

DRUG-INDUCED NUTRIENT DEPLETION

Pharmacists are often familiar with drug-nutrient interactions but may be less familiar with drug-induced nutrient depletion. This newsletter outlines medications commonly dispensed in community pharmacies which may potentially cause significant nutrient depletion. Nutrient level monitoring and supplementation may be warranted in some cases. Further details on specific nutrient deficiencies are found below in Table 1.

Table 1:

Medications	Nutrient	Evaluation/Monitoring	Recommendations
Anti-hyperglycemics <i>Metformin</i> ¹⁻⁴	Folate Vitamin B₁₂	Blood work every 1-3 years (sooner if development of/ worsening neuropathy or additional risk factors). Must obtain B ₁₂ levels before supplementing with folate.	Supplement if deficient or risk factors for deficiency e.g. other medications, poor diet, long-term use of metformin or higher doses of metformin.
Acid Reduction <i>H₂-Receptor Antagonists (H₂RAs)</i> ⁵⁻⁷	Iron	Monitor for symptoms of anemia (paleness, fatigue, weakness). Blood work may be necessary if experiencing anemic-like symptoms or if patient has pre-existing anemia.	Maintain adequate dietary iron intake. May need to increase dose if already taking iron supplements as acid suppression reduces absorption of supplemental iron.
	Vitamin B₁₂	B ₁₂ stores may take 2-5 years to be depleted. Obtain serum levels if taking acid suppressors chronically or if patient experiencing B ₁₂ deficiency symptoms (weakness, numbness, fatigue).	Supplement B ₁₂ if low intake (diet, alcoholism) or additional B ₁₂ -depleting medications. May require supplements if taking for > 2 years.
Acid Reduction <i>Proton Pump Inhibitors (PPIs)</i> ⁵⁻¹²	Iron & Vitamin B₁₂	As above. Evaluate if PPI drug therapy is necessary.	As above.
	Calcium	Evaluate if patient at risk for low bone mineral density (BMD) or fractures. Monitor calcium levels every 6-12 months during therapy.	Increased dietary intake or supplementation may be required. Encourage calcium citrate and vitamin D supplementation in those at risk for osteoporosis. Use the lowest effective dose of PPI for the shortest period of time. Deficiency tends to occur when taking PPIs > 1 year.
	Magnesium	Obtain baseline serum levels and monitor annually, especially if additional risk factors. (See risk factors in text.)	Supplement if low serum levels. Deficiency tends to occur when PPI used > 1 year.
Corticosteroids ^{6,13}	Calcium Vitamin D	Evaluate additional risk factors for low calcium or vitamin D. Evaluate if steroid dose equivalency will be greater than 7.5 mg prednisone. May monitor calcium every 6-12 months during therapy.	Supplement with calcium and vitamin D if low serum levels, additional risk factors for deficiency are present, patient is taking steroid for > 3 months (at doses ≥7.5 mg prednisone daily), or patient at risk of low BMD.
	Potassium	Monitor serum levels every 6-12 months if chronic steroid therapy (> 3 months). Patients taking highly mineralocorticoid steroids (hydrocortisone, cortisone, prednisone) are more likely to experience hypokalemia.	Supplementation or increased dietary intake may be warranted. If appropriate, consider switching to non-mineralocorticoid steroid such as betamethasone, dexamethasone, or triamcinolone.
Diuretics <i>Loop Diuretics</i> ^{6,14}	Calcium Potassium Magnesium	Monitor calcium, potassium, and magnesium levels within 6 weeks of starting therapy and then every 6-12 months.	Supplementation or increased dietary intake may be required. Addition of potassium-sparing diuretics in severe instances may be appropriate for low potassium or magnesium.
Diuretics <i>Thiazide Diuretics</i> ^{6,14,15}	Potassium Magnesium	Monitor levels within 6 weeks of starting therapy and then every 6-12 months.	As above. Thiazide diuretics deplete magnesium to a lesser extent than loop diuretics.
Dyslipidemics <i>Statins</i> ^{6,7,16}	Co-enzyme Q10 Vitamin D	Monitor for worsening muscle pain	No evidence that CoQ10 supplements reduce statin-related muscle side effects; however it is still recommended by some clinicians and unlikely to cause harm. If the patient is known to be vitamin D deficient a trial of vitamin D may be used to reduce muscle pain.

1. METFORMIN:

FOLATE & VITAMIN B₁₂: Vitamin B₁₂ and/or folate deficiency can cause megaloblastic anemia.¹⁷ When either vitamin is deficient, an impairment of DNA synthesis in heme cells can occur.¹⁷ Signs and symptoms of folate and B₁₂ deficiency include macrocytic cells (with or without anemia) and neurological dysfunction including dementia, progressive weakness and paresthesias; neuropathy may occur from vitamin B₁₂ deficiency.² Vitamin B₁₂ plays a role in red blood cell production, DNA synthesis and neurologic function.³ In a study of 799 patients with Type 2 diabetes, 9.5% were vitamin B₁₂-deficient, defined as B₁₂ ≤ 1101 pmol/L without folate deficiency (folate > 13nmol/L).¹⁸ Vitamin B₁₂-deficient patients had taken metformin for longer durations and at higher doses.¹⁸ The adjusted odds ratio for deficiency with metformin dose of < 1,000 mg compared to 1000-2000 mg and > 2,000 mg were 2.52 and 3.80 respectively.¹⁸ The adjusted odds ratio for deficiency with metformin use < 4 years compared with 4-10 years and >10 years were 4.65 and 9.21, respectively.¹⁸ Although vitamin B₁₂ deficiency can cause peripheral neuropathy, a study of B₁₂ deficiency in metformin patients did not report significantly greater incidences of neuropathy compared to those without B₁₂ deficiency (36.8 % vs 32.3%, p= 0.209).¹⁹

Most patients receive adequate folate from dietary sources but those who may not include alcoholics, those with poor diet and those with malabsorptive conditions such as celiac disease and inflammatory bowel disease. Patients on some anti-epileptic medications such as carbamazepine, gabapentin, phenytoin and valproate may be deficient.^{1,2} It is important to rule out vitamin B₁₂ deficiency before treating with folic acid in megaloblastic anemia as folic acid may worsen neurological symptoms in the presence of vitamin B₁₂ deficiency.² Routine testing of B₁₂ levels for metformin patients is not recommended but levels can be checked every 2-3 years or every 1-2 years in those at risk of developing B₁₂ deficiency (e.g. PPI users, vegetarians, elderly) or in those who are experiencing worsening peripheral neuropathy.^{3,4} Severe B₁₂ deficiency may cause peripheral neuropathy which may be mistakenly attributed to progression of diabetes.

2. ACID SUPPRESSORS

A. H₂RAs AND PPIs

IRON: Chronic acid suppression may reduce absorption of iron supplements/non-heme iron. Gastric acid has a role in absorption of non-heme iron; however the decreased absorption does not seem to have clinical significance. Long-term use of H₂RAs and PPIs is not associated with iron depletion in patients with normal iron stores. Patients should maintain adequate oral iron intake and supplements may be necessary if low serum levels of iron. Increased iron supplementation may be required in those previously diagnosed with anemia and currently taking supplements.^{5,6}

VITAMIN B₁₂: Gastric acid is needed to release B₁₂ from food for absorption. However, people usually have large vitamin B₁₂ stores which may take up to 2-5 years to deplete. Deficiency is usually mild and clinically insignificant but may be corrected with supplements. Supplements may be needed in those taking acid suppressors for > 2 years, those with low B₁₂ intake (alcoholics, vegetarians) or in those taking other medications known to reduce B₁₂ stores; supplemental vitamin B₁₂ is not influenced by acid suppression.⁷

B. PPIs Only

MAGNESIUM: Hypomagnesemia due to reduced intestinal absorption has been generally associated with patients taking a PPI for > 1 year.^{8,9} Providers may want to investigate patient magnesium levels before starting PPI therapy, intermittently during PPI therapy, or if the patient is on other medications known to cause low magnesium.⁸ Symptoms of low magnesium include muscle cramps, palpitations, high blood pressure, tremor, and dizziness.⁹ Common risk factors for low magnesium, caused by increased renal excretion, include loop and thiazide diuretics, aminoglycoside antibiotics, alcoholism, uncontrolled diabetes, and hypercalcemia.¹⁰

CALCIUM: Reduced acid secretion could reduce calcium absorption and inhibit osteoclastic activity. A meta-analysis of 11 cohort and case control studies found the relative risk of hip fracture in PPI users was 1.30 (95% CI, 1.19-1.43), relative risk (RR) of spine fracture was 1.56 (95% CI, 1.31-1.85) and any site fracture RR was 1.16 (95% CI, 1.02-1.32) compared to non-PPI users.²⁰ Additionally, a Nurses' Health study, with approximately 80,000 post-menopausal women, reported the risk of hip fracture was 2.02 per 1000 person years in PPI users compared to 1.51 per 1000 person years in non PPI users. The risk of hip fracture was 35% higher in PPI users of at least 2 years and 51% higher in those who were PPI users and former/current smokers.²¹ However, approximately 2000 Canadian women would need to be treated with a PPI for 1 year to see an additional fracture.¹¹ Overall, calcium supplementation along with vitamin D may be warranted especially if the patient is over 50, using a high dose PPI, or is on PPI for greater than one year; avoiding long-term PPI use is another appropriate strategy.¹¹ Calcium citrate is the recommended calcium supplement in these instances due to the lack of acidic environment for insoluble calcium absorption.¹²

3. CORTICOSTEROIDS

CALCIUM: Glucocorticoids reduce intestinal calcium absorption and increase urinary excretion.¹³ Bone loss is most noticeable in the first few months of use, followed by a slower steady loss of BMD over time.²² With long term use there is greater suppression of osteoblastic bone formation over osteoclastic bone resorption (seen earlier in course of steroid use).²² Generally this occurs with doses greater than 7.5 mg prednisone daily (or equivalent steroid dose).⁶

VITAMIN D: A Cochrane Review that included 5 randomized trials of patients taking systemic steroids compared calcium with vitamin D to calcium alone or placebo.²³ The analysis found significant improvement in lumbar spine (2.6 weighted mean difference) and radial (2.5 weighted mean difference) BMD. Vitamin D increases intestinal absorption of calcium and calcium renal resorption. Therefore, if calcium supplement is deemed appropriate, vitamin D should also be given concomitantly to further enhance calcium levels.

POTASSIUM: Supplements to prevent hypokalemia may be needed in some patients taking high mineralocorticoid drugs; alternately the steroid may be switched to one with low mineralocorticoid activity.⁶ Monitor patient potassium levels every 6-12 months if taking long-term steroid therapy or if additional risk factors for low potassium are present.⁶

4. DIURETICS

A. LOOP AND THIAZIDE

MAGNESIUM: Hypomagnesemia may occur due to increased excretion of magnesium and it generally occurs with higher doses of diuretics.¹⁴ Magnesium supplementation may improve co-existing hypokalemia.¹⁴ Thiazide diuretics deplete magnesium to a lesser extent than loop diuretics.⁶ Magnesium levels should be monitored within 6 weeks of starting the therapy and then every 6-12 months.⁶ If patients experience low magnesium, supplementation may be warranted or addition of a potassium-sparing diuretic may be appropriate as they also spare magnesium.⁶

POTASSIUM: Thiazides inhibit sodium and water reabsorption at the distal convoluted tubule which increases excretion of potassium.¹⁴ Correction of thiazide-induced hypokalemia may be impaired in the presence of hypomagnesemia as low magnesium may also contribute to low potassium.¹⁴ Potassium levels should also be monitored within 6 weeks of initiating therapy and then every 6-12 months.⁶ Again supplementation or addition of a potassium-sparing diuretic may be appropriate to manage low potassium along with maintaining adequate dietary intake.⁶

B. LOOP ONLY

CALCIUM: Loop diuretics increase calcium excretion (impaired reabsorption at the loop of Henle) while thiazides stimulate reabsorption of calcium potentially conferring protection from calcium stones and potential bone loss.^{12,15} In a clinical trial of 87 postmenopausal woman (with osteopenia) receiving bumetanide for one year, whole body BMD decreased 1.4% (2% BMD decrease at hip) compared to placebo despite supplementation with calcium and vitamin D.¹⁵ Evidence regarding loop diuretics and association with fractures have been conflicting.^{15,24} In a case-control study, the adjusted RR for hip fracture was 3.9% in those taking furosemide versus patients not taking furosemide.²⁵

5. STATINS

CO-ENZYME Q10: Coenzyme Q10 produces energy in mitochondria in virtually all cells and statins are known to reduce the synthesis of coenzyme Q10.¹⁶ However there is no evidence that the supplementation will reduce myopathy caused by statins.⁷ A 2015 meta-analysis of randomized trials suggested there is no significant benefit for CoQ10 supplements in reduction or prevention of statin-induced muscle pain but larger trials may be needed to confirm this.^{16,26} The use of supplemental CoQ10 is controversial as there is no evidence to support its use for treating statin-induced muscle pain; however, some clinicians will still recommend the supplementation for muscle side effects.⁶

VITAMIN D: Some studies have a suggested statin myopathy may be associated with low vitamin D levels.¹⁶ If the patient has been known to be deficient in vitamin D then it may be acceptable to check vitamin D levels and supplement along with re-challenging statin therapy.¹⁶

References:

1. Linnebank M, Moskau S, Semmler A, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. *Ann Neurol*. 2011;69(2):352-359.
2. Schrier S. Diagnosis and treatment of vitamin B12 and folate deficiency. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
3. PL Detail-Document, Management of Vitamin B12 Deficiency. *Pharmacist's Letter/Prescriber's Letter*. May 2016.
4. PL Article, Metformin. *Pharmacist's Letter/Prescriber's Letter*. May 2016.
5. PL Rumour vs Truth, Chronic Acid Suppressive Therapy Can Cause Iron Deficiency Anemia. *Pharmacist's Letter/Prescriber's Letter*. Sept 2006.
6. PL Detail-Document, Clinically Significant Drug-Induced Nutrient Depletion. *Pharmacist's Letter/Prescriber's Letter*. Jan 2000.
7. PL Rumour vs Truth, Patients on Acid Suppressive Therapy Should Take Supplemental Vitamin B12. *Pharmacist's Letter/Prescribers Letter*. Dec 2004.
8. Wolfe M. Overview and comparison of the proton pump inhibitors for the treatment of acid related disorders. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 07 March 2017. Available from www.uptodate.com. Subscription and login required.
9. PL Detail-Document, Treating Magnesium Deficiency. *Pharmacist's Letter/Prescriber's Letter*. November 2011.
10. Yu A. Causes of hypomagnesemia. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 16 March 2017. Available from www.uptodate.com. Subscription and login required.
11. PL Detail-Document, Proton Pump Inhibitors: Appropriate Use and Safety Concerns. *Pharmacist's Letter/Prescriber's Letter*. April 2016.
12. Rosen H. Calcium and vitamin D supplementation in osteoporosis. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
13. Rosen H, Saag K. Prevention and treatment of glucocorticoid-induced osteoporosis. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
14. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS Online: Thiazide Diuretics; [updated May 2012, cited 2017 March 08]. Available from: <https://www.e-therapeutics.ca>.
15. Rosen H. Drugs that affect bone metabolism. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
16. Rosenson R, Baker S. Statin Myopathy. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
17. Schrier S. Physiology of vitamin B12 and folate deficiency. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required.
18. Ko S, Ko S, Ahn Y, et al. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. *J Kor Med Science*. 2014;29(7):965.
19. Ahmed M, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. *BMC Pharmacol Toxicol*. 2016;17(1):44.
20. Yu E, Bauer S, Bain P, Bauer D. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med*. 2011;124(6):519-526.
21. Khalili H, Huang E, Jacobson B, et al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. *BMJ*. 2012;344:e372-e372.
22. Rosen H. Pathogenesis, clinical features and evaluation of glucocorticoid-induced osteoporosis. . In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 08 March 2017. Available from www.uptodate.com. Subscription and login required
23. Homik J, Suarez-Almazor ME, et al. Calcium and vitamin D for corticosteroid-induced osteoporosis. *Cochrane Database of Systematic Reviews* 1998, Issue 2. Art. No.: CD000952. DOI: 10.1002/14651858.CD000952.
24. Rejnmark L, Vestergaard P, Heickendorff L, et al. Loop diuretics increase bone turnover and decrease bmd in osteopenic postmenopausal women: results from a randomized controlled study with bumetanide. *J Bone Miner Res*. 2005;21(1):163-170.
25. Heidrich FE, Stergachis A, Gross K. Diuretic drug use and the risk for hip fracture. *Ann Int Med*. 1991;115:1-6.
26. Banach M, Serban C, Sahebkar A, et al. Effects of coenzyme q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2015;90(1):24-34