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# Magnesium – So Underappreciated

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**Magnesium is essential to many metabolic processes, yet hypomagnesemia is common in hospitalized patients, especially in the critically ill. With high morbidity and mortality rates reported in hypomagnesemic patients, prompt diagnosis and treatment is of utmost importance. A widely utilized serum magnesium test happens to be a poor predictor of magnesium status making diagnosis and management of magnesium disorders challenging. Current magnesium repletion practices may prove wasteful and ineffective in restoring magnesium levels. This article will review magnesium basics including assessment tests, etiologies of hypomagnesemia and provide guidance on effective ways of treating magnesium deficiency.**

## INTRODUCTION

Magnesium (Mg), the fourth most abundant cation in the body, is a co-factor in more than 300 enzymatic reactions and plays an important role in the synthesis of proteins, DNA and RNA.[1] It is crucial for muscle contraction and relaxation, nerve function, heart rhythm, vascular tone and bone formation.[2] Ninety-nine percent of total body Mg is intracellular (bone, skeletal muscle, soft tissue) with only ~1% found in serum and red blood cells (extracellular). A large percentage (70-80%) of serum Mg is ionized (easily filtered by the kidneys), 20-30% bound to proteins (mainly albumin), and only ~1-2% complexed with anions.[2-5]

Magnesium homeostasis is maintained by the intestines, bone and the kidneys. It is absorbed most efficiently in the ileum with some absorption occurring in the colon via a passive paracellular mechanism and stored in bone; excess Mg is excreted by the kidneys as well as through the feces. Only about 30-50% of total dietary Mg consumed is absorbed in the intestines as other nutrients present in the gut (fiber, phytates, oxalates, phosphates) can bind the cation and decrease its absorption. Magnesium status determines Mg absorption with more of this mineral absorbed if Mg levels are low. Kidneys reabsorb ~ 95% of filtered Mg and excrete only ~ 3 – 5% in the urine,[2,3,6] unless rapid infusions are given.

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**Table 1. Causes of Hypomagnesemia**[7,8,10]

- **Gastrointestinal losses**
  - Malabsorption (celiac, IBD)
  - Small bowel bypass surgery, short bowel syndrome, GI fistulas
  - Diarrhea, vomiting, nasogastric suction
  - Long-term use of proton pump inhibitors
  - Excessive use of laxatives
  - Primary intestinal hypomagnesemia
- **Decreased Mg intake**
  - Malnutrition, alcoholism
  - Low Mg diet
  - Parenteral nutrition lacking/low in Mg
- **Re-feeding syndrome**
- **Hungry bone syndrome**
- **Diabetic ketoacidosis**
- **Acute pancreatitis**
- **Renal losses**
  - Medications
    - Loop & thiazide diuretics
    - Aminoglycosides
    - Amphotericin
    - Cyclosporine
    - Tacrolimus
    - Cisplatin
    - Pentamidine
    - Foscarnet
    - Anti-EGFR antibodies
  - Significant diuresis
  - Renal tubular disorders
    - Gitelman syndrome
    - Bartter syndrome
- **Diabetes mellitus**
- **Volume expansion**

## Assessment of Magnesium Status

### *Serum Magnesium*

Several methods exist for evaluating Mg levels. The most common in clinical practice is the measurement of serum Mg concentration. The test is widely available and inexpensive, but does not correlate with tissue stores of magnesium. Serum Mg is a poor predictor of total body Mg content because only 0.3% of total body Mg is found in serum.[2]

### *Urinary Excretion Test*

The urinary Mg excretion test is not commonly used in clinical practice, as it requires collection of a 24-hr urine specimen, which can be challenging to obtain. Renal Mg excretion follows a circadian rhythm with the greatest amount of Mg excreted at night; therefore, having a complete 24-hr urine collection is essential for accurate assessment of absorption and excretion. High urinary Mg excretion is indicative of renal wasting whereas a low level may suggest inadequate intake or absorption.[2]

### *Magnesium Loading Test*

"Magnesium retention test" or "loading test" is a more sensitive indicator of Mg deficiency. It has been used to identify patients with suspected Mg deficiency while normomagnesemic. If more than 60-70% of Mg is excreted in the urine following an intravenous load, Mg deficiency is unlikely. This test, despite its better sensitivity, can still result in false positive or false negative results. Normal renal handling of Mg is necessary for this test to be useful. Magnesium losses due to diabetes, medications or alcohol ingestion may result in a false negative test, whereas with compromised renal function, one may see false positive results. Senescence may be a confounding factor as older individuals tend to retain more Mg than younger patients.[2,6] The Mg retention test should not be used in patients with renal impairment or in transplant patients receiving cyclosporine or tacrolimus, both of which cause urinary Mg wasting.

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## Hypomagnesemia

Hypomagnesemia is defined as a serum Mg concentration < 1.8 mg/dL (normal range: 1.8 mg/dL – 2.3 mg/dL).[5] Causes of hypomagnesemia include poor oral intake, omission of Mg from parenteral solutions, altered absorption and increased gastrointestinal losses in patients with diarrhea, malabsorption or bowel resection/bypass surgery. Patients with diabetes, renal tubular disorders, hyperthyroidism or hyperaldosteronism, refeeding and those following surgery are at risk for Mg deficiency. Many medications can also cause Mg wasting. Transplant patients are particularly prone to the development of Mg deficiency due to a direct effect of tacrolimus and cyclosporine on the renal tubules, which results in enhanced urinary Mg loss. See Table 1 for causes of hypomagnesemia.[2,7,8] Signs and symptoms of Mg deficiency are listed in Table 2. Ventricular arrhythmia is the most life-threatening complication of hypomagnesemia.

**Table 2. Signs and Symptoms of Mg Deficiency[5,8]**

**Cardiovascular**

- Ventricular arrhythmia
- Torsade de pointes

**Neuromuscular**

- Muscle weakness
- Positive Chvostek and Trousseau signs
- Generalized convulsion
- Tetany
- Vertigo, ataxia, nystagmus
- Athetoid and choreiform movements

**Other**

- Concurrent hypokalemia and hypocalcemia
- Metabolic alkalosis
- Anorexia

## Treatment of Hypomagnesemia

Hypomagnesemic patients usually do not develop symptoms until serum Mg falls below 1.2 mg/dL.[5] Asymptomatic patients should be treated with oral Mg supplements whenever feasible, whereas severe hypomagnesemia (Mg < 1 mg/dL) warrants treatment with parenteral Mg. Magnesium sulfate ($MgSO_4$) is the most commonly utilized preparation for intravenous administration; Mg oxide is the most commonly used oral supplement.[7] Intramuscular injections of Mg sulfate are associated with significant pain; therefore, a slow, continuous IV infusion is preferable. In symptomatic patients, Mg supplementation should be continued for 3-7 days as normalization of serum Mg will not be reflective of total body Mg stores.[6] Intravenous Mg repletion should be given slowly, over 8 – 24 hours. A rapid IV push over 1-4 hours (the most common way to administer Mg in the hospital setting) will increase serum Mg above physiologic levels exceeding the renal threshold and up to 50% of the infused Mg will be excreted in the urine.[5,8,9] Not only are the electrolyte shortages a significant reason to ensure efficacy, but more importantly, if patients are going to benefit from IV Mg, it must be retained in the patient.

There are no universal Mg repletion guidelines and different institutions have developed their own protocols. It has been suggested by consensus statements to give IV Mg sulfate (8-12 g) in the first 24 hrs, followed by 4-6 g daily for 3-4 days.[10] At our institution, hypomagnesemia is commonly treated with intravenous piggyback (IVPB) infusion of 1-2 g $MgSO_4$ over 1-4 hours. A practice change has been made to infuse Mg over a longer period of time (12-24 hours) for better retention to ensure that the Mg given to patients is retained, especially in the era of IV Mg shortages. Adding IV Mg to the standing IV fluid already infusing has been an effective way to achieve this.

As mentioned earlier, asymptomatic patients should be treated with oral Mg (See Table 3 for a listing of products). Supplements are usually given at doses ranging from 300 to 600 mg/day. As the absorption of Mg from the gastrointestinal tract is poor (only ~ 20-50% of oral Mg absorbed) and aggressive supplementation can lead to diarrhea,[11] it is recommended that Mg supplements be administered in divided doses 3-4 times/day to reduce their laxative side-effects.[6] See Table 4 for guidelines on treating hypomagnesemia with IV and oral supplements.

It should be noted that sufficient renal function

**Table 3. Oral Mg Supplements[11]**

| Product | Dose (mg) | Amount of elemental Mg/dose mg (mEq) |
|---|---|---|
| Mg oxide | 400 | 241.3 (20.1) / tablet |
| • Mag-Ox ® | 140 | 84.5 (6.93) / capsule |
| • Uro-Mag ® cap | | |
| Mg gluconate | 500 | 27 (2.25) / tablet |
| Magonate, liquid | | 54 (4.5) / 5 mL |
| Mg hydroxide (Milk of Magnesia) | 1200 | 501 (41.1) / 15 mL |
| Mg chloride (Slow-Mag ®) | 535 | 64 (5.33) / tablet |

***Note:*** *the recommended dietary allowance (RDA) for adult males is 400-420mg (16-17mEq) Mg/day; for adult females -- 310-360mg (13-15mEq) Mg/day.*

**Table 4: Guidelines for Treatment of Hypomagnesemia[10]**

| Condition | Treatment |
|---|---|
| Symptomatic hypomagnesemia<br>Serum Mg < 1 mg/dL | • Replace with IV magnesium sulfate<br>• 8-12 g in the first 24 hrs<br>• 4-6 g/day for the following 3-7 days<br>• Infuse IV Mg over 8-12 hours |
| Asymptomatic hypomagnesemia<br>Serum Mg > 1.2 mg/dL | • Replace with IV or oral Mg<br>• 2-8 g IV mg/day<br>• 300-600 mg oral Mg/day<br>• Administer oral Mg in divided doses 3-4 times/day to decrease GI side-effects |

***Note:*** *patients with compromised renal function should only be given 25 - 50% of the initial recommended amount for repletion and Mg levels monitored*

is needed prior to providing Mg supplementation. Hypermagnesemia may develop in patients with renal compromise and is commonly seen in patients with acute renal injury or advanced kidney disease. It can also be iatrogenic, for example when large doses of Mg-containing laxatives and antacids are used.[2,8] If a significant decrease in the glomerular filtration rate (GFR) is noted, the dosage of Mg supplementation should be reduced. Mg therapy should be ceased in severe hypermagnesemia (serum Mg > 4.8 mg/dL) and treated with IV calcium infusion and/or hemodialysis.[2,6]

## CONCLUSION

Hypomagnesemia can be detrimental to hospitalized patients. Since "normal" serum Mg does not rule out Mg deficiency, under-diagnosis is common. By recognizing the limitations of the widely utilized serum Mg level, clinicians are faced with an important responsibility to accurately identify patients at high risk for Mg deficiency. Patients with diabetes, poor diets, alcoholism, malabsorption, and those on chronic diuretic therapy fall into this high risk category. Treatment of hypomagnesemia should be dictated by patient's risk factors, clinical symptoms and kidney function. Most importantly, when IV Mg is used, it should be infused over a longer period of time to achieve efficacy and for cost-effective management of hypomagnesemia. ■

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