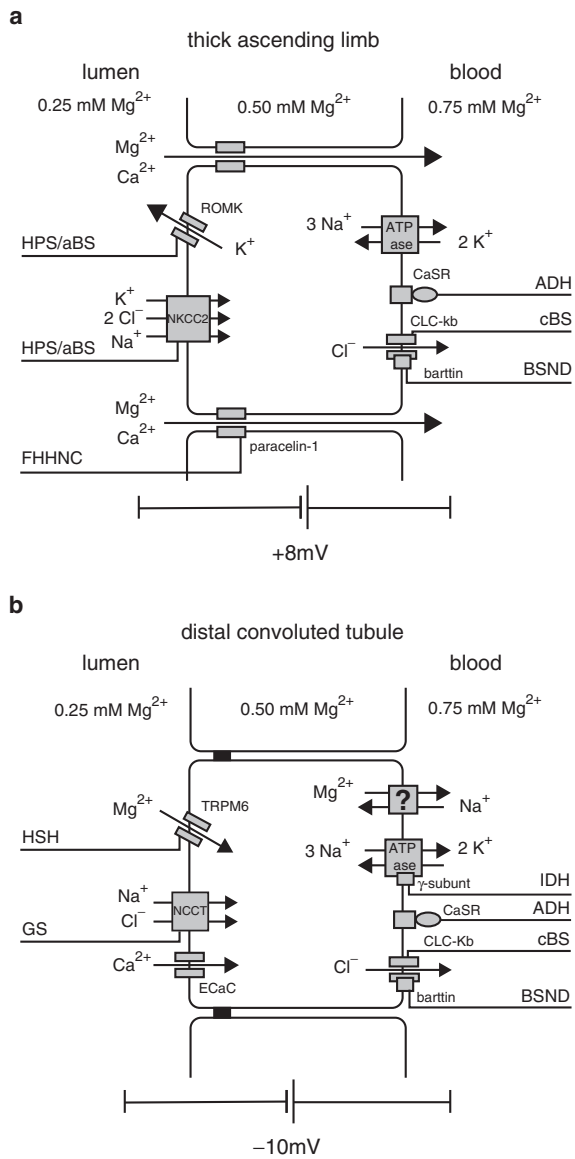

Fig. 5.3 **a** Magnesium reabsorption in the thick ascending limb (TAL) of Henle's loop. Paracellular reabsorption of magnesium and calcium is driven by lumen-positive transcellular reabsorption of NaCl. **b** Magnesium reabsorption in the distal convoluted tubule (DCT). Magnesium is reabsorbed actively via the transcellular pathway involving an apical entry step through a magnesium-selective ion channel and a basolateral exit, presumably mediated by a sodium-coupled exchange mechanism. *ADH* autosomal dominant hypoparathyroidism, *BSND* Bartter syndrome with sensorineural deafness, *CaSR* calcium sensing receptor, *cBS* classic Bartter syndrome, *CLC-Kb* chloride channel, *ECaC* epithelium calcium channel, *FHHNC* familial hypomagnesemia with hypercalciuria and nephrocalcinosis, *GS* Gitelman syndrome, *HPS/aBS* hyperprostaglandin E syndrome/antenatal Bartter syndrome variant, *IDH* isolated dominant hypomagnesemia, NKCC2 Na^+–K^+–$2Cl^-$ cotransporter, *ROMK* rat outer medulla K^+channel, *TRPM6* epithelial transcellular magnesium transporter (from [39], with permission)

paracellular pathway can be diminished as a result of paracellin-1 mutations (see Sect. 5.4.4.2) [39]. The major factor regulating Mg^{2+} transport in the TAL is Mg^{2+} serum concentration, whereas hypomagnesemia stimulates and hypermagnesemia inhibits the reabsorption of Mg^{2+} [36]. The proposed mechanism involves binding of Mg^{2+} to calcium sensing receptor (CaSR) on the basolateral membrane with subsequent modulation of adenylate cyclase activity and activation of phospholipase C, which results in the inhibition of apical (luminal) potassium channels [21]. This in turn reduces K^+ recycling and decreases activity of Na^+–K^+–$2Cl^-$ cotransporter NKCC2, preventing establishment of positive lumen voltage. Obviously, binding of Ca^{2+} to basolateral CaSR should have similar effect on Mg^{2+} handling. Thus, hypercalcemia also inhibits Mg^{2+} and Ca^{2+} reabsorption in the TAL resulting in hypercalciuria and hypermagnesuria [47]. The role of magnesium feedback loop via CaSR is debated because the affinity of the receptor for magnesium is quite low. In experimental studies, a number of hormones including PTH, calcitonin, glucagons, and vasopressin have been shown to increase magnesium transport in the TAL but none has a primary importance. All of them work through adenylate cyclase activity and activation of phospholipase C. Metabolic acidosis, hypokalemia, and phosphate depletion inhibit magnesium reabsorption in the TAL [36]; however, the mechanism remains unknown (Table 5.1).

The distal tubule reabsorbs 5–10% of filtered Mg^{2+} (Fig. 5.2). Mg^{2+} enters the tubular cell via a recently identified membrane protein TRPM6, which

Table 5.1 Factors affecting magnesium tubular reabsorption

Factor	TAL	DT	Total effect
Volume expansion	↓	?	↓
Hypomagnesemia	↑	No change	↑
Hypermagnesemia	↓	No change	↓
Hypercalcemia	↓	No change	↓
Hypocalcemia	↑	No change	↑
Phosphate depletion	↓	↓	↓
Metabolic acidosis	↓?	↓	↓?
Metabolic alkalosis	?	?	↑?
PTH	↑	↑?	↑
Loop diuretics	↓	No change	↓
Thiazide diuretics	↑?	↓?	No change

TAL thick ascending limb of Henle, *DT* distal tubule, *PTH* parathyroid hormone

functions as a Mg^{2+} channel (Fig 5.3b). Mutation of TRPM6 is responsible for familial hypomagnesemia with secondary hypocalcemia, an autosomal recessive disorder characterized primarily by intestinal malabsorption of Mg^{2+} (see Sect. 5.4.4.1) [38, 45]. TRPM6 is expressed in intestine and highly expressed in the distal tubule. Evaluation of these patients reveals additional defect of magnesium renal handling. Compared with normal individuals these patients have lower threshold for magnesium urinary wasting during magnesium sulfate infusion [38, 39]. Some data suggest that Mg^{2+} exits the basolateral membrane via not identified Na^+–Mg^{2+} exchanger. The driving force for the exchange is a high-sodium concentration gradient between extracellular (140 meq L^{-1}) and intracellular (10–15 meq L^{-1}) compartments, which favors Na^+ entry and Mg^{2+} exit. Because Mg^{2+} transport in the distal tubule operates close to its maximal capacity, it is believed that the DCT plays minor role in regulating Mg^{2+} homeostasis. However, some evidence suggests that this segment regulates the final urine magnesium excretion. Both phosphate depletion and metabolic acidosis increase magnesium urinary losses, which were localized to the TAL and the DCT (Table 5.1). Amiloride, a potassium and magnesium sparing diuretic, causes hyperpolarization of the membrane voltage that increases the driving force for Mg^{2+} entry. The result is increased Mg^{2+} reabsorption in the DCT. Interestingly, thiazide-type diuretics have little effect on Mg^{2+} handling. Thiazide diuretics primarily act on the Na^+–K^+–$2Cl^-$ cotransporter NKCC2, which is located in the DCT. The resulting decrease in transmembrane voltage diminishes Mg^{2+} reabsorption in this segment [13, 36]. However, both human studies and animal micropuncture studies fail to demonstrate increase in Mg^{2+} excretion after treatment with thiazide diuretics [47]. These findings are puzzling when compared with evaluation of patients with Gitelman syndrome, who have inactivating mutation of NCCT and most universally show renal magnesium wasting. One possible explanation to this discrepancy could be the modest impairment of Na^+ transport in proximal tubule caused by some thiazide diuretics due to partial inhibition of carbonic anhydrase [48]. This effect is not clinically important and does not contribute to net diuresis since the excess fluid and sodium delivered out of the proximal tubule are reabsorbed in the TAL. This may account for mild increase of Mg^{2+} reabsorption in the TAL counterbalancing Mg^{2+} wasting in the distal segment.

5.3.3 Regulation of Magnesium Serum Concentration

In contrast to other ions, serum Mg^{2+} concentration is not under tight hormonal regulation. Bone, the major intracellular Mg reservoir, does not readily exchange with extracellular Mg^{2+}, and equilibration with bone stores may take several weeks [41]. These physiological observations have very important clinical implications. First, negative magnesium balance due to low intake or decreased intestinal absorption can be compensated only by increased renal reabsorption. Fractional excretion of Mg^{2+}, which is normally between 3 and 5%, may decrease to 0.5% with magnesium depletion due to extrarenal losses. Thus, patients treated with intravenous fluids containing dextrose and sodium chloride may develop hypomagnesemia rather quickly, especially in the presence of tubular damage and the inability to conserve Mg^{2+}. Second, the human body has no good protection against hypermagnesemia in the presence of impaired renal function.

5.4 Magnesium Deficiency and Hypomagnesemia

Hypomagnesemia is a common problem occurring in 7–11% of hospitalized patients and in as many as 60% of intensive care unit (ICU) patients. Magnesium deficiency can be demonstrated in up to 40% of patients with other electrolyte and acid–base abnormalities, especially hypokalemia, hypophosphatemia, hypocalcemia, and metabolic alkalosis. Hypomagnesemia in ICU patients is associated with a higher mortality [44, 46]. Hypomagnesemia may cause multiple cardiac, neuromuscular, and metabolic abnormalities; however, cardiac and neurological symptoms can also frequently be attributed to coexisting metabolic abnormalities such as hypokalemia or hypocalcemia. Also, many patients with significant hypomagnesemia remain completely asymptomatic. Thus, the clinical significance of mild hypomagnesemia remains somewhat controversial. Table 5.2 summarizes the clinical signs of hypomagnesemia and their proposed mechanisms. Magnesium is a cofactor in all reactions that require ATP, and it is essential for the activity of Na^+–K^+–ATPase. The impaired function of Na^+–K^+–ATPase activity with secondary intracellular hypokalemia is the major effect of hypomagnesemia [1, 44].

Because extracellular magnesium accounts for only 1% of total body magnesium, serum Mg^{2+} concentration may not reflect the overall magnesium status. Unfortunately,

Table 5.2 Clinical signs of magnesium deficiency and proposed mechanism

Clinical sign	Mechanism
Metabolic	
Hypokalemia	↓ Na^+–K^+–ATPase activity, renal K^+ wasting
Hypocalcemia	↓ PTH, ↓ $1.25(OH)_2D$, end-organ resistance to PTH, and $1,25(OH)_2D$
Cardiac	
Electrocardiographic abnormalities (nonspecific T-wave abnormalities, U waves, prolonged QT, and QU intervals)	↓ Na^+–K^+–ATPase activity, Intracellular hypokalemia
Arrhythmias (ventricular ectopy, ventricular tachycardia, Torsdaes de pointes, ventricular fibrillation)	↓ Na^+–K^+–ATPase activity, Intracellular hypokalemia, especially in presence of myocardial hypoxic damage
Neuromuscular system	
Muscle tremor and twitching	Hypomagnesemia-induced excitation of glutamate-sensitive NMDA receptors
Tetany	
Positive Trousseau and Chvostec signs	
Seizures	
Paresthesias	
Muscle weakness	

PTH parathyroid hormone, *$1.25(OH)_2D$* active vitamin D, *NMDA N*-methyl-D-aspartate-type glutamate receptors

no simple clinical test is available to measure body magnesium stores. The magnesium tolerance test has been used for many years and is thought to be the most accurate way to assess magnesium status. The test is performed by collecting twice 24-h urine for magnesium – one collected before and second after the administration of 2.0 mg kg^{-1} of parenteral Mg^{2+}. Retention of more than 20% of the administered Mg^{2+} is suggestive of magnesium depletion. Even though clinical studies show good correlation between the results of the test and magnesium status assessed by skeletal and muscle magnesium content, the test's clinical use remains limited [34, 44]. The test is invalid in patients with impaired renal function or in presence of diuretics affecting magnesium renal handling. The duration of the test is another limiting factor in the ICU setting.

5.4.1 Metabolic Abnormalities in Hypomagnesemia

Hypokalemia is a frequent finding in hypomagnesemic patients. Some conditions may result in simultaneous loss of potassium and magnesium; however, hypomagnesemia by itself can induce hypokalemia via two mechanisms: intracellular potassium depletion and renal potassium wasting. Hypomagnesemia induces impairment of Na^+–K^+–ATPase function, which causes K^+ leakage from cells with subsequent K^+ loss in the urine. The exact mechanism of renal K^+ wasting in hypomagnesemia remains unknown; some data suggest a defect in the TAL [1, 34].

Hypocalcemia is present in about half of the patients with severe hypomagnesemia. Multiple mechanisms, contributing to hypocalcemia, have been identified. The first identified cause is a suppression of PTH secretion by hypomagnesemia. Most hypomagnesemic–hypocalcemic patients have either low or normal (inappropriately low for low calcium concentration) PTH levels, which increase rapidly following magnesium supplementation. A second observation suggests end-organ resistance to PTH. PTH-induced calcium release from isolated bone is impaired when Mg^{2+} concentration falls below 1 mg dL^{-1}. Several studies suggest that this effect may be even of greater importance than reduced PTH secretion, because last effect requires more severe hypomagnesemia. Hypomagnesemia also impairs secretion of active vitamin D ($1.25(OH)_2D$) and causes end-organ resistance to this hormone [1, 34, 44]. The exact mechanisms for these effects are unknown.

5.4.2 Effect of Hypomagnesemia on the Cardiovascular System

One of the major effects of magnesium depletion is an impaired function of Na^+–K^+–ATPase with subsequent

intracellular hypokalemia. The intracellular hypokalemia may potentially produce depolarized resting membrane potential predisposing to ectopic excitation and tachyarrhythmias. A reduced outward K^+ gradient diminishes K^+ efflux during repolarization that is needed to terminate cardiac action potential. As a result, the most common electrocardiographic (ECG) abnormalities seen in hypomagnesemia reflect abnormal cardiac repolarization and include nonspecific T-wave abnormalities, U waves, and prolonged QT interval. Association of hypomagnesemia with ventricular arrhythmias, especially during myocardial ischemia, is of great clinical importance and is reviewed extensively in the literature [2, 34, 44].

5.4.3 Effect of Hypomagnesemia on Neuromuscular System

Isolated magnesium depletion may induce multiple symptoms of neuromuscular irritability including tetany, muscle twitching, tremor, and positive Chvostec and Trousseau signs. Tonic–clonic generalized convulsions were described as a first manifestation of hypomagnesemia and sometimes can be triggered by noise. Data from animal studies suggest that effect of magnesium deficiency on brain neuronal excitability is mediated via *N*-methyl-D-aspartate (NMDA)-type glutamate receptors. Glutamate is a major excitatory neurotransmitter in the brain acting as an agonist at NMDA receptors. Extracellular Mg^{2+} normally blocks NMDA receptors, thus hypomagnesemia may release the inhibition of NMDA receptor with subsequent glutamate-mediated depolarization of the postsynaptic membrane and enhancement of epileptiform electrical activity [1, 34, 44].

5.4.4 Causes of Hypomagnesemia

Magnesium deficiency can be induced by either decreased intake or increased losses. Because bone magnesium reservoir does not readily exchange magnesium with plasma pool, negative magnesium balance can cause hypomagnesemia rather quickly. This is in contrast to calcium metabolism, where negative balance is compensated by PTH-induced Ca^{2+} release from bone. Decreased intake of magnesium can be secondary to diminished amount of enteric Mg^{2+} delivery or reduced absorption (Table 5.3). Magnesium wasting can be via gastrointestinal or renal route. Approach to the differential diagnosis of hypomagnesemia will be discussed in the Sect. 5.4.4.3.

5.4.4.1 Extrarenal Causes of Hypomagnesemia

Nutritional Deficiency

Since magnesium is present in almost all foods in significant amounts, hypomagnesemia is almost never observed in normal individuals even on a strict diet. In clinical practice, hypomagnesemia can be found in circumstances of severe protein-calorie malnutrition, pure magnesium-free parenteral feeding, and alcoholism [34]. Patients receiving pure parenteral nutrition without magnesium supplementation are at risk for developing hypomagnesemia. This is particularly true in ICU patients as those patients are sicker and often have additional risk factors for hypomagnesemia, including renal magnesium wasting secondary to nephrotoxin-induced tubulopathy.

Intestinal Malabsorption

Different malabsorption syndromes including celiac and inflammatory bowel disease can be associated with hypomagnesemia. In case of fat malabsorption, free fatty acids in the intestinal lumen combine with cations (saponification) and form nonabsorbable soaps. This process can interfere with Mg^{2+} absorption [25, 34].

Congenital defect of magnesium absorption has been recently described. This condition manifests as hypomagnesemia with secondary hypocalcemia, which usually responds to magnesium repletion. Both X-linked recessive and autosomal recessive inheritances were described. Affected patients were found to have mutation in TRMP6 gene that encodes a new protein involved in transcellular transport of Mg^{2+} in the intestinal lumen and the DCT (Figs. 5.1 and 5.3b). The major reason of hypomagnesemia in these patients is intestinal malabsorption; however, additional tubular defect in Mg^{2+} renal reabsorption has also been confirmed. The hypomagnesemia is usually severe and can manifest with seizures in infants. High doses of enteral magnesium are required to keep serum magnesium and calcium levels close to normal range [38, 45].

Intestinal Losses

Generally, secretions from the lower gastrointestinal tract have much higher magnesium concentrations (up to 16 mg dL^{-1}) than from the upper gastrointestinal tract. As a result, patients with biliary or pancreatic fistulas, iliostomy or gastric drainage rarely develop hypomagnesemia. In contrast, chronic diarrhea and short bowel syndrome can be associated with hypomagnesemia [30, 34, 44].

Table 5.3 Causes and proposed mechanisms of magnesium deficiency

Mechanism of magnesium deficiency	Disorder
Low intake	No magnesium in intravenous fluids
	Starvation
	Anorexia
Malabsorption: saponification by fat	Fat malabsorption syndromes
	Pancreatitis
Malabsorption: congenital defect due to TRMP6 mutation	Congenital hypomagnesemia with hypocalcemia
Increased gastrointestinal losses	Nasogastric suction
	Vomiting
	Short bowel syndrome
	Diarrhea
	Laxative abuse
Increased cutaneous loss	Extensive burns
Increased renal losses	Volume expansion (hyperaldosteronism)
	Osmotic diuresis (glucose, mannitol, urea)
	Diuretics (loop diuretics, mannitol)
	Polyuric phase of ATN including kidney transplant
	Postobstructive diuresis
	Drugs (cisplatin, carboplatin, amphotericin B, cyclosporine, tacrolimus, pentamidine, foscarnet, aminoglycosides)
	Inborn defects:
	Gitelman's syndrome
	Isolated familial hypomagnesemia
	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
	Autosomal dominant hypocalcemia
Electrolyte imbalance	Hypercalcemia
Increased cellular uptake of magnesium	Hungry bone syndrome

Cutaneous Losses

Sweat Mg^{2+} concentration does not exceed 0.5 mg dL^{-1}; therefore, contribution of cutaneous magnesium loss during exertion is not significant. Observed decrease in Mg^{2+} concentration most likely is secondary to intracellular shift of magnesium. Patients with severe burns can be prone to develop hypomagnesemia due to losses with cutaneous exudates [34].

Redistribution to the Intracellular Compartment

Rarely refeeding syndrome can cause hypomagnesemia. In this condition, rapid cellular uptake of water, glucose, potassium, phosphorus, and magnesium may result in electrolyte abnormalities including hypomagnesemia [7].

Hungry Bone Syndrome

Some patients with hyperparathyroidism develop hypocalcemia and hypomagnesemia after parathyroidectomy. Cessation of high bone turnover state due to PTH-induced bone resorption results in high rate of bone formation, which is thought to be responsible for Ca^{2+} and Mg^{2+} sequestration into bone tissue [17].

5.4.4.2 Renal Causes of Hypomagnesemia

Since 60% of filtered magnesium is reabsorbed passively in the TAL, any factor that blocks reabsorption of sodium and chloride in this segment promotes urinary loss of magnesium. In the ICU setting, magnesium renal losses can be especially hazardous in patients with low magnesium intake. Expansion of extracellular

fluid volume as a result of hyperaldosteronism or inappropriate antidiuretic hormone secretion can result in mild hypomagnesemia. Hypermagnesuria can occur during polyuric phase of acute tubular necrosis (ATN), postobstructive, osmotic diuresis, and recovery from postischemic injury of transplanted kidney [1].

Hypercalcemia

Hypercalcemia directly induces renal Mg^{2+} wasting, the effect that is clearly observed in patients with malignant bone metastases [5]. Hypercalcemia results in increased glomerular filtration of Ca^{2+} and increased Ca^{2+} reabsorption in the TAL. Most likely, since Mg^{2+} and Ca^{2+} share the same paracellular transporter for their reabsorption in the TAL, increased delivery and reabsorption of Ca^{2+} results in decreased uptake of Mg^{2+}. In primary hyperparathyroidism, direct effect of PTH-induced increase in Mg^{2+} reabsorption is counterbalanced by the hypercalcemia-induced Mg^{2+} wasting. The net result is usually normal magnesium handling in this clinical situation [34, 47].

Diuretics

Loop diuretics block chloride and sodium reabsorption in the TAL and when used in large amounts can cause profound hypomagnesemia. Hypomagnesemia can also be associated with osmotic diuretics (mannitol, glucose in diabetic hyperglycemia). Interestingly, thiazide diuretics that block NCCT and mimic Gitelman syndrome do not cause significant hypermagnesuria and hypomagnesemia (see Sect. 5.3.2).

Other Medications

Medication-induced tubular damage may cause hypermagnesuria in a polyuric phase of ATN. Some medications can induce specific tubular defect resulting in hypermagnesuria.

Aminoglycosides cause tubular damage that typically presents with hypokalemia, hypocalcemia, and hypomagnesemia [11, 24, 34, 40]. Hypomagnesemia can also be an isolated finding in patients receiving aminoglycosides and can occur few weeks after discontinuation of the antibiotic treatment and persist for several months. Most reported adult patients who were treated with high total dose of aminoglycosides had normal therapeutic levels suggesting that cumulative dose of aminoglycosides is a predictor of development of magnesuria. However, normal cumulative dose does not exclude development of Bartter-like syndrome. Importantly, no correlation has been found between aminoglycoside-induced ATN and hypomagnesemia in both preclinical and clinical studies. All clinically available aminoglycosides including gentamicin, amikacin, and tobramycin can cause similar tubular defect. Also topically administered for extensive burn injury, neomycin can cause classical metabolic triad of hypokalemia, hypocalcemia, and hypomagnesemia presenting with seizures in children [4, 34]. Even symptomatic hypomagnesemia as a complication of accepted 3–5 mg kg^{-1} day^{-1} standard dose regimen is relatively rare; asymptomatic hypomagnesemia can be observed in up to 30% of adult patients. For our knowledge, all reported pediatric cases, who developed Bartter-like syndrome during the treatment with aminoglycosides, had complete recovery of the tubular function after cessation of antibiotic treatment [24, 40]. The exact mechanism of gentamicin-induced Bartter-like syndrome is unknown. Low PTH levels despite hypocalcemia suggest possibility that gentamicin may activate calcium-sensing receptor on the TAL and the DCT [11].

Cisplatin is a widely used antineoplastic agent for solid tumors. Nephrotoxicity is a well-appreciated complication of cisplatin toxicity [3]. Hypomagnesemia is observed in more than 50% of patients receiving monthly cycles of cisplatin and does not correlate with the incidence of cisplatin-induced acute renal failure. Renal magnesuria can manifest during treatment and continue for months or even years after cessation of cisplatin treatment. Some patients may develop permanent tubular damage manifesting with hypokalemic metabolic acidosis, hypermagnesuria, and hypocalciuria [32]. Close resemblance to Gitelman syndrome suggests distal tubular defect; however, exact mechanism of cisplatin-induced tubulopathy remains unknown. Carboplatin, an analog of cisplatin, appears to be less nephrotoxic and rarely causes acute renal failure in adults [34]. Prospective study of 651 pediatric patients treated with either cisplatin or carboplatin in combination with ifosfamide demonstrated hypomagnesemia in 12.5 and 15.6% of patients receiving cisplatin or carboplatin, respectively, and was significantly higher than in control group. In all groups, the frequency of hypomagnesemia was decreasing during the follow-up period of 2 years, but serum magnesium remained lower in platinum-treated patients in the end of the study [43].

Amphotericin B-induced nephrotoxicity is the major side effect of this potent antifungal medication. Nephrotoxicity can present with acute renal failure due to tubular necrosis, potassium wasting, distal renal tubular acidosis, or magnesium wasting. Interestingly,

amphotericin-induced hypermagnesuria is usually accompanied by hypocalciuria suggesting distal tubular defect somewhat similar to cisplatin toxicity. Hypocalciuria prevents hypomagnesemia-induced hypocalcemia; the resulting serum calcium levels are usually normal [6, 18].

Calcineurin inhibitors may induce renal Mg^{2+} wasting and hypomagnesemia in posttransplant patients. Mg^{2+} loss does not correlate with trough cyclosporine levels [34], most likely, because of poor correlation between cyclosporine trough levels and area under the curve [12]. In contrast, tacrolimus trough level is a good predictor of the drug area under the curve [15], and tacrolimus-induced magnesium urine loss correlates well with tacrolimus levels [31]. Interestingly, retrospective analysis of patients with biopsy proven cyclosporine nephrotoxicity shows that hypomagnesemia is an additional risk factor for fast decline of renal function [22]. It has been proposed that some of the neurological symptoms that were always attributed to cyclosporine toxicity can actually be a consequence of the drug-induced hypomagnesemia [34].

Intravenous pentamidine and foscarnet can cause Mg^{2+} renal wasting and hypomagnesemia, which is often accompanied by hypocalcemia [34].

Inherited Tubular Defects of Magnesium Handling

Bartter syndrome includes a group of inherited disorders characterized by chloride wasting, hypo-kalemic metabolic alkalosis, and usually hypercalciuria. Affected children usually present with failure to thrive in infancy or early childhood. Classic Bartter syndrome is caused by inactivation mutation of gene coding for the chloride channel CLC-Kb (Fig. 5.3) in the TAL and the DCT. Hypomagnesemia can be detected in up to 50% of patients with this mutation. Neonatal forms of Bartter syndrome, resulting from abnormal Na^+–K^+–$2Cl^-$ cotransporter NKCC2, potassium channel ROMK, or Barttin, are rarely associated with disturbances of magnesium homeostasis [33, 39].

Gitelman's syndrome is a variant of Bartter syndrome characterized by potassium and magnesium urine loss and hypocalciuria. Patients with Gitelman's syndrome usually have milder symptoms than Bartter patients and present after the age of 6 years with metabolic abnormalities including mild hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. Some patients can be asymptomatic and others complain of transient episodes of weakness, tetany, abdominal pains, and salt craving. The defect in most studied families is a result of inactivating mutation of thiazide-sensitive Na^+–Cl^- cotransporter (NCCT) that is mainly located in the DCT (Fig. 5.3b) [33, 39]. The exact mechanisms responsible for hypocalciuria and hypermagnesuria remain poorly understood.

Isolated hypomagnesemia is a rare congenital disorder with either autosomal dominant or autosomal recessive mode of inheritance. Clinical presentation may vary from asymptomatic cases to generalized convulsions in early childhood. Laboratory findings include hypermagnesuria, hypomagnesemia, and hypocalciuria without any other electrolyte abnormalities. Whereas a genetic locus in the autosomal recessive form has not been yet identified, in the autosomal dominant form a locus was mapped to chromosome 11q23. The identified gene FXYD2 encodes the Na^+–K^+–ATPase g-subunit localized in the distal tubule. The mechanism by which FXYD2 mutations cause hypermagnesuria remains unclear [29, 39].

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is distinguished from other congenital hypomagnesemic syndromes by the presence of significant calcium, in addition to magnesium, renal wasting. Most FHHNC patients present in early childhood with nephrocalcinosis and/or renal stones, failure to thrive, polyuria, and polydipsia. Nephrocalcinosis and renal stones resulting from hypercalciuria are the major clinical findings. Nephrocalcinosis-related renal insufficiency, distal acidification, and concentrating defects have been also described. Some patients may develop symptomatic hypocalcemia. This syndrome is also associated with frequent ocular abnormalities including corneal calcifications, choreoretinitis, keratoconus, and macular coloboma. The association of hypercalciuria and hypermagnesuria was suggestive of the TAL reabsorptive defect. Indeed, genetic analysis revealed a locus on chromosome 3q and determined that mutated gene is responsible for paracellin-1 protein (Fig. 5.3a). Paracellin-1 is a member of the claudin family of tight junction proteins, which is expressed only in the TAL and distal tubule. Paracellin-1 is also known as claudin-16; both names are used in the literature that can be confusing. This protein plays a critical role in the paracellular Ca^{2+} and Mg^{2+} reabsorption in the TAL. Paracellin-1 gene expression is also shown in cornea and retinal epithelium in animals explaining the link with ocular abnormalities observed in some patients [34, 39, 42].

Autosomal dominant hypocalcemia results from activating mutation of calcium-sensing receptor. CaSR is expressed in the parathyroid gland and the TAL. Activation of CaSR causes a clinical picture

resembling primary hypoparathyroidism including hypocalcemia and inadequately low PTH levels. In the parathyroid gland activation of the CaSR results in diminished PTH secretion, whereas in the kidney activation of the CaSR contributes to decreased reabsorption of Ca^{2+} and Mg^{2+} in the TAL. Resulting hypomagnesemia helps to differentiate these patients from primary hypoparathyroidism [39].

5.4.4.3 Clinical Approach to the Diagnosis of Hypomagnesemia

The serum Mg^{2+} concentration remains the most practical clinical test to assess magnesium deficit. In contrast to other electrolytes, the plasma magnesium concentration is not always a routine screening blood test. The presence of hypomagnesemia should be suspected in pediatric patients with chronic diarrhea, hypocalcemia, and unexplained neurological or muscular symptoms. It is reasonable to perform serum magnesium screening in most ICU patients on admission. Hypomagnesemia is defined as a decrease in serum Mg^{2+} concentration to levels less than 1.5 mg dL^{-1}. If hypomagnesemia is confirmed on two consecutive blood draws, the diagnosis can often be obtained from careful medical history and clinical picture (Table 5.3). ICU patients are prone to develop hypomagnesemia due to coexistence of two or more factors as, for example, due to low intake and increased gastrointestinal or renal loss. If the cause of hypomagnesemia remains unclear, the differential diagnosis between renal and extrarenal losses can be performed using 24-h urinary magnesium excretion, fractional excretion of Mg^{2+} (FEMg), or urine magnesium to creatinine ratio. The latter two tests are easier to perform since they do not necessitate 24-h urine collection. FEMg can be calculated from the following formula:

$$\text{FEMg} = (\text{UMg} \times \text{PCr}) \times 100/(0.7 \times \text{PMg} \times \text{UCr}),$$

where UMg and UCr are urine concentrations and PMg and PCr are plasma concentrations of magnesium and creatinine, respectively. The plasma concentration of magnesium is multiplied by 0.7 to estimate the free (not bound to albumin) concentration of magnesium, since only free magnesium is available for glomerular filtration.

The normal renal response is to diminish magnesium excretion in the presence of hypomagnesemia to very low levels. In adults, 24-h urine magnesium excretion falls to lower than 20 mg and FEMg to less than 1–2%. Urine excretion of more than 20–30 mg and fractional excretion above 2% are suggestive of renal magnesium loss. Normal values of urine magnesium to creatinine ratio in different age groups are summarized in Table 5.4 [1, 28].

5.4.4.4 Treatment of Hypomagnesemia

Monitoring of magnesium status becomes a routine screening test in severely sick children. It is of primary importance in ICU pediatric patients maintained with parenteral nutrition for a long time. Parenteral nutrition should contain magnesium; otherwise, these patients are prone to develop hypomagnesemia. In most patients, hypomagnesemia can be prevented by sufficient daily magnesium supplementation (Table 5.5 [49]).

If hypomagnesemia develops, the treating physician should try to answer the following questions to optimize the treatment:

1. What is the etiology of magnesium deficit? Can the etiologic factor(s) be withdrawn or ameliorated?
2. Is the patient symptomatic with regard to magnesium depletion?
3. Does the patient need magnesium repletion? If he does, what is the best route for the repletion and what is the appropriate dosage?

If hypomagnesemia is attributed to loop diuretic or tubular-toxic medication, then the possibility of switching to another medication should be considered. Patients with renal magnesium wasting may benefit from the addition of potassium-sparing diuretics, such as amiloride or triamterene, which decrease magnesium renal losses in the distal tubule.

The second question is not always easy to answer. Most hypomagnesemic pediatric patients do not present

Table 5.4 Urine magnesium to creatinine ratio (mg mg^{-1}) limits (5th and 95th percentile) by age groups [28]

Age (years)	0.1–1	1–2	2–3	3–5	5–7	7–10	10–14	14–17
5th percentile	0.1	0.09	0.07	0.07	0.06	0.05	0.05	0.05
95th percentile	0.48	0.37	0.34	0.29	0.21	0.18	0.15	0.13

Magnesium concentration measured using colorimetric reaction with xylidil blue (from [28], with permission)

Table 5.5 Dietary reference intake of magnesium by age [49]

0–6 months	50 mg
6–12 months	70 mg
1–10 years	150–250 mg
11–18 years	300–400 mg
>18 years	300–400 mg
Pregnant/lactating	+150 mg

with neurological, muscular, or cardiac symptoms. However, other electrolyte abnormalities frequently coexist in these patients. It can be difficult to differentiate if these electrolyte abnormalities result from magnesium deficit or independent of magnesium renal wasting. For example, hypokalemia is often associated with hypomagnesemia and can result from the tubular wasting. On other hand, hypomagnesemia by itself causes hypokalemia due to impaired Na^+–K^+–ATPase function and loss in the urine. Thus, in some cases differentiation may be practically impossible.

Obviously, symptomatic magnesium depletion needs repletion. The importance of treating asymptomatic hypomagnesemia remains controversial. Most authors recommend to replete any hypomagnesemic patient with significant underlying cardiac disease, convulsive disorder, or concurrent hypokalemia or hypocalcemia. Also severe asymptomatic magnesium depletion (<1.2–1.4 mg dL^{-1}) should be corrected [1, 34, 44]. In asymptomatic patients with mild hypomagnesemia, we suggest to assess, if possible, magnesium balance, and in case of negative balance provide sufficient magnesium supplementation.

The route of magnesium repletion depends on the urgency of the clinical situation. Obviously, the seizing patient should be given magnesium intravenously (2–5 mg kg^{-1} of elemental magnesium) over 8–24 h. Small bolus of 1–2 mg kg^{-1} can be given over 5 min in the beginning (Table 5.6). Because extracellular magnesium does not readily equilibrate with intracellular stores, fast infusion rapidly increases the plasma concentration but does not correct the total body magnesium. Furthermore, since plasma magnesium concentration is the major regulator of magnesium renal handling, acute rise in magnesium concentration results in hypermagnesuria with loss of up to 50% of infused magnesium [1]. Therefore, slow continuous intravenous infusion over 24 h is effective and safe. The dose may be repeated or adjusted to maintain serum Mg^{2+} concentration above 1–1.2 mg dL^{-1}. As mentioned, magnesium uptake by cells is very slow and days may be needed to correct intracellular magnesium deficit. Thus, once started magnesium repletion should be continued for 3–7 days despite normal blood magnesium concentration [1, 34]. The main adverse effects of fast magnesium repletion are due to development of hypermagnesemia. These side effects include facial flushing, hypotension, loss of deep tendon reflexes, and atrioventricular block. Monitoring of deep tendon reflexes can be used in nonparalyzed ICU patients. In addition, intravenous administration of magnesium sulfate results in decrease in plasma Ca^{2+} concentration due to binding of Ca^{2+} and sulfate ions. Therefore, in case of concurrent hypocalcemia calcium replacement should precede the magnesium repletion. Another disadvantage of magnesium sulfate salt is the fact that sulfate cannot be reabsorbed in the distal tubule; the resulting negative luminal potential increases potassium renal loss [34].

Oral magnesium replacement is usually used either in mild cases or for continued replacement after initial intravenous repletion (Table 5.6). The advantage of oral replacement is a slow elevation in magnesium serum concentration preventing hypermagnesemia and its side effects. Multiple oral Mg^{2+} salts are available. Bioavailability of oral magnesium preparations is assumed to approximately 33% in patients with normal intestinal function. Side effects include diarrhea in high doses and metabolic abnormalities. Mg^{2+} hydroxide and

Table 5.6 Magnesium preparations and dosages

Preparation	Amount of elemental magnesium	Route and forms	Dosage (mg elemental magnesium per kg)
Sol magnesium sulfate 50%	50 mg/1 mL	IV	2–5 mg kg^{-1} (0.05–0.1 mL kg^{-1}) over 8–24 h, repeat if needed
Magnesium sulfate granules	10 mg/100 mg (50 mg/5 g)	PO granules	10–20 mg kg^{-1} $dose^{-1}$ 3–4 times daily
Magnesium oxide	60 mg/100 mg	PO tablets, capsules	10–20 mg kg^{-1} $dose^{-1}$ 3–4 times daily
Magnesium gluconate	5.4 mg/100 mg	PO tablets	10–20 mg kg^{-1} $dose^{-1}$ 3–4 times daily

Mg^{2+} oxide can exaggerate metabolic alkalosis, whereas Mg^{2+} sulfate and gluconate may potentially worsen K^+ wasting. Patients on magnesium replacement therapy should be monitored for magnesium, potassium, calcium, and bicarbonate levels [34].

5.5 Hypermagnesemia

In normal individuals most of the filtered magnesium load is reabsorbed in the TAL; the process is regulated mainly by magnesium serum concentration. Increased magnesium load results in decreased Mg^{2+} reabsorption and excretion of the excess Mg^{2+} in the urine. This mechanism is so efficient that hypermagnesemia usually is not seen in the presence of normal kidney function. In clinical practice, hypermagnesemia usually occurs in two settings: compromised renal function or excessive magnesium intake.

5.5.1 Causes of Hypermagnesemia

5.5.1.1 Renal Failure

In chronic renal failure, the remaining nephrons adapt to the decreased filtered magnesium load by increasing their fractional excretion of magnesium. This adaptive mechanism preserves normal magnesium serum concentration even in the presence of advanced renal failure. In patients with creatinine clearance below 15 mL min^{-1} mild hypermagnesemia can be observed. Severe hypermagnesemia can be seen in patients who receive exogenous magnesium as antacids or laxatives [8, 34].

5.5.1.2 Excessive Magnesium Intake

Hypermagnesemia can be seen in patients with normal kidney function when magnesium intake exceeds the renal excretory capacity. It is rarely observed in children, but is a well-appreciated complication of large magnesium infusions in pregnant women with preeclampsia. Severe hypermagnesemia has been described in children with Epsom salt (containing Mg^{2+} sulfate) poisoning, in laxative abusers, or in patients receiving magnesium as a cathartic [8, 20]. Hypermagnesemia from oral magnesium salts is more common in patients with bowel inflammatory disease, obstruction, or perforation [34]. Extreme hypermagnesemia with hypercalcemia has been described in pediatric and adult patients with Dead Sea water poisoning, since the ingested water contains very high concentrations of both calcium and magnesium [35].

5.5.1.3 Miscellaneous

Mild to moderate hypermagnesemia can be occasionally observed in patients with familial hypocalciuric hypercalcemia, tumor lysis syndrome, milk-alkali syndrome, hypothyroidism, Addison disease, lithium therapy, and theophylline intoxication [34]. Neonates born prematurely with asphyxia or hypotonia are often hypermagnesemic. Spontaneous return to normal values occurs within 72 h. Whether hypermagnesemia plays a pathophysiological role in asphyxic child remains unknown. Hypermagnesemia can be dangerous in neonates born from magnesium-treated eclamptic mothers [9]. Low glomerular filtration rate observed in neonates may slow the normalization of serum magnesium level.

5.5.2 Symptoms of Hypermagnesemia

Symptoms of hypermagnesemia usually correlate well with plasma magnesium concentration. Mild hypermagnesemia is usually asymptomatic, whereas severe hypermagnesemia can potentially be a fatal condition. Initial manifestations are seen when magnesium concentration exceeds 4–5 mg dL^{-1} and include nausea, vomiting, flushing, headache, drowsiness, and diminished deep tendon reflexes. Plasma magnesium concentrations between 7 and 12 mg dL^{-1} are often associated with somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, bradycardia, ileus, urinary retention, and ECG changes. Further elevation of magnesium concentration above 12 mg dL^{-1} may result in flaccid muscular paralysis, respiratory depression, AV heart block, and cardiac arrest (Table 5.7).

5.5.2.1 Cardiovascular System

Hypotension usually appears when magnesium concentration exceeds 5–6 mg dL^{-1} and is thought to be the result of peripheral vasodilatation. Mg^{2+} is an effective calcium-channel blocker both intracellular and extracellular; it also modulates the function of K^+ channels in cardiac muscle and aortic smooth muscle cells [2]. ECG changes are common with magnesium concentrations above 8 mg dL^{-1} but nonspecific. Sinus or junctional bradycardia, AV and His bundle conduction block, prolonged QRS duration, and Q-T intervals can be observed [34]. Complete heart block and cardiac arrest may occur at plasma concentrations above 18 mg dL^{-1}.

Table 5.7 Clinical manifestations and treatment of hypermagnesemia

Plasma magnesium concentration (mg dL^{-1})	Clinical signs	Treatment
2.5–4	Usually asymptomatic	Cessation of magnesium supplements
4–6	Nausea, vomiting, flushing, headache, drowsiness, and diminished deep tendon reflexes	As above Forced diuresis with normal saline and loop diuretics
6–12	Somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, bradycardia, ileus, urinary retention, and ECG changes (prolongation of the P-R interval, increased duration of the QRS complex and Q-T interval, increased height of the T waves)	As above IV calcium gluconate 10% 0.2–0.3 mL kg^{-1} by slow infusion Fluid resuscitation Dialysis in the presence of renal failure or ineffectiveness of forced diuresis to decrease magnesium levels
>12	Flaccid muscular paralysis, respiratory depression, coma, AV heart block, and cardiac arrest (>18 mg dL^{-1})	As above Respiratory support

5.5.2.2 Neuromuscular System

Increased concentrations of extracellular Mg^{2+} produce curare-like effect by inhibition of acetylcholine release and decreased impulse transmission across the neuromuscular junction [2]. Clinical manifestations progress from hyporeflexia to flaccid muscle paralysis, respiratory depression, smooth muscle paralysis with urinary retention, and ileus. Central nervous system depression manifests with somnolence, lethargy, and coma in severe hypermagnesemia [34].

5.5.2.3 Hypocalcemia

Hypermagnesemia can suppress the PTH secretion [10]. Resulting mild hypocalcemia is usually asymptomatic and thought not to be clinically important.

5.5.3 Treatment of Hypermagnesemia

Most cases of hypermagnesemia can be prevented by avoidance of magnesium-containing preparations in patients with advanced renal failure (Table 5.7). Mild hypermagnesemia in the presence of preserved renal function usually requires only discontinuation of magnesium supplementation. The next step of treatment is forced diuresis using normal saline infusion and loop diuretics, which results in increased magnesium wasting. In cases of severe symptoms, especially cardiac toxicity, intravenous calcium is given as a magnesium antagonist. In patients with renal failure, dialysis is the only way to clear the magnesium excess. Both hemodialysis and peritoneal dialysis have been successfully used for this application. Hemodialysis provides higher KT/V and thus is more effective in magnesium clearance. The typical dialysate for hemodialysis contains 0.6–1.2 mg dL^{-1} of magnesium; however, Mg^{2+}-free dialysate can also be used [20, 34].

Take-Home Pearls

- About 70% of serum magnesium (not protein bound) is freely filtered at the glomerulus to the Bowman space. The majority of filtered magnesium is reabsorbed in the loop of Henle via paracellular passive transport, which is facilitated by a tight junction protein paracellin-1 and is driven by the transepithelial voltage. A small amount of filtered magnesium is reabsorbed in the distal tubule via transcellular active transport.
- Hypokalemia, hypocalcemia, cardiac and neurological abnormalities are clinical signs of hypomagnesemia.
- Secretions from the lower gastrointestinal tract have much higher magnesium concentrations (up to 16 mg dL^{-1}) than from the upper gastrointestinal tract, thus chronic diarrhea can result in hypomagnesemia.
- Renal loss of magnesium can occur during polyuric phase of ATN, postobstructive and osmotic diuresis, recovery from postischemic injury of transplanted kidney, and treatment with loop diuretics, amphotericin, calcineurin inhibitors, and cisplatin.
- Rare inherited tubular defects of magnesium handling include Gitelman syndrome, isolated familial hypomagnesemia, familial hypomagnesemia with hypercalciuria and nephrocalcinosis as well as autosomal dominant hypocalcemia.
- 7–10 day course of magnesium supplementation is necessary to correct a symptomatic hypomagnesemia.

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