HYPER- AND HYPOMAGNESEMIA

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Disclosure of Financial Relationships

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Neither I nor my spouse have anything to disclose.

Disorders of Mg²⁺ metabolism

- Review selected aspects of Mg²⁺ metabolism
- Hypomagnesemia
  - Incidence
  - Causes and pathogenesis
  - Signs and symptoms
  - Diagnosis
  - Treatment
- Hypermagnesemia
  - Causes
  - Signs and symptoms
  - Diagnosis and treatment
Plasma magnesium concentration

<table>
<thead>
<tr>
<th>Type</th>
<th>mg/dL</th>
<th>meq/L</th>
<th>mmol/L</th>
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<tr>
<td>Free</td>
<td>1.3</td>
<td>1.1</td>
<td>0.55</td>
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<tr>
<td>Complexed</td>
<td>0.4</td>
<td>0.32</td>
<td>0.16</td>
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<tr>
<td>Protein bound</td>
<td>0.4</td>
<td>0.32</td>
<td>0.16</td>
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<tr>
<td>TOTAL</td>
<td>2.1</td>
<td>1.75</td>
<td>0.87</td>
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(1.9-2.3) (1.5-2.0) (0.7-1.0)

Magnesium metabolism

Magnesium absorption

Absorption in the small bowel has two components

- Predominantly active saturable transport at low intraluminal concentrations via Mg channel TRMP6
- Linear paracellular passive component at higher concentrations
Key points re Mg\(^{2+}\) metabolism

- Mg\(^{2+}\) balance and plasma Mg\(^{2+}\) are a function of absorption (both active and passive) and renal reabsorption in the loop and distal nephron

- Plasma Mg\(^{2+}\) under normal conditions is the principal regulator of urinary Mg\(^{2+}\) excretion

Hypomagnesemia

Effects of magnesium depletion

Adapted from Shils, ME. Medicine 1969; 48:61
Prevalence of hypomagnesemia in hospitalized patients

Causes of hypomagnesemia

- Gastrointestinal loss
- Renal loss
- Cellular uptake (e.g., refeeding in the alcoholic, hungry bone syndrome)

Gastrointestinal loss

- Decreased absorption and inadequate intake
  - Small bowel malabsorption
  - Small bowel bypass
  - Familial hypomagnesemia with secondary hypocalcemia
  - PPI inhibitors
- Increased secretory loss (diarrhea)
- Acute pancreatitis

PPI Inhibitors

- Hypomagnesemia with hypocalcemia and in some cases seizures, has been described with the chronic use of omeprazole and other PPIs.
- Hypomagnesemia with these drugs is most often associated with concomitant diuretics
- Presumed due to impaired intestinal absorption as UMg is appropriately low.
- Responds to high-dose oral Mg supplementation.

Perazella MA. Kidney Int 2013; 83:553.
Hypomagnesemia with secondary hypocalcemia

- Autosomal recessive disorder due to mutations in TRPM6 resulting in impaired active Mg\(^{2+}\) absorption
- There is also impairment of Mg\(^{2+}\) transport in the distal tubule (FEMg is variable)
- Presents shortly after birth with seizures and tetany predominantly in males
- Treatment is high dose oral supplementation (passive absorptive pathway is functional)

Renal magnesium wasting

Both acquired and familial causes of renal Mg\(^{2+}\) wasting are due to decreased reabsorption of Mg\(^{2+}\) in one of two tubular segments:

- Thick ascending limb of Henle’s loop
- Distal nephron (distal convoluted tubule and cortical connecting segment)

Ascending limb of the loop of Henle

Inhibition of Mg\(^{2+}\) reabsorption in the TAL

I. Impaired loop function

II. Mutant Claudin 16 and 19
Causes of impaired loop function and hypomagnesemia (typically with hypercalciuria)

- Loop diuretics and Bartter’s syndrome
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)
- Autosomal dominant hypocalcemia – Activated Ca/Mg receptor inhibits K channel and downregulates claudin 16
- Nephrotoxins
  - Aminoglycosides (binding to CaMg receptor)
  - Cisplatin (also inhibits distal nephron Mg transport)
  - Pentamidine
  - Calcineurin inhibitors (reduce expression of claudin 16 and also inhibit distal nephron Mg transport)

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)

- Mutation in the claudin 16/19 genes → loss of cation selectivity in the paracellular pathway ↓ reabsorption of Ca²⁺/Mg²⁺ with increased urinary loss.
- Presents in childhood or adolescence with hypocalcemia, recurrent nephrolithiasis and nephrocalcinosis and progresses to renal insufficiency.

Other causes of loop dysfunction with hypomagnesemia

- Hypercalcemia – also due to competition with Ca²⁺ reabsorption
- Volume expansion – eg, 1° aldo
- Alcohol
- Recovery from ATN
- Postobstructive diuresis

Early distal nephron

- Ca²⁺ channel
- TRPM5
- Na-Cl cotransporter
- Na⁺
- Mg²⁺ channel
- TRPM6
- Na⁺
- Mg²⁺
- Na⁺
- 3Na/1Ca exchanger
- 3Na/1Mg exchanger
- CI channel
- Na⁺ ATPase pump
- EGF receptor
- Pro-EGF → EGF
Late distal nephron and CCT

Predicted effects of inhibition of NaCl cotransporter by thiazides or defective gene (Gitelman’s syndrome)

Paradox

Predicted relationship between Na+ and Mg2+ transport in late distal nephron/CCT
How to explain the paradoxical effects of inhibition of the Na-Cl cotransporter

**Hypothesis:** There is predominant expression of Ca^{2+} channels in the early distal tubule and predominant expression of Mg^{2+} channels in the late distal nephron.

Gitelman’s syndrome

- Autosomal recessive disorder, and often is not diagnosed until late childhood or even adulthood
- Abnormality in the gene coding for the thiazide-sensitive Na-Cl co-transporter in the distal tubule
- Typically presents with cramps, tetany, hypokalemia, alkalosis, hypocalciuria, and hypomagnesemia
- May be associated renal salt-wasting with polyuria, nocturia, fatigue and tendency for low BP

Hereditary causes of isolated hypomagnesemia

- Tubular Na-K-ATPase subunit dysfunction
  - **Autosomal dominant**
- Mutations affecting processing of pro-EGF which reduces activity of TRPM6 (anti-EGF antibody cetuximab has similar effect to inhibit ECF receptor)
  - **Autosomal recessive**
- Hypomagnesemia with secondary hypocalcemia, due to mutations in TRPM6
  - **Autosomal recessive**

Diagnostic approach to hypomagnesemia

- Measure 24 hr UCa
  - > 250 CTAL
    - Diuretics
    - Nephrotoxins
    - H+H
    - Thiazides
    - ADRHH (NaKATPase)
- Measure 24 hr UMa or FE Mg
  - > 20 mg > 2-2.5%
    - Renal loss
  - < 20 mg < 2-2.5%
    - GI loss
- Measure 24 hr UMa
  - < 150 Distal nephron
    - Gitelman’s
    - Thiazides
    - Hypomagnesemia with secondary hypocalcemia
    - Diarrhea and Malabsorption
  - EGF disorders (Cetuximab)
Effects of hypomagnesemia

- Parathyroid hormone
  - Inhibition of PTH secretion
  - Inhibition of PTH action at bone
- Ion channels
  - Activation of Ca\(^{2+}\) and K\(^{+}\) channels in myocardial ventricular cells
  - Activation of Cl\(^{-}\) and K\(^{+}\) channels in CTAL

Signs and symptoms of hypomagnesemia

- Non-specific symptoms
  - Anorexia, nausea, apathy
- Hypocalcemia
  - Tetany, seizures, positive Chvostek and Trousseau signs
- Hypokalemia
  - Weakness, arrhythmias
  - Increased susceptibility to ventricular arrhythmias during myocardial ischemia

Treatment of hypomagnesemia

Treatment varies with severity of the clinical manifestations:

- **Tetany, hypocalcemia and or arrhythmias** — parenteral administration over 8-24 hrs, to maintain PMg > 1.0 mg/dL
- **Asymptomatic hypomagnesemia** — Slow oral replacement with sustained release preparation (2-8 tablets [5-7 meq/tablet])/d

Correcting hypomagnesemia with Mg supplements can remove the stimulus to Mg retention and most of the administered Mg will be excreted in the urine.

Include amiloride in patients with persistent urinary wasting due to thiazide diuretics and Gitelman's syndrome.

Key points re hypomagnesemia

- Hypomagnesemia is due to excess GI or renal losses
- GI losses -- decreased absorption (PPIs) and secretory losses
- Renal losses in the TAL -- congenital defect or acquired impairment in Na transport.
- Renal losses in the distal nephron are due to impaired Na transport or selective defect in Mg reabsorption (congenital and acquired [cetuximab])
- Renal causes -- hypercalciuria in the TAL, hypocalciuria in the early DT and normocalciuria in the late distal nephron.
- Sx: ↓Ca, ↓K and susceptibility to ventricular arrhythmias
- Diagnosis of renal wasting is made by FEMg >2.5%
- Rx: Symptomatic—IV; chronic — slow Mg and amiloride
Hypermagnesemia

Causes of hypermagnesemia

Urinary Mg\(^{2+}\) excretion can increase rapidly -- more than 5X in response to a Mg\(^{2+}\) load. For this reason, hypermagnesemia is typically only seen in the setting of renal failure and/or when a very large Mg\(^{2+}\) load is given in one of 3 ways:

- Intravenously
- Orally
- As an enema

Magnesium infusion

(Commonly used to treat eclampsia)

- Usual level achieved = 5-7 meq/L
- Hypocalcemia due to PTH suppression via the CASR is not uncommon
- Hyperkalemia may also occur, due to suppression of K\(^{+}\) excretion
- Hypermagnesemia resolves quickly with cessation of infusion

Oral ingestion

Massive oral ingestion can overwhelm renal excretion particularly when renal function is impaired

- Accidental poisoning with Epsom salts in children
- Laxative abuse
- Treatment of drug overdose with Mg as a cathartic
- More likely in the presence of GI disorders (gastitis, colitis)
- Unrecognized renal insufficiency in the elderly
- Extreme ↑Mg\(^{2+}\) and ↑Ca\(^{2+}\) occurs with Dead Sea water poisoning as it contains very high concentrations of Mg\(^{2+}\) and Ca\(^{2+}\)
Magnesium enemas

- Substantial quantities of magnesium can be absorbed from the large bowel.
- In normal subjects, 400-800 mmol MgSO4 per rectum has been shown to raise Mg to 7-19 mg/dL.
- In renal failure Mg containing enemas can be fatal.

Other causes of mild hypermagnesemia

- Familial hypocalciuric hypercalcemia
- Hypercatabolic states, such as the tumor lysis syndrome, with cellular release of Mg^{2+}
- Theophylline intoxication
- Lithium ingestion
- Milk-alkali syndrome
- Adrenal insufficiency, perhaps due to volume depletion and hemoconcentration

Signs and symptoms of hypermagnesemia

Three types of symptoms are seen when the PMg exceeds 4 meq/L (4.8 mg/dL):
- Cardiovascular effects (Ca and K channel blockade)
- Hypocalcemia (from PTH suppression)
- Neuromuscular effects (curare-like)

Nausea, vomiting, and flushing can also be seen. Hyperkalemia has been described.

Clinical manifestations and PMg^{2+} level

- **PMg^{2+} 4-6 meq/L** (4.8-7.2 mg/dL)
  - Lethargy, drowsiness, and diminished DTRs
- **PMg^{2+} 6-10 meq/L** (7.2-12 mg/dL)
  - Somnolence, hypocalcemia, absent DTRs, hypotension, bradycardia, ECG changes
- **PMg^{2+} >10 meq/L** (>12 mg/dL)
  - Muscle paralysis, complete heart block, cardiac arrest
Treatment of hypermagnesemia

- If renal function is normal, cessation of Mg$^{2+}$ therapy allows prompt restoration of normal levels.
- If renal function is impaired, hemodialysis is effective; typically lowers levels to nontoxic range within 3-4 hours.
- In cases with severe symptoms and need for acute therapy, 100-200 mg elemental Ca$^{2+}$ over 5-10 minutes is effective antagonist.

Key points re hypermagnesemia

- Hypermagnesemia is typically caused by increased intake (antacids, cathartics) in the presence of renal insufficiency or intestinal disease.
- Symptoms reflect neuromuscular effects, cardiovascular effects and hypocalcemia.
- Treatment in the presence of impaired renal function usually requires hemodialysis.