Disorders of Magnesium Metabolism: Hypomagnesemia and Hypermagnesemia

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ABSTRACT
Magnesium ions are essential to all living cells. As the second most abundant intracellular cation, magnesium has a crucial role in fundamental metabolic processes such as DNA and protein synthesis, oxidative phosphorylation, enzyme function, ion channel regulation, and neuromuscular excitability. 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. Most patients with hypomagnesemia are asymptomatic and symptoms usually do not arise until the serum magnesium concentration falls below 1.2 mg/dL. The first step to determine the likely cause of the hypomagnesemia is to measure urinary magnesium and calcium. 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). Hypermagnesemia is defined as a serum magnesium level >2.3 mg/dL (>0.96 mmol/L or >1.9 mEq/L) and much less common than hypomagnesemia. Hypermagnesemia occurs primarily in patients with acute or chronic kidney disease. Neuromuscular symptoms are the most common presentation of magnesium intoxication. Evaluation of hypermagnesemia includes the determination magnesium, potassium, phosphate, and calcium levels as well as renal biochemistry. Patients with normal renal function and mild asymptomatic hypermagnesemia require no treatment except the removal of all sources of exogenous magnesium. Treatment includes the administration of intravenous calcium gluconate or chloride.

Key words: *Magnesium, Hypomagnesemia, Hypermagnesemia, Neuromuscular symptoms, Treatment*

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 important in health and disease. Epidemiological studies have shown a high prevalence of hypomagnesaemia and lower intracellular magnesium concentrations in diabetics. Benefits of magnesium supplementation on the metabolic profile of diabetics have been observed in some, but not all, clinical trials, and so larger prospective studies are needed to determine if dietary magnesium supplementation is associated with beneficial effects in this group [2]. Epidemiological studies have suggested that a relatively young

gestational age is associated with magnesium deficiency during pregnancy, which not only induces maternal and fetal nutritional problems but also leads to other consequences that might affect the offspring throughout life [3]. There is also evidence that magnesium and calcium compete with one another for the same binding sites on plasma protein molecules [4]. It was shown that magnesium antagonizes calcium-dependent release of acetylcholine at motor endplates [5]. Thus, magnesium may be considered a natural 'calcium antagonist'. While calcium is a powerful 'death trigger', magnesium is not [6]. Magnesium inhibits calcium-induced cell death [7]. It is anti-apoptotic in mitochondrial permeability transition and antagonizes calcium-overload-triggered apoptosis.

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 [8]. Magnesium is found in a wide variety of foods, and at particularly high levels in unrefined whole grain cereals, green leafy vegetables, nuts, seeds, peas and beans [1]. The recommended dietary intake of magnesium, which reflects the amount that meets the needs of almost all (98%) healthy individuals, is 320mg/day (13.3mmol/day) for adult females and 420mg/day (17.5mmol/day) for adult males [9]. 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) [8].

MAGNESIUM HOMEOSTASIS

The intestine secretes about 40mg of magnesium per day and about 20mg is absorbed in the large bowel. Gastrointestinal magnesium absorption is mediated by a saturable transcellular active pathway, as well as by non saturable paracellular passive transport [10]. Paracellular transport involves the passive absorption of magnesium through the small spaces between the epithelial cells regulated by the tight junction proteins including claudins, occludin, and zona-occludens-1 [11]. The transcellular pathway involves the active transport of magnsium to the blood through the interior of the epithelial cell mediated by apical Transient receptor potential channel melastatin member 6 (TRPM6) and TRPM7 magnesium channels. Intestinal absorption is regulated by a variety of factors. Magnesium absorption is altered by dietary Mg^{2+} intake which regulates the expression of TRPM6 in the colon [12]. When dietary magnesium intake is normal, transcellular transport mediates 30% of intestinal magnesium absorption [13]. This fraction increases up to ~80% when dietary magnesium intake is low [11]. When dietary magnesium is high, then the majority of intestinal magnesium absorption occurs via the paracellular pathway owing to changes in the electrochemical gradient. Patients with chronic renal disease often associated with hypomagnesaemia have low $1,25(OH)_2D$ levels, demonstrating that that 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] can stimulate intestinal Mg^{2+} absorption [14]. Claudins 2 and 12, which are involved in paracellular Ca^{2+} transport, are regulated by $1,25(OH)_2D$, indicating that these claudins are also involved in paracellular Mg^{2+} absorption. A regulatory role for the calcium-sensing receptor (CaSR) could explain the interaction between Mg^{2+} and Ca^{2+}.

Magnesium homeostasis is maintained by urinary excretion of approximately 100mg/day. Regulation of renal magnesium excretion maintains physiologic serum concentrations at between 0.75 and 0.95mmol/l (1.8–2.3mg/dl) in healthy humans [1]. A proportion of circulating

magnesium is protein bound, such that only 70% of total plasma magnesium is ultrafilterable [15]. In adults, a small fraction of filtered magnesium is reabsorbed in the proximal tubule. In contrast to most other ions, which are primarily reabsorbed in the proximal tubule, the thick ascending limb of the loop of Henle is the main site of magnesium reabsorption. 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 [16]. Through compensatory mechanism, the kidneys can lower magnesium excretion to as little as 0.5% of the filtered load in the presence of hypomagnesemia; decreased intake, redistribution from extracellular to intracellular space, or increased intestinal loss [16].

Magnesium transport in the thick ascending limb is mainly passive in nature, which occurs via a paracellular pathway driven by the electrical gradient that results from potassium exit across the apical membrane through renal outer medulla potassium (ROMK) channels [17]. The apical ROMK channels which represent the first (Kir1.1) of 7 subfamilies mediates apical recycling of potassium back to the tubular lumen and generation of lumen-positive voltage that drives paracellular magnesium transport. Paracellin-1 (claudin-16) and claudin 19 is expressed in tight junctions of the thick ascending limb of the loop of Henle and is required for selective paracellular magnesium conductance [18]. The apical Na^+–K^+–2Cl cotransporter (NKCC2) mediates apical absorption of Na, K, and Cl into the thick ascending loop cells (Figure 4). Na^+/ K^+ -ATPase also mediates Na^+ exit through the basolateral membrane and generates the Na^+ gradient for Na^+ absorption. The kidney-specific Cl channel, CLC-Kb mediates Cl exit through the basolateral membrane. The Ca^{2+} / Mg^{2+} - sensing receptor (CASR), a member of the G-protein-coupled receptor family, is an important regulator of magnesium homeostasis [19]. This receptor is located in the basolateral membrane of thick ascending limb cells and in the distal convoluted tubule, as well as in cells of the parathyroid glands that secrete parathyroid hormone (PTH). The CaSR upon stimulation, magnesium transport is decreased. In hypomagnesemic or hypocalcemic states, the rates of calcium and magnesium reabsorption in the loop of Henle are increased via CaSR mediated stimulation of the Na+–K+–2Cl– cotransporter and the apical ROMK channel [20].

In the distal convoluted tubule magnesium is absorbed by transcellular active transport. As there is little magnesium reabsorption beyond the distal tubule, this segment ultimately regulates urinary magnesium excretion. TRPM6 is also expressed in the apical membrane of distal convoluted tubule. The TRPM6 Mg^{2+} channel that is regulated by epithelial growth factor (EGF), allows Mg^{2+} to enter the cell. Mutations of the epithelial growth factor (EGF) have been associated with reduced expression of TRPM6 and thus, with hypomagnesemia [13]. Cancer medications that are EGF receptor inhibitors (eg, cetuximab, panitumumab) can also cause hypomagnesemia [21]. The apical K^+ channel Kv1.1 (ROMK1) maintains transmembrane voltage that is the driving force for TRPM6- mediated magnesium absorption by establishing favorable luminal potential. Kir4.1 (ROMK4) is responsible for recycling of K^+ at the basolateral site of the cell. The key molecule at the basolateral membrane is the Na^+/ K^+-ATPase, whose expression is regulated by transcription factor HNF1B. The Na^+/K^+-ATPase activity is stimulated by its gamma–subunit. Basolateral K^+ channel Kir4.1 and the gamma-subunit of Na^+/K^+-ATPase also increase magnesium reabsorption by generating a sodium gradient, making it possible for NCC (Na-Cl Cotransporter) to facilitate sodium transport from the apical lumen to the cytosol. The basolateral Mg^{2+} transporter remains to be identified. It has been proposed that

absorbed magnesium is extruded via a magnesium/sodium exchanger SLC41A1 family across the basolateral membrane [11]. NCC and ClC-Kb are responsible for Na^+ and Cl^+ transport in the distal convoluted tubule. Cyclin M2 (CNNM2) has also been identified as a gene involved in renal Mg^{2+} handling. In the kidney, CNNM2 was predominantly found along the basolateral membrane of distal tubular segments involved in Mg^{2+} reabsorption [11].

HYPOMAGNESEMIA

Hypomagnesemia is usually defined as serum magnesium, 0.7mmol/L, 1.4mEq/L, or 1.7 mg/dl. Biochemical hypomagnesemia is common, with a prevalence of up to 15% in the general population and up to 65% in patients in the intensive care units [22, 23].

Etiology of Hypomagnesemia

Hypomagnesemia results from negative magnesium balance that develops in the setting of decreased oral intake, increased gastrointestinal or renal losses, or a shift of magnesium from the extracellular to intracellular compartment. In some cases, more than one of these may be present. Most frequently, hypomagnesemia is an acquired disorder; only in rare instances does hypomagnesemia have an underlying hereditary etiology [24]. Table 1 summarizes the etiologies of hypomagnesemia.

Table 1: Causes of hypomagnesemia

Decreased magnesium intake	Alcohol use disorder Increased requirements during lactation Malnutrition Starvation Total parenteral nutrition Mg-free intravenous fluids Dietary deficiency; low oxalate diet & cellulose phosphate
Increased gastrointestinal magnesium loss	Chronic diarrhea Malabsorption syndrome Steatorrhea Small bowel bypass Chronic proton pump inhibitor use Intestinal resection Primary infantile hypomagnesemia
Increased renal magnesium excretion	Extracellular fluid volume expansion Alcohol use disorder Physiologic loss during pregnancy Parathyroidectomy Hypercalcemia Diabetic ketoacidosis Hypersecretion of aldosterone, thyroid hormones, or vasopressin Medication: loop and thiazide diuretics; amphotericin; pentamidine; cisplatin; foscarnet; ciclosporin; proton-pump inhibitors
Redistribution of magnesium from extracellular to intracellular	Acute pancreatitis: magnesium and calcium saponification in necrotic fat Hungry bone syndrome Insulin therapy Refeeding syndrome Correction of acidosis Catecholamine excess Massive blood transfusion

Hereditary causes	Intestinal and renal: hypomagnesemia with secondary hypocalcemia (HSH; TRPM6 mutations) Renal: Bartter syndrome; Gitelman syndrome; familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC; claudin-16 [paracellin-1] and claudin-19 mutations); autosomal dominant hypomagnesemia with hypocalciuria (Na+/K+- ATPase γ subunit mutations); isolated recessive hypomagnesemia; autosomal dominant hypocalcemia (Ca2+/Mg2+-sensing receptor activating mutations).

Alcoholics and individuals on magnesium-deficient diets or on parenteral nutrition for prolonged periods can become hypomagnesemic without abnormal gastrointestinal or kidney function. The addition of 4-12 mmol of magnesium per day to total parenteral nutrition has been recommended to prevent hypomagnesemia.

The transfer of magnesium from extracellular space to intracellular fluid or bone is a frequent cause of decreased serum magnesium levels. This depletion may occur as part of hungry bone syndrome, in which magnesium is removed from the extracellular fluid space and deposited in bone following parathyroidectomy or total thyroidectomy or any similar states of massive mineralization of the bones [25, 26]. Redistribution of magnesium from extracellular to intracellular compartment may also occur, following insulin therapy for diabetic ketoacidosis and may be related to the anabolic effects of insulin driving magnesium, along with potassium and phosphorus, back into cells. Hyperadrenergic states, such as alcohol withdrawal, may cause intracellular shifting of magnesium and may increase circulating levels of free fatty acids that combine with free plasma magnesium. The hypomagnesemia that sometimes is observed after surgery is attributed to the latter. Hypomagnesemia is a manifestation of the refeeding syndrome, a condition in which previously malnourished patients are fed high carbohydrate loads, resulting in a rapid fall in phosphate, magnesium, and potassium, along with an expanding extracellular fluid space volume, leading to a variety of complications. Acute pancreatitis can also cause hypomagnesemia. The mechanism may represent saponification of magnesium in necrotic fat, similar to that of hypocalcemia. However, postoperative states or critical illnesses in general are associated with low magnesium levels, without pancreatitis necessarily being present [27, 28].

Impaired gastrointestinal magnesium absorption is a common underlying basis for hypomagnesemia, especially when the small bowel is involved, due to disorders associated with malabsorption, chronic diarrhea, or steatorrhea, or as a result of bypass surgery on the small intestine. Because there is some magnesium absorption in the colon, patients with ileostomies can develop hypomagnesemia. An emerging association, described with increasing frequency, is the association with proton pump inhibitors (PPIs), widely used to reduce gastric acid secretion [29]. The likely mechanism is decreased gastrointestinal absorption. Hypomagnesemia with secondary hypocalcemia is a rare autosomal-recessive disorder characterized by profound hypomagnesemia associated with hypocalcemia [30]. Pathophysiology is related to impaired intestinal absorption of magnesium accompanied by renal magnesium wasting.

Urinary magnesium losses may result from hereditary conditions, medications, and other causes. Inherited tubular disorders that result in urinary magnesium wasting are stated in table 2. Loop diuretics (including furosemide, bumetanide, and ethacrynic acid), produce large increases in magnesium excretion through the inhibition of the electrical gradient necessary for magnesium reabsorption in the thick ascending loop of Henle (TAL). Long-term thiazide diuretic therapy also may cause magnesium deficiency, through enhanced magnesium excretion and, specifically, reduced renal expression levels of the epithelial magnesium TRPM6 channel [31]. Many nephrotoxic drugs, including cisplatin, amphotericin B, cyclosporine, tacrolimus, and

pentamidine, can produce urinary magnesium wasting by a variety of mechanisms, some of which are still unknown. For instance, tacrolimus causes hypomagnesemia through down-regulation of TRPM6 channels [31]. Urinary magnesium wasting due to immunosuppressive regimens that include calcineurin inhibitors (eg, cyclosporine, tacrolimus) is partly the reason that hypomagnesemia frequently develops after kidney transplantation. Other causal factors in these patients include post-transplantation volume expansion, metabolic acidosis, insulin resistance, decreased gastrointestinal absorption due to diarrhea, low dietary magnesium intake, and use of drugs such as diuretics or proton pump inhibitors [32]. In contrast, aminoglycosides are thought to activate the CaSR on the TAL and distal convoluted tubule (DCT), producing magnesium wasting [33]. Cisplatin- and amphotericin B induced magnesium deficiency is associated with hypocalciuria, which suggests injury to the DCT. In a rat model, showed that cisplatin treatment results in EGF and TRPM6 down-regulation, causing renal Mg^{2+} wasting [34]. Some data suggest that magnesium loss associated with cisplatin treatment is mainly the result of lowered intestinal absorption rather than, as presently thought, the result of increased renal elimination. Chemotherapeutic agents that are EGF receptor inhibitors (eg, cetuximab, panitumumab) can cause hypomagnesemia [21]. Other causes of renal magnesium wasting, and the likely mechanisms, include the following: Aldosterone excess induces chronic volume expansion, with subsequent increase in magnesium excretion; Hypercalcemia induces stimulation of the CaSR followed by inhibition of magnesium reabsorption; Alcohol ingestion induces tubular dysfunction preventing magnesium absorption but reversible within 4 weeks of abstinence [35]. Magnesium wasting can be seen as part of renal tubular dysfunction that is observed with recovery from acute tubular necrosis or during a post-obstructive diuresis.

Hereditary Hypomagnesemia

Hereditary forms of hypomagnesemia develop in the setting of renal magnesium wasting and/or intestinal magnesium malabsorption (Table 2).

Symptoms of familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) usually become evident in the first few months of life. Affected individuals present with symptoms including polyuria, polydipsia, urinary tract infections, hypomagnesemia, inappropriately high rates of urinary magnesium excretion, hypercalciuria, nephrocalcinosis, nephrolithiasis, hypocitraturia, elevated PTH levels, renal insufficiency and, in rare instances, generalized seizures [36]. The risk of permanent neurologic impairment in patients with FHHNC is relatively low. FHHNC is caused by mutations in the gene CLDN16, which encodes for paracellin-1 (claudin-16), a tight junction protein that form the paracellular pathway for calcium and magnesium reabsorption in the TAL [37].

Activating mutations of the Ca^{2+} / Mg^{2+} - sensing receptor also referred to as autosomal-dominant hypocalcemia with hypercalciuria (ADHH) is another disorder of urinary magnesium wasting [38]. Affected individuals present with hypocalcemia, hypercalciuria, and polyuria, and about 50% of these patients have hypomagnesemia. Clinically, ADH can be mistaken for primary hypoparathyroidism, as there is decreased PTH secretion in the setting of mild to moderate hypocalcemia. Patients can be asymptomatic or have symptoms related to hypocalcemia during childhood. The majority of affected individuals have hypomagnesemia and renal magnesium wasting. ADH must be differentiated from primary hypoparathyroidism because there is an increased risk of hypercalciuria, nephrocalcinosis and even irreversible reduction of renal function in individuals with ADH who are treated with vitamin D. Only patients with ADH with symptomatic hypocalcemia should be treated with calcium and vitamin D. In ADHH, activating mutations of the CaSR gene located basolaterally in TAL and DCT

leads to a shift in the set point of the mutant receptor to a level of enhanced sensitivity by increasing the apparent affinity of the mutant receptor for extracellular calcium and magnesium. This results in diminished PTH secretion and decreased reabsorption of divalent cations in the TAL and DCT, which leads to loss of urinary calcium and magnesium. In other cases, a basolateral protein (cyclin M2 protein) mutation has been described [39].

Autosomal dominant hypomagnesemia with hypocalciuria also called isolated dominant hypomagnesemia with hypocalciuria is a condition associated with few symptoms other than chondrocalcinosis [40]. Patients always have hypocalciuria and variable (but usually mild) hypomagnesemic symptoms. Mutation in the gamma subunit of the basolateral Na^+ / K^+ - ATPase in the DCT is thought to produce a disturbed routing of the Na^+ / K^+ - ATPase complex to the basolateral membrane, leading to reduced expression of the Na^+ / K^+ -ATPase on the cell surface [41]. Consequently, the entry of potassium is reduced and the cell depolarizes to some extent, leading to closing of the TRPM6 channel and magnesium wasting.

Isolated recessive hypomagnesemia with normocalcemia IRH with normocalcemia is an autosomal-recessive disorder in which affected individuals present with symptoms of hypomagnesemia early during infancy. Hypomagnesemia due to increased urinary magnesium excretion appears to be the only abnormal biochemical finding. IRH is distinguished from the autosomal-dominant form by the lack of hypocalciuria [40]. IRH is due to a mutation of the EGF precursor protein pro-EGF, which is expressed in the basolateral membrane of the distal convoluted tubule. This results to inadequate stimulation of renal epidermal growth factor receptor (EGFR), and thereby insufficient activation of the epithelial Mg^{2+} channel TRPM6, which results in magnesium wasting [13]. In IRH, mutation in the cytoplasmic domain of the pro-EGF precursor protein prevents EGF secretion into the basolateral space. This leads to decreased TRPM6 mediated magnesium uptake by the distal convoluted tubule from the luminal membrane, and to renal magnesium wasting [13].

Hypomagnesemia with secondary hypocalcemia (HSH), also called primary intestinal hypomagnesemia, is an autosomal-recessive disorder that is characterized by very low serum magnesium levels and low calcium levels [30]. HSH is an autosomal recessive disorder of intestinal and renal magnesium transport caused by mutations of TRPM6. TRPM6 mutations cause a defect in the active transcellular pathway of intestinal magnesium absorption [24]. Patients usually present within the first 3 months of life with the neurologic signs of hypomagnesemic hypocalcemia, including seizures, tetany, and muscle spasms. Untreated, HSH may result in permanent neurologic damage or may be fatal. Hypocalcemia is secondary to parathyroid failure and peripheral parathyroid hormone resistance as a result of sustained magnesium deficiency. Usually, the hypocalcemia is resistant to calcium or vitamin D therapy. Normocalcemia and relief of clinical symptoms can be attained by administration of high oral doses of magnesium, up to 20 times the normal intake. As large oral amounts of magnesium may induce severe diarrhea and noncompliance in some patients, parenteral magnesium administration must sometimes be considered. Alternatively, continuous nocturnal nasogastric magnesium infusions have been proven to efficiently reduce gastrointestinal adverse effects. Patients with HSH require intravenous magnesium during convulsive episodes and lifelong high-dose oral magnesium replacement [30].

Table 2: Hereditary causes of hypomagnesemia, and the affected genes and proteins.

Type	Gene	Protein
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	*CLDN16*	Paracellin-1 (claudin-16), found at tight junctions in thick ascending limb of the loop of Henle and distal convoluted tubule
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular manifestation	*CLDN19*	Claudin-19, found at tight junctions in the thick ascending limb of the loop of Henle and to a much lesser extent in the distal convoluted tubule
Autosomal dominant hypomagnesemia with hypocalciuria	*FXYD2*	γ subunit of basolateral Na^+ / K^+ -ATPase in distal convoluted tubule
Isolated recessive hypomagnesemia with normocalciuria	*EGF*	The pro-EGF–Pro1070Ala mutation leads to impaired basolateral sorting of pro-EGF, resulting in decreased stimulation of the EGF receptor, which is localized at the basolateral membrane of distal convoluted tubule
Hypomagnesemia with secondary Hypocalcemia	*TRPM6*	TRPM6 is expressed in distal convoluted tubule and in intestine
Activating mutations of the extracellular Ca2+/Mg2+-sensing receptor	*CASR*	Ca^{2+} / Mg^{2+} -sensing receptor in chief cells of parathyroid gland and basolateral membrane in thick ascending limb of the loop of Henle and distal convoluted tubule
Gitelman syndrome	*SLC12A3*	NCCT in distal convoluted tubule
Antenatal Bartter syndrome type I	*SLC12A1*	NKCC2 in thick ascending limb of the loop of Henle
Antenatal Bartter syndrome type II	*KCNJ1*	ROMK in thick ascending limb of the loop of Henle
Classic Bartter syndrome type III	*CLCNKB*	CLCKB in thick ascending limb of the loop of Henle
Bartter syndrome with sensorineural deafness type IV	*BSND*, or *CLCNKA* plus *CLCNKB*	Barttin acts as an essential β subunit for CLCKA and CLCKB, which are located in the basolateral membrane of thick ascending limb of the loop of Henle

Abbreviations: CLCKA and CLCKB, renal chloride channels; EGF, epidermal growth factor; NA, not available; NCCT, sodium–chloride cotransporter; NKCC2, Na+–K+–2Cl– cotransporter;; pro-EGF, epidermal growth factor precursor protein; ROMK, renal outer medulla potassium channel; TRPM6, transient receptor potential cation channel, subfamily M, member 6.

Gitelman syndrome and Bartter syndrome are two hereditary renal salt-wasting disorders characterized by hypokalemic chloride-resistant metabolic alkalosis, elevated plasma levels of renin and aldosterone, and normal blood pressure. Hypomagnesemia and renal magnesium wasting are distinctive features of Gitelman syndrome. By contrast, there is doubt as to whether magnesium metabolism is ever markedly abnormal in patients with true Bartter [1]. Gitelman syndrome is an autosomal-recessive condition caused by mutations of the SLC12A3 gene, which encodes the thiazide-sensitive NaCl cotransporter (NCCT) expressed in the distal convoluted tubule [42]. NCCT reabsorbs approximately 7% of the filtered sodium chloride load. A minority of patients with Gitelman syndrome has been diagnosed with mutations of CLCNKB, the gene that encodes the basolaterally located renal chloride channel CLCKB, which is expressed along the thick ascending limb and distal convoluted tubule and mediates chloride efflux from tubular epithelial cells to the interstitium. The overlap between Gitelman syndrome and classic Bartter syndrome type III is probably related to the fact that CLCKB is present in both the thick ascending limb of the loop of Henle and the distal convoluted tubule. Patients with Gitelman syndrome usually become symptomatic later in life than those with Bartter syndrome; that is, during adolescence or early adulthood.This syndrome is characterized by hypokalemia, hypomagnesemia, and hypocalciuria [43]. Hypomagnesemia is found in most patients with Gitelman syndrome and is assumed to be secondary to the primary defect in the NCCT, but some data point to magnesium wasting as a primary abnormality [44]. Some studies have indicated

that magnesium wasting in Gitelman syndrome may be due to down-regulation of TRPM6 in the DCT.

Classic Bartter syndrome is caused by mutations of the CLCNKB gene [45]. The antenatal form of Bartter syndrome is life threatening. Antenatal Bartter syndrome type I is caused by mutations in the Na^+ –K^+ –2Cl– cotransporter gene (SLC12A1) and is clinically and biochemically very similar to antenatal Bartter syndrome type II, which is caused by mutation of the potassium channel ROMK1 gene [46]. In utero, polyuria of the affected fetus leads to polyhydramnios between 24 and 30 weeks of gestation and premature delivery. Postnatally, infants rapidly develop renal salt wasting, hypokalemic metabolic alkalosis, hypercalciuria and, as secondary consequences, nephrocalcinosis and osteopenia. Hypermagnesuria is not a characteristic feature of this disease. Increased magnesium reabsorption in the distal nephron or increased renal prostaglandin synthesis, which is observed in antenatal Bartter syndrome, might contribute to increased magnesium reabsorption in the distal convoluted tubule. Bartter syndrome type IV is the combination of the infantile variant of Bartter syndrome and sensorineural deafness, which can develop during the first month of life. Bartter syndrome type IV is caused by mutation of the BSND (infantile Bartter syndrome with sensorineural deafness) gene or by simultaneous mutationof both the CLCNKA (which encodes the renal chloride channel CLCKA) and CLCNKB genes [47]. Hypomagnesemia is detected in only up to 50% of affected individuals with classic Bartter syndrome. Patients usually become symptomatic during infancy or early childhood, and present with polyuria, polydipsia, growth retardation and developmental delay. Disturbed magnesium homeostasis is not a common finding in patients with antenatal Bartter syndrome.

Clinical manifestations of hypomagnesemia

The clinical features of hypomagnesemia are presented in table 3. Many patients with magnesium deficiency and hypomagnesemia remain asymptomatic. As magnesium deficiency is usually secondary to other disease processes or drugs, the features of the primary disease may complicate or mask magnesium deficiency. Signs and symptoms of magnesium deficiency are usually not seen until the magnesium concentration decreases to 0.5 mmol/l (1.2mg/dL) or lower [48]. Furthermore, the clinical manifestations may depend more on the rate of development of magnesium deficiency and/or the total body deficit rather than the actual serum magnesium concentration. Long-term magnesium deficiency may have a role in chronic diseases such as atherosclerosis, myocardial infarction, hypertension, and renal calculi.

Hypomagnesemia is frequently associated with metabolic abnormalities such as hypokalemia and hypocalcemia. Infact, the classic sign of severe hypomagnesemia (< 1.2 mg/dL) is hypocalcemia. The copresentation of hypokalemia and hypocalcemia makes it difficult to distinguish the clinical manifestations related to the magnesium deficiency [49]. Magnesium and potassium are closely related thus, hypokalemia is common in patients with hypomagnesemia, occurring in 40-60% of cases [50]. Hypokalemic metabolic alkalosis with occurs in some variants of hereditary hypomagnesemia [51]. Intracellular magnesium deficiency causes low intracellular potassium and an inability of the kidney to conserve potassium. This is partly due to underlying disorders that cause magnesium and potassium losses, including diuretic therapy and diarrhea. The mechanism for hypomagnesemia-induced hypokalemia relates to the intrinsic biophysical properties of ROMK channels mediating K^+ secretion in the TAL and the distal nephron. A decrease in intracellular magnesium concentration in the TAL and collecting duct cells results in increased K^+ secretion through the ROMK channels. Evidence also suggests

that K^+ wasting may be due to a hypomagnesemia-induced decline in ATP and the subsequent removal of ATP inhibition of the ROMK channels responsible for secretion of K^+ in the TAL and collecting duct [52]. Hypokalemia cannot be corrected by treatment with calcium, vitamin D, or both, until the magnesium depletion is corrected. The hypokalemia of magnesium deficiency contributes to the cardiac manifestations of hypomagnesemia, but may delay the onset of tetany. Up to one-third of patients with hypomagnesemia in intensive care units may have hypocalcemia [53]. Symptomatic hypocalcemia is usually seen in moderate to severe magnesium deficiency and there is a positive correlation between serum magnesium and calcium concentrations in these patients. Hypocalcemia in patients with severe hypomagnesemia is attributable to several pathophysiologic processes: (a) a decrease in PTH secretion due to Impaired magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP), (b) end organ resistance to the action of PTH, (c) decrease in serum concentration of 1,25 dihyroxy vitamin D due to impaired synthesis of 1α-hydroxylase, causing reduced intestinal calcium absorption, and (d) resistance to 1, 25 dihydroxy vitamin D [53, 54]. Hypocalcemia of magnesium deficiency cannot be corrected by treatment with calcium, vitamin D, or both. Magnesium therapy alone will restore serum calcium concentration to normal.

Table 3: Clinical features of hypomagnesemia

Electrolyte disturbance	Hypokalemia Hypocalcemia
Neuromuscular and central nervous system	Carpopedal spasm Convulsions Muscle cramps Muscle weakness, fasciculations, tremors Vertigo Nystagmus Depression, psychosis Athetoid movements and choreform movements
Cardiovascular	Atrial tachycardias, fibrillation Supraventricular arrhythmias Ventricular arrhythmias Torsade de pointes Digoxin sensitivity
Complications of magnesium deficiency	Altered glucose homeostasis Atherosclerotic vascular disease Hypertension Myocardial infarction
Others	Osteoporosis Migraine Asthma Chronic fatigue syndrome Athletic performance

The earliest manifestations of symptomatic magnesium deficiency are usually neuromuscular and neuropsychiatric disturbances [54]. The most common clinical manifestation is hyperexcitability manifested as positive Chvostek and Trousseau signs, tremor, fasciculations,

and tetany. Trousseau sign is the precipitation of carpal spasm by reduction of the blood supply to the hand with a tourniquet or blood pressure cuff inflated to 20 mm Hg above systolic blood pressure applied to the forearm for 3 minutes. Chvostek sign is an involuntary twitching of the facial muscles elicited by a light tapping of the facial nerve just anterior to the exterior auditory meatus. Other manifestations include apathy, hyperreflexia, acute organic brain syndromes, depression, generalized weakness, anorexia, and vomiting. Other manifestations include convulsions, athetoid movements, nystagmus, dysphagia, apathy, muscle cramps, hyperreflexia, acute organic brain syndrome, depression, generalized weakness, reversible psychiatric manifestations, anorexia, and vomiting. Occasionally hemiparesis, aphasia, and reduced respiratory muscle power have also been found. Several mechanisms contribute to these features. The threshold of axon stimulation is decreased and nerve conduction velocity is increased when serum magnesium concentration is low. By competitively inhibiting the entry of calcium into the presynaptic nerve terminals, magnesium influences the release of neurotransmitters at the neuromuscular junction and causes hyper responsive neuromuscular activity. The release of calcium from the sarcoplasmic reticulum in muscle is increased and the reuptake of calcium is reduced in magnesium deficiency. The net effect is a muscle that is more readily contractible to a given stimulus and that is less able to recover from the contraction, i.e., prone to tetany [54].

The effect of magnesium deficiency on the central nervous system is even more complicated and less well understood. The cardiovascular effects of magnesium deficiency include effects on electrical activity, myocardial contractility, potentiation of digitalis effects, and vascular tone [53]. Thus hypomagnesemia can cause cardiac arrhythmias including atrial and ventricular tachycardia, prolonged QT interval and torsades de pointes (a repetitive, polymorphous ventricular tachycardia with prolongation of the QT interval). Magnesium depletion also increases the susceptibility to arrhythmogenic effects of drugs such as isoproterenol and cardiac glycosides. The effects of magnesium deficiency on the heart are further complicated by intracellular potassium depletion and hypokalemia. Hypomagnesemia and magnesium depletion may contribute to digoxin toxicity, even in the presence of apparently therapeutic concentration of serum digoxin and routine monitoring of serum magnesium concentration in digitalized patients has been recommended [53]. Epidemiologic studies also show an association between magnesium deficiency and coronary artery disease [55]. The ionic basis of the effect of magnesium depletion on cardiac arrhythmia may be related to impairment of the membrane sodium-potassium pump and the increased outward movement of potassium through the potassium channels in cardiac cells, leading to shortening of the action potential and increasing susceptibility to cardiac arrhythmia [56]. Chondrocalcinosis has been described as a complication of chronic hypomagnesemia, especially in patients with Gitelman syndrome and those with autosomal dominant hypomagnesemia with hypocalciuria [1].

Patients with diabetes mellitus are often magnesium deficient, expressed by hypomagnesemia [57]. Magnesium deficiency decreases insulin sensitivity and secretion [47]. Moreover, magnesium deficiency is inherently related to the pathogenesis and development not only of diabetic microangiopathy but also of lifestyle-related diseases, such as hypertension and hyperlipidemia [58]. Magnesium deficiency may be a link with both inflammation and vascular stiffness in certain populations [59].

Diagnosis of hypomagnesemia

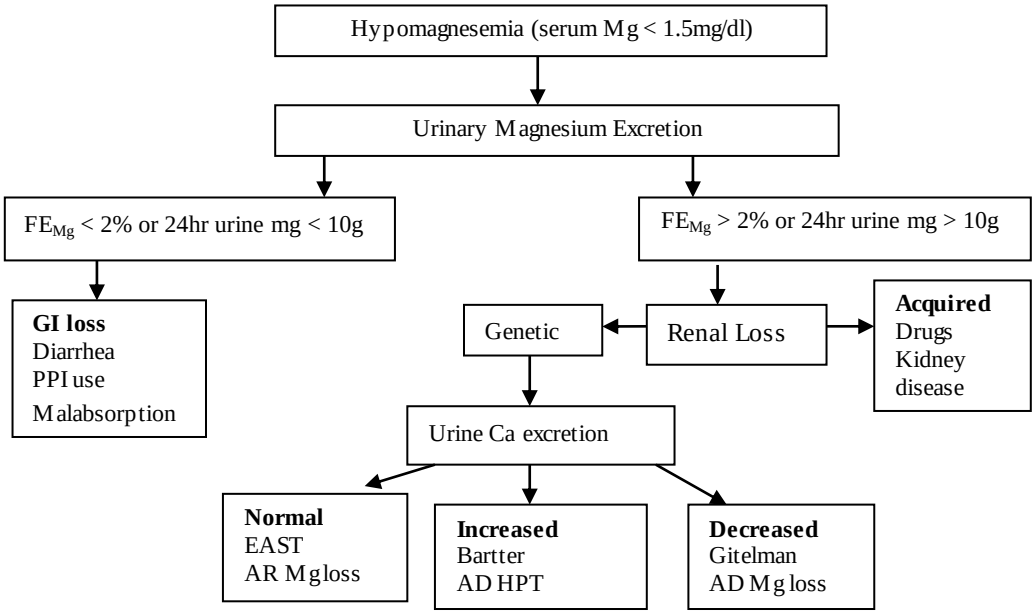
Diagnosis of hypomagnesemia should be considered in patients with risk factors and with unexplained hypocalcemia or hypokalemia. Hypomagnesemia is diagnosed in patients with serum magnesium concentration < 1.8 mg/dL (< 0.70 mmol/L). Severe hypomagnesemia usually

results in concentrations of < 1.25 mg/dL (< 0.50 mmol/L). Associated hypocalcemia and hypocalciuria are common. Hypokalemia with increased urinary potassium excretion and metabolic alkalosis may be present. Magnesium deficiency should be suspected even when serum magnesium concentration is normal in patients with unexplained hypocalcemia or refractory hypokalemia. Magnesium deficiency should also be suspected in patients with unexplained neurologic symptoms and alcohol use disorder, with chronic diarrhea, or after cyclosporine use, cisplatin-based chemotherapy, or prolonged therapy with amphotericin B or aminoglycosides [60].

The diagnostic algorithm of hypomagnesemia is presented in figure 1. In the setting of hypomagnesemia, assessment of urinary magnesium excretion helps differentiate renal magnesium wasting from extrarenal magnesium loss. The kidney's physiologic response to hypomagnesemia is to increase reabsorption. As a circadian rhythm underlies renal magnesium excretion, it is important to collect a 24-h urine specimen to assess magnesium excretion and absorption accurately. When sampled via a 24 h collection, magnesium excretion in the urine is expected to be less than 1 mmol (<24 mg) per day [1]. More severe magnesuria indicates renal magnesium wasting. It is more convenient in clinical practice to measure fractional urinary magnesium excretion and urinary calcium-creatinine ratio, as this requires only a spot urine sample. The formula used to calculate the FE_{Mg} is the same as that for fractional excretion of sodium [61].

FE_{Mg} = (urine Mg × serum creatinine)/ [(0.7 × serum Mg) × urine creatinine] × 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 extra-renal magnesium wasting like poor intake, gastrointestinal losses, or a shift of magnesium into cells [62]. An FE_{Mg} above 4% in a subject with normal kidney function indicates renal magnesium wasting [62]. 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) [43]. 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) [43].



PPI-proton pump inhibitors, EAST-epilepsy, ataxia, sensorineural deafness and salt-wasting renal tubulopathy syndrome., AR Mg loss-autosomal recessive renal magnesium wasting., AD Mg loss-autosomal dominant renal magnesium wasting., AD HPT-autosomal dominant hypoparathyroidism

Figure 1: Diagnostic algorithm for evaluation of hypomagnesemia

In a patient with renal magnesium wasting, measurement of urinary magnesium excretion might be misleading if it is performed when the patient is in a fasting basal state; the rate of excretion might not be elevated if the kidneys have reached their low tubular reabsorptive maximum. In this setting, renal magnesium wasting can be diagnosed on the basis of detection of hypermagnesuria after administration of magnesium in the magnesium retention test or magnesium tolerance test [1].

Treatment of Hypomagnesemia

Patients with mild to moderate deficiency (1.2 mg/dL to 1.7 mg/dL) should be treated with diet or oral magnesium supplements [63]. Patients with alcohol use disorder are treated empirically. In such patients, deficits approaching 12 to 24 mg/kg are possible. About twice the amount of the estimated deficit should be given in patients with intact renal function because about 50% of the administered magnesium is excreted in urine. Oral magnesium salts (eg, magnesium gluconate 500 to 1000 mg orally 3 times a day) are given for 3 to 4 days. Oral treatment is limited by the onset of diarrhea [60].

Parenteral administration is reserved for patients with severe, symptomatic hypomagnesemia who cannot tolerate oral drugs. Sometimes a single injection is given in patients with alcohol use disorder who are unlikely to adhere to ongoing oral therapy. When magnesium must be replaced parenterally, a 10% magnesium sulfate solution (1 g/10 mL) is available for IV use and a 50% solution (1 g/2 mL) is available for IM use. The serum magnesium concentration should be monitored frequently during magnesium therapy, particularly when magnesium is given to patients with renal insufficiency or in repeated parenteral doses. Patients with renal insufficiency should receive 25% to 50% of the initial dose

recommended for patients with normal kidney function. In these patients, treatment is continued until a normal serum magnesium concentration is achieved. Thus, establishment of adequate kidney function is required before administering any magnesium supplementation [60].

In severe, symptomatic hypomagnesemia (eg, magnesium < 1.25 mg/dL [< 0.5 mmol/L] with seizures or other severe symptoms), 2 to 4 g of intravascular (IV) magnesium sulfate is given over 5 to 10 minutes. When seizures persist, the dose may be repeated up to a total of 10 g over the next 6 hours. In patients in whom seizures stop, 10 g in 1 L of 5% D/W (dextrose in water) can be infused over 24 hours, followed by up to 2.5 g every 12 hours to replace the deficit in total magnesium stores and prevent further drops in serum magnesium. When serum magnesium is ≤ 1.25 mg/dL (< 0.5 mmol/L) but symptoms are less severe, magnesium sulfate may be given IV in 5% D/W at a rate of 1 g/hour as slow infusion for up to 10 hours. In less severe cases of hypomagnesemia, gradual repletion may be achieved by administration of smaller parenteral doses over 3 to 5 days until the serum magnesium concentration is normal [60].

Concurrent hypokalemia or hypocalcemia should be specifically addressed in addition to hypomagnesemia. These electrolyte disturbances are difficult to correct until magnesium has been repleted. Additionally, hypocalcemia can be worsened by isolated treatment of hypomagnesemia with intravenous magnesium sulfate because sulfate binds ionized calcium [60].

HYPERMAGNESEMIA

Hypermagnesemia is defined as a serum magnesium level >2.3 mg/dL (>0.96 mmol/L or >1.9 mEq/L) and can be further characterized as mild (~2.3–4.0 mg/dL or ~0.96–1.64 mmol/L or ~1.9–3.3 mEq/L), moderate (~4.0–7.0 mg/dL or ~1.64–2.88 mmol/L or ~3.3–5.8 mEq/L), or severe (>7.0 mg/dL or >2.88 mmol/L or >5.8 mEq/L) [64]. Hypermagnesemia is much less common than hypomagnesemia due to the capacity of the normally functioning kidney to eliminate excess magnesium via a compensatory mechanism. The incidence of hypermagnesemia varies from 5.7–9.3% in hospital populations [65]. Nearly all hypermagnesemia goes undiagnosed [66].

Etiology of Hypermagnesemia

Causes of hypermagnesemia are listed in Table 4. Hypermagnesemia occurs primarily in patients with acute or chronic kidney disease. In these individuals, some conditions, including the administration of magnesium salts or magnesium-containing drug, malnourishment, and alcoholism, can increase the risk of hypermagnesemia. Hypothyroidism and especially cortico-adrenal insufficiency are other recognized renal causes. Hyperparathyroidism and alterations in calcium metabolism involving hypercalcemia and/or hypocalciuria can lead to hypermagnesemia through an increased calcium-induced magnesium absorption in the renal tubule. Patients with familial hypocalciuric hypercalcemia (FHH), a rare autosomal dominant condition, can manifest hypermagnesemia [67, 68]. Lithium-based psychotropic drugs can also lead to hypermagnesemia by reducing excretion.

Hypermagnesemia may rarely develop even without renal impairment, mostly in the elderly, where an underlying bowel condition may lead to increased absorption through decreased gut motility. Patients treated with anticholinergics or opioids, or those with inflammatory bowel diseases are at higher risk [69]. Drug formulations such as laxatives and

antacids that contain magnesium (e.g., magnesium oxide) can lead to increased values of magnesium, especially in elderly patients with renal function impairment.

Table 4: Causes of hypermagnesemia

Redistribution	Acute acidosis
Excessive intake	Antacids Cathartics Swallowing salt water laxatives Parenteral Urethral irrigation
Renal failure	Chronic renal failure Acute renal failure Rhabdomyolysis
Others	Lithium ingestion Familial hypocalciuric hypercalcemia Hypothyroidism Addison's disease Milk alkali syndrome Depression

Magnesium oxide is relatively safe however; its prolonged use may lead to risks of hypermagnesemia [70]. Periodic evaluation is a recommendation in elderly patients treated with magnesium oxide for extended periods. Nevertheless, magnesium intake under 1000 mg/day seems to be relatively safe [71]. Severe hypermagnesemia has also been described after the administration of bowel preparation agents (e.g., sodium picosulphate magnesium citrate) (68). Moreover, excessive oral intake can lead to hypermagnesemia in patients on hemodialysis, as ingestion primarily influences plasma levels in these patients [72]. Patients with milk-alkali syndrome due to the ingestion of large amounts of calcium and absorbable alkali are more susceptible to develop hypermagnesemia. Since magnesium is useful in the management of eclampsia (e.g., therapeutic serum magnesium level 1.7 to 3.5 mmol/L), excessive infusion can induce iatrogenic hypermagnesemia. Newborns of mothers who have received magnesium sulfate parenterally during labor may present with toxicity even with normal serum magnesium levels.

Magnesium levels can increase in hemolysis patients. Red blood cells contain three times as much magnesium as compared to plasma. The rupture of these cells pours magnesium into the plasma. However, symptomatic hypermagnesemia occurs only in the case of aggressive hemolysis. Tumor lysis syndrome, rhabdomyolysis, and acidosis (e.g., decompensated diabetes with ketoacidosis) can also induce hypermagnesemia through extracellular shifts.

Consequencies of hypermagnesemia

Clinical manifestations of hypermagnesemia are presented in table 5. Patients with symptomatic hypermagnesemia can present different clinical manifestations depending on the level and the time in which the electrolyte disturbance has occurred. Hypermagnesemia is generally well tolerated. Clinically, one of the earliest effects of magnesium intoxication presents as mild hypermagnesemia (less than 7 mg/dL) which may be asymptomatic or paucisymptomatic: weakness, nausea, dizziness, and confusion [53]. Signs and symptoms may proceed in moderate hypermagnesemia (7 to 12 mg/dL) including; Decreased or disappearance

of deep tendon reflexes, worsening of the confusion state and sleepiness, bladder paralysis, flushing, headache, and constipation. A slight reduction in supine as well as erect blood pressure, bradycardia, and blurred vision caused by diminished accommodation and convergence are usually present. Severe hypermagnesemia (greater than 12 mmol/dL) include muscle weakness proceeding to flaccid paralysis of voluntary and/or respiratory muscles, leading to depressed respiration, more evident hypotension and bradycardia, prolongation of the P-R interval, increased QRS duration and QT intervals, atrioventricular block, and lethargy are common. Coma and cardiorespiratory arrest can occur for higher values (over 15 mg/dL). Hypermagnesemia may cause paralytic ileus due to smooth muscle paralysis and may impair blood clotting due to interference with platelet adhesiveness, thrombin generation time and clotting time. Other nonspecific manifestations of magnesium intoxication include vomiting and cutaneous flushing.

Table 5: Clinical manifestations of hypermagnesemia

Neuromuscular	Confusion Lethargy Respiratory depression Absent tendon reflexes Paralytic ileus Bladder paralysis Muscle weakness/paralysis
Cardiovascular	Hypotension Bradycardia Inhibition of AVand inteventricular conduction Heart block Cardiac arrest
Others	Nausea, vomiting

Neuromuscular symptoms are the most common presentation of magnesium intoxication, as a result of blockage of neuromuscular transmission and depression of the conduction system of the heart and sympathetic ganglia [53]. The neurologic manifestations are the result of the inhibition of acetylcholine release from the neuromuscular endplate due to increased extracellular magnesium levels. The effects on the neuromuscular junctions are antagonized by calcium, and therefore the effects of hypermagnesemia are exaggerated in the presence of hypocalcemia. Hypotension is caused by the negative ion tropic effect of hypermagnesemia [73]. Other potential factors contributing to the hypotension include the effect of magnesium on the central nervous system, skeletal muscle paralysis, and depression of the carotid-baro receptor. Magnesium works as a physiologic calcium blocker leading to a fall in serum calcium concentration. Increased magnesium levels determine substantial electrophysiological and hemodynamic effects of hypermagnesemia. Moreover, the potential concomitance of hyperkalemia increases the risk of cardiac arrhythmias and cardiac arrest. Hypocalcemia commonly reported in preeclemptic patients treated with magnesium is due to suppression of PTH secretion by hypermagnesemia [53]

Diagnostic evaluation of hypermagnesemia

Sometimes the diagnosis of hypermagnesaemia can be challenging since checking serum magnesium is not routine. Many clinicians are unfamiliar with this uncommon condition as symptoms are non-specific and the characteristic clinical picture is an expression of overt disease. Hypermagnesaemia shares similar symptoms; neurologic or cardiorespiratory depression with other wide range of disorders. These disorders include: Acute renal failure, hypercalcemia, hyperkalemia, hypoparathyroidism, hypothyroidism, lithium toxicity, hemolysis, and rhabdomyolysis Evaluation of a patient suspected of having hypermagnesemia includes the determination of serum and urine magnesium, potassium, phosphate, and calcium levels. The clinical evaluation of renal function with urinary output and determination of the basic metabolic panel focusing on renal biochemistry: glomerular filtration rate, blood urea nitrogen, creatinine, glucose, urine specific gravity, determination of arterial blood gas and ECG.

Treatment and management of hypermagnesemia

Most cases of hypermagnesemia can be prevented. Patients with normal renal function (GFR over 60 ml/min) and mild asymptomatic hypermagnesemia require no treatment except the removal of all sources of exogenous magnesium. One must consider that the half-time of elimination of magnesium is approximately 28 hours. The possibility of hypermagnesemia should be anticipated in any patient receiving magnesium treatment, especially if the patient has reduced renal function; serum magnesium concentration should be monitored daily. In more severe cases, close monitoring of the ECG, blood pressure, and neuromuscular function and early treatment is necessary. Treatment includes administration of intravenous calcium gluconate or chloride [Dosage: 1 g in 2 to 5 min (repeatable over 5 minutes)] [53]. This usually causes a dramatic improvement in the patient's clinical condition due to the antagonist action of calcium against effects of magnesium in neuromuscular and cardiac function. Therapy may include the administration of intravenous normal saline (e.g., at 150 ml/hour). Administration of glucose and insulin many also help to promote magnesium entry into the cells. Severe clinical conditions require increasing renal magnesium excretion through the administration of intravenous loop diuretics (e.g., furosemide 1 mg/kg). Occasionally, exchange transfusion or hemodialysis is performed when kidney function is impaired, or the patient is symptomatic from severe hypermagnesemia. This approach usually removes magnesium efficiently (up to 50% reduction after a 3- to 4-hour treatment). Dialysis can, however, increase the excretion of calcium leading to the development of hypocalcemia, thus possibly worsening the symptoms and signs of hypermagnesaemia.

The use of diuretics must be associated with infusions of saline solutions to avoid further electrolyte disturbances (e.g., hypokalemia) and metabolic alkalosis. The clinician must perform serial measurements of calcium and magnesium. In association with electrolytic correction, it is often necessary to support cardiorespiratory activity. As a consequence, the treatment of this electrolyte disorder can frequently require intensive care unit admission [67]. Particular clinical conditions require a specific approach. Magnesium therapy should be withdrawn in certain instances. During the management of eclampsia, the magnesium infusion is stopped if urine output drops to less than 80 mL (in 4 hours), deep tendon reflexes are absent, or the respiratory rate is below 12 breaths/minute. A 10% calcium gluconate or chloride solution (10 mL intravenously repeatable over 5 minutes) can serve as an antidote.

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