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Medications Causing Hypomagnesemia

Hypomagnesemia is a clinically significant yet often under-recognised consequence of common medications. PPIs, diuretics, antibiotics, and oncology agents can deplete magnesium gradually or abruptly, increasing the risk of neuromuscular, cardiovascular, and metabolic dysfunction.
Despite its impact, magnesium status is rarely monitored leaving a preventable deficiency unaddressed in many at-risk patients.

The following medications can cause reduced magnesium levels and have a varying level of mild, moderate and severe side effects in the body. Additional magnesium supplementation is recommended to compensate for magnesium losses due to these medications:[1,2,3]

- Proton pump inhibitors[4,5,6]
- Thiazide and loop diuretics
- Chemotherapy Agents[7,8,9]
- Immunosuppressants
- Bisphosphonates
- Monoclonal antibodies
- Digoxin and cardiac glycosides
- Oral Contraceptives
- Insulin (high dose/rapid infusion)
- Antimicrobials (aminoglycosides, pentamidine, antivirals such as foscarnet and the polyene antifungal amphotericin B)
- Beta adrenergic agonists (fenoterol, salbutamol, theophylline)
- Laxatives such as Lactulose, Movicol, and Senna®

Deficiency

Clinical signs are usually totally absent with a chronic latent intracellular deficit of magnesium however more severe deficiency may present with neuromuscular, cardiovascular, or CNS symptoms (e.g., cramps, arrhythmias, seizures, fatigue). Magnesium deficiency has been linked to a range of neuropsychiatric disorders, including depression, anxiety, restless legs and cognitive decline.

The international prevalence of magnesium deficiency is high[10,11]

Group	Estimated Prevelance
General adult population	10-30%
Older adults (>70 yrs)	35-40%
Hospitalised patients	11-65%
Type 2 diabetes	25-38%
Chronic disease populations	20-8% (varies)

Clinical Approach to Restoring Magnesium Levels

1. Identify At-Risk Patients

- **Clinical symptoms**: fatigue, muscle cramps, insomnia, anxiety, headaches, restless legs, palpitations, constipation
- **Risk factors**: age >60, diabetes, alcohol use, PPI or diuretic use, chronic stress, high-performance athletes, poor diet
- **Lab clues**: low-normal serum magnesium (<0.85 mmol/L), low potassium or calcium (magnesium is needed to regulate both)

2. Choose the Right Form of Magnesium

Not all forms are equal — match the **magnesium salt** to the patient's symptoms and tolerance:

Form	Common Use Case	Elemental Mg	GI Tolerance
Magnesium glycinate	Sleep, anxiety, neuromuscular health	~14%	High
Magnesium citrate	Mild constipation, general support	~16%	Moderate
Magnesium malate	Energy, fibromyalgia, muscle pain	~10%	High
Magnesium threonate	Cognitive focus, mood, sleep architecture	~8%	High
Magnesium oxide	Laxative effect, low bioavailability	~60%	Poor
Magnesium chloride	Broad systemic use, high solubility	~12%	Moderate

Doses typically aim for **200–400 mg elemental magnesium daily**, in divided doses.

Nutritional biochemistry would indicate using multiple magnesium forms creates a broader absorption profile, targets more tissues, and may lead to faster and more complete replenishment[12] However if Monotherapy is more appropriate for the patient then Magnesium Chloride offers rapid absorption due to its affinity with the water molecules present in the body and is useful in patients with gut issues, inflammation or IBD of any cause

Further to this, the two main pathways of absorption respond to different magnesium compounds:

- Passive diffusion (favoured by soluble salts like citrate, chloride, and threonate)
- Active transport (favoured by amino acid chelates like glycinate and malate)

As such the pathways saturate at different rates, so by combining magnesium forms you can influence symptomatic relief and wellbeing at a faster rate.[ii]

3. Optimise Intake Through Diet

Recommend:

- **Magnesium-rich foods:** leafy greens, legumes, pumpkin seeds, almonds, whole grains, cacao
- **Reduce depleting factors:** high caffeine, alcohol, processed food, chronic stress

4. Monitor Symptoms Over Labs - "If someone improves on magnesium, that is the test."

Because serum magnesium is a poor reflection of total body magnesium, most doctors track **clinical improvement** rather than relying on lab confirmation:
Follow-up laboratory tests such as RBC magnesium or magnesium loading tests can confirm improved magnesium status.

Continuing Clinical Approach to Restoring Magnesium Levels

5. Address Absorption Issues

In cases of chronic deficiency consider:

- Avoiding interfering medications (e.g., PPIs, loop diuretics)
- Timing of supplementation to be 2 hours away from other medicines
- Optimising magnesium supplement doses. Consider multiple times per day (e.g., AM/PM)
- Using multiple forms (e.g., citrate and glycinate and chloride and amino acid chelate)
- Checking gut health (SIBO, IBD, leaky gut)

In Summary

Raise magnesium levels by:

- **Combining symptom tracking,**
- **Strategic supplementation (form and dose),**
- **Dietary changes,**
- **Smart clinical suspicion.**
- **Treat the person, not just the lab result -don't rely on the serum magnesium level.**

Proton Pump Inhibitors (PPIs) - Long Term PPI Use: Risk of Hypomagnesemia

Proton pump inhibitors (PPIs) such as omeprazole, esomeprazole, pantoprazole, and others have been associated with **hypomagnesemia**, particularly when used **chronically** (>1 year). This effect is **clinically significant** and can lead to **neuromuscular, cardiac, and metabolic complications**.[14,15]

This is high risk for the following:

- Long term use (> 1 year
- Older age
- Concurrent diuretic use
- Baseline magnesium depletion
- Chronic diarrohea or GI surgery
- Diabetes
- Alcohol abuse

Mechanism: How PPIs Cause Magnesium Loss

1. Inhibition of Active Magnesium Absorption via TRPM6/7.

- Magnesium absorption is pH-dependent and TRPM6 is less efficient at neutral/alkaline pH.
- TRPM6 and TRPM7 are magnesium-permeable channels in the distal small intestine and colon. These channels require acidic luminal conditions to function optimally.

CONTINUING PPI RISK OF HYPOMAGNESEMIA

• PPIs reduce gastric acidity, which in turn raises intestinal pH, impairing TRPM6 function and reducing active Mg^{2+} absorption.

2. Reduced Bioavailability of Magnesium Compounds

At higher intestinal pH, magnesium salts become less bioavailable to the body

Insoluble forms are not absorbable, particularly in patients also on low-magnesium diets, thiazide diuretics, or antibiotics.

Additional consideration for people on PPIs- Increased Magnesium Renal Loss May Exacerbate Risk

While the primary mechanism of PPI-induced hypomagnesemia is impaired intestinal absorption via pH-sensitive TRPM6/7 channels, renal magnesium losses may exacerbate or sustain deficiency. This is especially relevant when co-administered with nephrotoxic drugs, diuretics, or in the context of chronic kidney disease or tubulointerstitial nephritis. Assess urinary magnesium to distinguish renal vs GI causes, and monitor renal function regularly in chronic PPI users

PPI Clinical Guidance[19]

1. Baseline and Ongoing Monitoring

- **Assess serum magnesium** before initiating long-term PPI therapy, especially in at-risk patients (elderly, diabetics, renal impairment, or those on diuretics).
- Re-check magnesium **annually** or sooner if the patient develops symptoms or is on interacting medications.
  - Mild symptoms: fatigue, muscle cramps, tremor, irritability, tinnitus, headaches
  - Severe symptoms: Tetany, seizures, cardiac arrhythmias, QT prolongation, syncope
- Any **unexplained fatigue, muscle issues, or neurological symptoms** in a patient on PPIs should prompt magnesium evaluation.
- Consider monitoring **calcium and potassium** as secondary imbalances may occur.

2. Evaluate the Need for Continued PPI Use

- Review the indication and duration of therapy: many patients are maintained on PPIs beyond the recommended period.
- Consider step-down therapy (e.g., H2 blockers) if clinically appropriate or intermittent dosing, or non-pharmacologic management (e.g., dietary/lifestyle changes for GERD).
- If PPI cannot be withdrawn, **ensure risk mitigation.**

3. Consider magnesium supplementation

- Use magnesium chloride, citrate or taurate if mono magnesium supplementation is indicated due to better absorption in higher pH.

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REFERENCES :

1. Gröber U. Magnesium and Drugs. Int J Mol Sci. 2019 Apr 28;20(9):2094. doi: 10.3390/ijms20092094. PMID: 31035385; PMCID: PMC6539869.
2. Almaani S, Paik J, Witjas R, et al. Magnesium and drugs: an overview of drug-induced magnesium depletion. J Clin Pharmacol. 2019;59(1):5-20.
3. Weingart C, Klein C, Resch KL. Hypomagnesemia: Practice Essentials. EMCrit. 2024.
4. Hara M, Akamatsu T, Ohya Y, et al. Mechanisms of proton pump inhibitor–induced hypomagnesemia. Acta Physiol (Oxf). 2022;234(1):e13846.
5. Huber RM, Huber C, Matzi V, et al. Proton-pump inhibitor–induced hypomagnesemia: a clinical and mechanistic review of current evidence. QJM. 2010;103(6):387-94.
6. Koulouridis I, Reino EM, Wald R, et al. Multiple electrolyte disorders triggered by proton pump inhibitor therapy. JAMA Intern Med. 2023;183(3):e107-15
7. Christensen SB, Jacobsen J, Sengeløv H. Hypomagnesemia is a frequent complication to chemotherapy with cisplatin affecting up to 90% of patients if no corrective measures are initiated. PubMed; 1999. PMID: 10212589.
8. Wolf FI, Trapani V. Magnesium and its transporters in cancer: a potential therapeutic target. Magnes Res. 2012;25(3):112-7.
9. Forster R, Melichar B, Maurel M, et al. Panitumumab has a stronger affinity for EGFR than cetuximab, and the risk of hypomagnesemia is significantly higher with panitumumab. Anticancer Res. 2004;24(3):713-6.
10. Pitliya A, Vasudevan SS, Batra V, Patel MB, Desai A, Nethagani S, Pitliya A. Global prevalence of hypomagnesemia in type 2 diabetes mellitus - a comprehensive systematic review and meta-analysis of observational studies. Endocrine. 2024 Jun;84(3):842-851. doi: 10.1007/s12020-023-03670-7. Epub 2023 Dec 30. PMID: 38159172.
11. Fritzen R, Davies A, Veenhuizen M, Campbell M, Pitt SJ, Ajjan RA, Stewart AJ. Magnesium Deficiency and Cardiometabolic Disease. Nutrients. 2023; 15(10):2355. https://doi.org/10.3390/nu15102355
12. Costello et al., “Magnesium salts vary in their solubility, absorption mechanisms, and site of action. Using multiple forms maximises uptake.”. Clinical Kidney Journal, 2016 (PMID: 27775656
13. DiNicolantonio et al., “Combining magnesium forms may provide broader tissue saturation and functional benefit.” .Open Heart, 2018 (PMID: 29531784)
14. Markovits N, Loebstein R, Halkin H, Bialik M, Landes-Westerman J, Lomnicky J, Kurnik D. The association of proton pump inhibitors and hypomagnesemia in the community setting. J Clin Pharmacol. 2014 Aug;54(8):889-95. doi: 10.1002/jcph.316. Epub 2014 May 6. PMID: 24771616.
15. William JH, Danziger J. Proton-pump inhibitor-induced hypomagnesemia: Current research and proposed mechanisms. World J Nephrol. 2016 Mar 6;5(2):152-7. doi: 10.5527/wjn.v5.i2.152. PMID: 26981439; PMCID: PMC4777786.
16. Souza CC, Rigueto LG, Santiago HC, Seguro AC, Girardi AC, Luchi WM. Multiple electrolyte disorders triggered by proton pump inhibitor-induced hypomagnesemia: Case reports with a mini-review of the literature. Clin Nephrol Case Stud. 2024 Jan 4;12:6-11. doi: 10.5414/CNCS111284. PMID: 38222324; PMCID: PMC10783169.
17. Koulouridis I, Reino EM, Wald R, et al. Multiple electrolyte disorders triggered by proton pump inhibitor therapy. JAMA Intern Med. 2023;183(3):e107-15
18. Rosner MH, Ha N, Palmer BF, Perazella MA. Acquired Disorders of Hypomagnesemia. Mayo Clin Proc. 2023 Apr;98(4):581-596. doi: 10.1016/j.mayocp.2022.12.002. Epub 2023 Mar 3. PMID: 36872194.
19. Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, Pottie K, Farrell B. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev. 2017 Mar 16;3(3):CD011969. doi: 10.1002/14651858.CD011969.pub2. PMID: 28301676; PMCID: PMC6464703..