Magnesium overview

• Magnesium is considered an ‘essential’ mineral

• After potassium, magnesium is the second most abundant intracellular ion found in nature

• Over 600 enzymatic reactions in the body involve magnesium

• Magnesium is critical to muscle relaxation, energy metabolism and protein synthesis

• Due to soil depletion and food processing, deficiency of magnesium is a common clinical finding
  - It is estimated nearly 55% of the adult population in the US is deficient in magnesium

• Recommended Daily Allowances (RDAs) of magnesium for adult males is 420 mg and adult females 320 mg

Pathologies commonly associated with magnesium deficit

<table>
<thead>
<tr>
<th>Magnesium Deficiency</th>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td>- Stroke</td>
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<tr>
<td>- Arrhythmias</td>
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<tr>
<td>- Hypertension</td>
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<tr>
<td>- Myocardial Infarct</td>
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<tr>
<td>- Vascular calcifications</td>
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<tr>
<td><strong>Neurologic &amp; Cognitive</strong></td>
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<tr>
<td>- Epilepsy</td>
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<td>- Parkinson’s</td>
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<tr>
<td>- Depression</td>
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<tr>
<td>- Cerebral infarct</td>
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<tr>
<td>- Vascular calcifications</td>
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<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>- Asthma</td>
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<tr>
<td>- Cystic Fibrosis</td>
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<tr>
<td>- Chronic Obstructive Pulmonary Disease (COPD)</td>
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<td>- Muscle Cramps</td>
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<tr>
<td>- Diabetes- Diabetic Pre-Eclampsia</td>
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<td>- T-cell deficiency</td>
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<tr>
<td>- Some malignancies</td>
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</table>
Functions of magnesium in the body are many and varied

• Energy metabolism:
  − Glycolysis, Citric Acid Cycle and Electron Transport Chain

• Protein Synthesis:
  − DNA replication, RNA transcription, amino acid synthesis

• Genomic and genetic stability

• Cell signaling and cell proliferation, membrane function

• Muscle metabolism including cardiac, striated and smooth

• Neurologic:
  − Neuropeptide synthesis, Calcium and NMDA receptor antagonist

• Nutrient metabolism for Vitamin D, B-complex and glutathione

Magnesium as co-factor in energy metabolism

• Glycolytic Pathway:
  – involved in each step, converting glucose to pyruvate as it enters the Kreb’s/Citric Acid cycle. 8 enzymatic steps

• Kreb’s Cycle:
  – involved the majority of conversions

• Mitochondria/Electron Transport:
  – ATP and ADP are bound to magnesium for molecular stability and transport, and therefore, dependent

Patients with diabetes benefit from magnesium supplementation in 4 categories:
- Insulin sensitizing effect
- Calcium antagonism
- Stress regulating
- Endothelium stabilizing effects
Patients with Magnesium deficiency demonstrated increased risk to hypertension, lipid per oxidation and dyslipoproteinemia affecting both the endothelium and vascular smooth muscle.
Common clinical signs and symptoms associated with magnesium deficiency include:

- Most headaches
- Fatigue
- Muscle tension
- Muscle cramping
- Constipation
- Hypertension
- Insomnia
- Tinnitus
- Diabetes
- Cardiac arrhythmia
- Depression
- Paresthesia in upper extremities
- TMJ, clenching and bruxism of jaw and teeth
- Anxiety, ADHD
- PMS, menstrual cramps
- GI distress, vomiting, nausea
- Insulin resistance or hypoglycemia
Common clinical signs and symptoms associated with magnesium deficiency include:

| General: Anxiety, lethargy, weakness, agitation, depression, dysmenorrhea, hyperactivity, headache, irritability, dysacusis, low stress tolerance, loss of appetite, nausea, sleep disorders, impaired athletic performance. |
| Musculature: Muscle spasm, cramps in the soles of the feet, leg cramps, facial muscles, masticatory muscles, and calves, carpopedal spasm, back aches, neck pain, urinary spasms, magnesium deficiency tetany. |
| Nerves/CNS: Nervousness, increased sensitivity of NMDA receptors to excitatory neurotransmitters, migraine, depression, nystagmus, paraesthesia, poor memory, seizures, tremor, vertigo. |
| Gastrointestinal tract: Constipation. |
| Cardiovascular system: Risk of arrhythmias, supraventricular or ventricular arrhythmias, hypertension, coronary spasm, decreased myocardial pump function, digitalis sensitivity, Torsade de pointes, death from heart disease. |
| Electrolytes: Hypokalaemia, hypocalcaemia, retention of sodium. |
| Metabolism: Dyslipoproteinemia (increased blood triglycerides and cholesterol), decreased glucose tolerance, insulin resistance, increased risk of metabolic syndrome, disturbances of bone and vitamin D metabolism, resistance to PTH, low circulating levels of PTH, resistance to vitamin D, low circulating levels of 25(OH)D, recurrence of calcium oxalate calculi. |
| Miscellaneous: Asthma, chronic fatigue syndrome, osteoporosis, hypertension, altered glucose homeostasis. |
| Pregnancy: Pregnancy complications (e.g., miscarriage, premature labor, eclampsia). |

Dr. Andrea Rosanoff argues that “…by 1957, low magnesium was shown to be, strongly, convincingly, a cause of atherogenesis and the calcification of soft tissues… this research was widely and immediately ignored as cholesterol and the high saturated-fat diet became the culprits to fight.”

Life-style precedents for Mg deficiency

• Stress

• Poor diet with an increased intake of refined, processed, and commercially prepared foods

• Increased consumption of meats and dairy products

• Gastro-intestinal disorders

• Increased consumption of alcohol, coffee, tea and carbonated beverages

• Some common medications including diuretics, asthma medications, birth control pills, proton pump inhibitors, and others
Magnesium: Gain vs Loss in food

- Magnesium content in vegetables has seen declines from 25-80% since pre-1950 figures
  - Typical grain refining processes for bread and pasta remove 80-95% of total magnesium

- RDA recommends ~ 400 mg/day in male, which is the lowest dose to prevent disease
  - Therefore it is not optimum

- Average daily adult consumption is 200 -300 mg

- Average adult loss per day (via fecal and urinary excretion) is about 200 to 300 mg

### Table 3. Drug-induced magnesium loss and hypomagnesemia [63–65].

<table>
<thead>
<tr>
<th>Drug Group (Drug Substance)</th>
<th>Mechanism/Effect</th>
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<tbody>
<tr>
<td>Aminoglycosides (e.g., gentamicin, tobramycin, amikacin)</td>
<td>increased renal magnesium loss, secondary hyperaldosteronism</td>
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<tr>
<td>Antimicrobial medication (Pentamidine)</td>
<td>increased renal magnesium loss</td>
</tr>
<tr>
<td>Antiviral medication (foscarnet)</td>
<td>nephrotoxicity, increased renal magnesium loss</td>
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<tr>
<td>Beta adrenergic agonists (e.g., Fenoterol, salbutamol, theophylline)</td>
<td>increased renal magnesium excretion, metabolic abnormalities (magnesium shift into cells)</td>
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<tr>
<td>Bisphosphonates (pamidronate)</td>
<td>renal impairment, magnesium excretion</td>
</tr>
<tr>
<td>Chemotherapeutic agents (e.g., amsacrine, cisplatin)</td>
<td>nephrotoxicity, cisplatin accumulates in renal cortex, increased renal magnesium loss</td>
</tr>
<tr>
<td>Immunosuppressants (cyclosporine, sirolimus)</td>
<td>2- to 3-fold increased urinary magnesium excretion (→ magnesium wasting)</td>
</tr>
<tr>
<td>Loop diuretics, esp. long-term use (e.g., furosemide)</td>
<td>increased renal magnesium loss, secondary hyperaldosteronism</td>
</tr>
<tr>
<td>Monoclonal antibody (e.g., cetuximab, panitumumab)</td>
<td>EGFR blockade in the nephron impairs the active transport of magnesium (→ magnesium wasting)</td>
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<tr>
<td>Polyene antifungals (amphotericin B)</td>
<td>nephrotoxicity</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>loss of active magnesium absorption via transient receptor potential melastatin-6 and -7 (TRPM6/7)</td>
</tr>
<tr>
<td>Thiazide diuretics, esp. long-term use (e.g., hydrochlorothiazide)</td>
<td>increased renal magnesium loss, secondary hyperaldosteronism</td>
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</tbody>
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Assessing Magnesium Deficiency

- Magnesium deficiency is a primarily a clinical diagnosis with the most common signs and symptoms being:
  - Muscle tension
  - Headache
  - Constipation
  - Insomnia
  - Muscle Cramps
- Testing for Magnesium:
  - Test RBC magnesium: Mg is an intracellular mineral
  - Reference range: 4.2 to 6.8 mg/dL
  - Functional range: 6.0 - 7.0 mg/dL based on clinical experience.
“Every known illness is associated with a magnesium deficiency, and magnesium is the most critical mineral required for electrical stability of every cell in the body. A magnesium deficiency may be responsible for more diseases than any other nutrient.”

--Norman Shealy, MD PhD
Types of magnesium and their common uses

- Magnesium citrate: energy
- Magnesium malate: muscle lactic acid excess
- Magnesium glycinate: for sensitive gastrointestinal health and issues
- Magnesium oxide: bowel cleansing only
- Magnesium chloride: some claim most bioavailable
- Magnesium orotate: May have benefit in myocardial disease
- Magnesium threonate: used in neuroprotective studies

Typical dosing of magnesium

For issues not related to Gastrointestinal health

• Dose: 200 -300 mg BID
• Often prescribed with B-complex
• Caution patients about possible adverse GI signs:
  • Nausea
  • Vomiting
  • Loose stool
• Can use Mg glycinate in cases of potential gut sensitivity

For issues related to Gastrointestinal health

• Regularizing bowel function:
  • 200 to 300 mg every 2 -3 hours till evacuation complete
  • Track total magnesium needed to induce
  • Reduce by 25% daily as maintenance
• Magnesium oxide for chronic fecal retention

Summary

• Magnesium deficiency is pandemic and overlooked in clinical relevance.
• Magnesium is ubiquitously prevalent in metabolism being involved in over 600 pathways.
• Magnesium deficiency is involved in all major health conditions including heart disease, diabetes, fatigue, arthralgia, myalgia, mood disorders and insomnia.
• Magnesium deficient diagnosis is primarily a clinical diagnosis.
• Magnesium supplementation is safe, inexpensive and accessible and highly effective.