

Metformin With Either Histamine H₂-Receptor Antagonists or Proton Pump Inhibitors: A Polypharmacy Recipe for Neuropathy via Vitamin B₁₂ Depletion

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According to the most recent data from the Centers for Disease Control and Prevention, 25.8 million people in the United States (8.3% of the population) have diabetes (1). Type 2 diabetes accounts for 90–95% of diabetes diagnoses, and >85% of people with type 2 diabetes are overweight or obese (1). Increased BMI, which is common in the type 2 diabetes population, has a well-established association with symptoms of gastroesophageal reflux disease (GERD) (2,3). Central adiposity is an important risk factor in the development of reflux and, subsequently, erosive esophagitis, Barrett's esophagus, esophageal adenocarcinoma, and gastric cardia adenocarcinoma (2,3).

Increased BMI is not the only risk factor for the development of GERD, particularly among people with diabetes. Among those with type 2 diabetes, peripheral neuropathy is an independent risk factor for erosive esophagitis (4). In this population, there is a greater incidence of erosive esophagitis among individuals with neuropathy than among those without neuropathy, although those with and without neuropathy experience similar GERD symptoms (4). Approximately 60–70% of people with diabetes have mild to severe forms of nervous system damage, which may partly explain why low-grade esophageal dysplasia is twice as likely in individuals with than in those without diabetes (1,5). Additionally, both asymptomatic

and symptomatic reflux is more prevalent in individuals with diabetes than in those without diabetes (6,7). Likewise, type 2 diabetes has been demonstrated to be a risk factor for symptomatic GERD (8).

Among individuals with diabetes, 40.7% experience symptomatic GERD, and 70% of those use oral antidiabetic medications. Thus, it is likely that millions of individuals are managing blood glucose and GERD concomitantly with oral medications (1,7). Therefore, it is important to assess the drug interactions and clinical sequelae that may occur with this particular polypharmacy scenario. This article addresses the potential for vitamin B₁₂ depletion induced by concomitant use of metformin and acid-suppressing medications to contribute to neuropathy among individuals with diabetes.

Vitamin B₁₂, Diabetes, and Neuropathy

Vitamin B₁₂ is a water-soluble micronutrient that serves as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase (9–11). As a result, B₁₂ is important for the production of S-adenosylmethionine, nucleic acid methylation, and hemoglobin synthesis, as well as protein and fat metabolism (9,11). The signs and symptoms of vitamin B₁₂ deficiency can be easily mistaken for those of diabetic neuropathy. These include paresthesias, diminished vibratory sensation, diminished proprioception, loss of cutaneous sensation, muscle

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weakness, abnormal reflexes, urinary and fecal incontinence, loss of vision, reduced sensory nerve conduction velocities, and axonal degeneration, as well as evoked potential and magnetic resonance imaging abnormalities consistent with demyelination (12–15).

Most individuals with diabetes have mild to severe forms of nervous system damage (1). B₁₂ supplementation, alone or in combination with other substances, has been demonstrated to improve multiple aspects of diabetic neuropathy, including lower-extremity epidermal nerve fiber density, cutaneous sensitivity, pain, paresthesia, autonomic symptoms, and ulnar motor and median sensory nerve conduction velocities (16–25).

Although numerous forms of vitamin B₁₂ exist, supplement and pharmaceutical formulations typically contain vitamin B₁₂ as cyanocobalamin, a synthetic form that the body readily converts to the active forms methylcobalamin and 5-deoxyadenosylcobalamin (26). Because of the liberation of cyanide during the conversion of cyanocobalamin to its active forms, individuals with Leber's optic neuropathy (a genetic disorder exacerbated by chronic cyanide intoxication) should not be administered cyanocobalamin (26). Administration of vitamin B₁₂ in forms other than cyanocobalamin (e.g., methylcobalamin), eliminates the risk of cyanide toxicity and subsequent neuropathy.

Successful strategies for managing diabetic neuropathy with B₁₂ are summarized below.

- Intrathecal injections (2,500 µg in 10 mL saline, monthly) of methylcobalamin have been shown to improve paresthesia and burning pain in individuals with diabetes (16).
- Oral administration of two 250-mg methylcobalamin capsules three times daily for 4 months resulted in improvement of both somatic and autonomic symptoms and regression of diabetic neuropathy signs (17).

- Oral methylcobalamin (2 mg), in combination with 3 mg L-methylfolate and 35 mg pyridoxal-5'-phosphate (MC-LMF-PP) twice daily for 4 weeks and then once daily for 48 weeks, was reported to result in significant improvement in peripheral nerve sensitivity (19).
- Likewise, oral MC-LMF-PP twice daily for 6 months demonstrated significant improvement in epidermal nerve fiber density, as assessed by biopsy, in 8 of 11 patients (73%) (20).
- Patients receiving a 500-µg methylcobalamin intravenous injection three times per week for 6 months were reported to have improvement in pain, paresthesia, and nerve conduction velocities (21).
- Methylcobalamin injections of 500 µg administered intramuscularly three times per week for 4 weeks, followed by 500 µg administered orally three times a day for an additional 8 weeks, improved spontaneous pain and numbness (22).
- Oral supplementation with methylcobalamin (1,500 µg daily for 24 weeks) in individuals with diabetes has been demonstrated to improve tingling, upper limb symptoms, ataxia, signs of impaired position sense, vibration sense, pinprick sensation, and knee reflexes (25).

These reports all noted improvement in diabetic neuropathy without also documenting baseline B₁₂ levels. Therefore, it is reasonable to assume that the neuropathy that responded to B₁₂ supplementation could have been, at least in part, B₁₂ deficiency neuropathy rather than diabetic neuropathy.

Metformin-Induced Vitamin B₁₂ Depletion

In 1969, Berchtold et al. (27) noted that patients managed with metformin therapy for 2–3 months malabsorbed vitamin B₁₂. Since then, B₁₂ deficiency among individuals managed with metformin has been reported to occur at an incidence rang-

ing between 5.6 and 36% (Table 1) (28–34). The broad range of incidence rates reported in Table 1 may be attributed to cumulative drug-induced B₁₂ depletion related to both the dosage and the duration of metformin use (35–38). However, findings of cumulative effects are not entirely consistent throughout the literature (33).

Individuals treated with metformin have lower B₁₂ levels and worse diabetic neuropathy than individuals managed with medications other than metformin (37,39). It has been suggested that neuropathy may be the result, in part, of the sequelae of B₁₂ depletion, including elevations in homocysteine and methylmalonic acid levels (37). Although metformin is a common first-line pharmacotherapy and the primary biguanide used for the management of type 2 diabetes, less clinically relevant biguanides, including buformin and phenformin, also have been demonstrated to affect B₁₂ levels (29,40,41).

Mechanisms

Various reports have attributed metformin-induced B₁₂ depletion to:

- A metformin-induced decrease in bile acid secretion promoting small intestinal bacterial overgrowth, which, in turn, causes increased intrinsic factor–vitamin B₁₂ complex binding to bacteria and decreased intestinal absorption (40)
- Decreased intrinsic factor secretion (29)
- Decreased intestinal absorption resulting from metformin's antagonism of the calcium-dependent B₁₂-intrinsic factor cell surface receptors in the ileum (42)

Mitigation

Vitamin B₁₂ levels have been shown to improve as a result of:

- B₁₂ supplementation (35,42)
- Cessation of metformin therapy (28,29,40)
- Administration of the antibiotic doxycycline (100 mg daily for 8 days) (40)
- Oral calcium supplementation (42)

TABLE 1. Incidence of Vitamin B₁₂ Deficiency Among Individuals Managed With Metformin

Study	Sample Size (n)	Individuals With B ₁₂ Deficiency (n)	Individuals With B ₁₂ Deficiency (%)
Tomkin et al., 1971 (28)	71	4*	5.6
Adams et al., 1983 (29)	33	—†	—
Hermann et al., 2004 (30)	53	19‡	36
Pflipsen et al., 2009 (31)	195	44	23
Qureshi et al., 2001 (32)	70	23	33
Calvo Romero and Ramiro Lozano, 2012 (33)	81	7	8.6
Sato et al., 2013 (34)	62	8	13

*Twenty-one individuals (30%) were identified as having B₁₂ malabsorption.

†Twelve individuals (36%) were identified as having B₁₂ malabsorption.

‡Individuals identified as being deficient had ≥1 abnormal B₁₂ marker (e.g., subnormal/reduced cobalamin, reduced holotranscobalamin, elevated homocysteine, and elevated methylmalonic acid)

A study examining individuals undergoing metformin therapy for 4 months examined the potential for calcium supplementation to aid in the mitigation of B₁₂ malabsorption. After 3 months of metformin therapy, calcium carbonate, 1.2 g/day, was administered for 1 month. From the third to the fourth month, serum holotranscobalamin II levels increased by 53 ± 15% (42).

Histamine H2 Receptor Antagonist/Proton Pump Inhibitor–Induced Vitamin B₁₂ Depletion

In general, acid suppressors including both histamine H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have been documented to interfere with B₁₂ absorption (43–47). In 1980, Steinberg et al. (48) found that, while undergoing treatment with H2RAs, patients were able to absorb unbound B₁₂ (i.e., B₁₂ from a vitamin supplement) but not protein-bound B₁₂ (i.e., B₁₂ from food sources). Numerous subsequent articles have also reported H2RA-induced B₁₂ depletion (49–51). When protein-bound B₁₂ absorption was assessed before and after H2RA therapy, a 53% drop in absorption was noted (from 5.3% before treatment to 2.5% after treatment) (49). When protein-bound B₁₂ absorption was assessed before and after ranitidine therapy, an 89% drop in absorption was

noted (from 7.66% before treatment to 0.84% after treatment) (52). Other studies analyzing ranitidine have also noted decreases in B₁₂ (53). In addition to H2RAs, studies have noted an inverse correlation between duration of PPI therapy and B₁₂ levels (54–57).

Mechanisms

Various reports have attributed acid suppressor–induced B₁₂ depletion to decreased gastric acid, pepsin, and intrinsic factor output (49,50,53,58,59).

Mitigation

In H2RA-induced B₁₂ depletion, B₁₂ levels have been shown to improve as a result of:

- B₁₂ supplementation as crystalline B₁₂ in the form of oral supplementation, as opposed to protein-bound B₁₂ ingestion (from food sources) (43,49,51)
- Discontinuation of H2RA therapy (48,53)

In PPI-induced B₁₂ depletion, strategies to improve B₁₂ levels include:

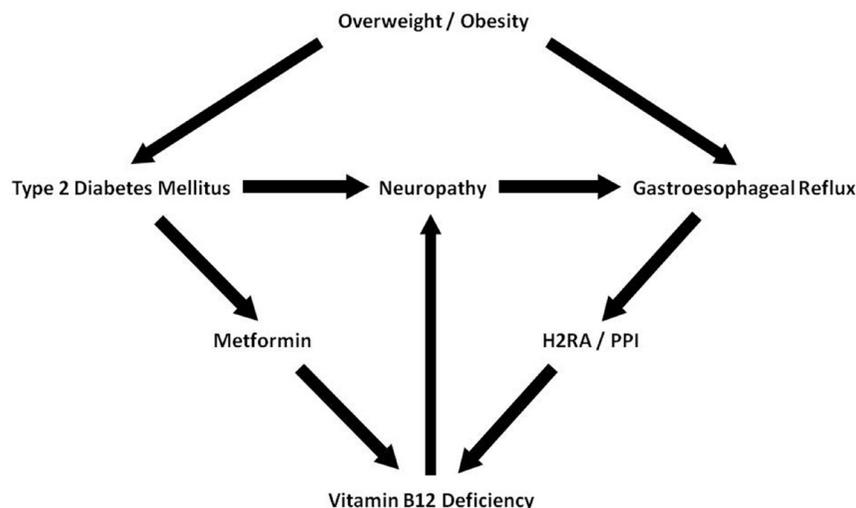
- B₁₂ supplementation, potentially in dosages beyond recommended daily allowance levels, including administration via cyanocobalamin nasal spray, 500 µg in one nostril once weekly for 8 weeks (44,56,57)
- Genotyping; S-mephenytoin hydroxylase, a polymorphic cyto-

chrome P450 (CYP) enzyme identified as CYP2C19, catalyzes the metabolism of PPIs (60). The polymorphism of S-mephenytoin hydroxylase has been shown to influence B₁₂ levels in those using PPIs. Therefore, genotyping may be useful in identifying individuals with a greater predisposition to B₁₂ depletion while undergoing long-term PPI therapy (60). Those who poorly metabolize PPIs would have increased acid suppression and therefore more interference with B₁₂ absorption. Conversely, those with elevated metabolism of PPIs would have poor acid suppression and less interference with B₁₂ absorption.

Figure 1 shows a schematic flowchart of the sequelae resulting from type 2 diabetes and GERD managed with metformin and acid-suppressing medications.

Discussion

Prevalence rates of both obesity and type 2 diabetes continue to increase over time (1,61). As previously mentioned, 70% of people with diabetes take oral antidiabetic agents, and 40.7% have symptomatic GERD. Thus, millions of people are most likely managing hyperglycemia and GERD concomitantly with oral medications (1,7). Additionally, PPIs and H2RAs are often overused (62).



■ **FIGURE 1.** Schematic representation of the sequelae of overweight/obesity and type 2 diabetes with regard to neuropathy and GERD. A positive feedback exists among neuropathy, GERD, management with acid-suppressing medications, and vitamin B₁₂ deficiency. The figure illustrates an additive effect of concomitant metformin and acid-suppression therapy leading to neuropathy via compounded vitamin B₁₂ depletion.

Regardless of the appropriateness of acid-suppressing medication use, in 2013 the acid-suppressing PPI esomeprazole was second in sales only to the antipsychotic aripiprazole (63). Given the increases in obesity and type 2 diabetes prevalence rates and the high consumption of PPIs, the potential exists for increasing concomitant use of antidiabetic and acid-suppressing medications.

Monotherapy with either metformin, an H₂RA, or a PPI can deplete vitamin B₁₂. In a recent study, 22.2% of individuals in a nondiabetic control group were found to be B₁₂ deficient, an incidence that did not differ statistically from that of the experimental groups of metformin users (21.9%) or PPI users (25.6%). However, a significant difference was found between control subjects and the 34.2% of concomitant users of metformin and PPI who were B₁₂ deficient (64). This study supports the notion that concomitant therapy has an additive effect. Because metformin and acid-suppressing medications have been demonstrated to deplete B₁₂ independently and to

have a compounded effect when used concomitantly, it is important to recognize the potential for neuropathy to develop as a result of this likely polypharmacy scenario.

Pharmacists, clinicians, and patients need to be aware of the potential for polypharmacy-induced B₁₂ depletion and the potential for subsequent neuropathy. Awareness is particularly important because metformin and acid-suppressing medications are commonly used in the diabetic population, which has a high prevalence of neuropathy (60–70%) (1). Thus, what is generally thought of as “diabetic” neuropathy may be, at least in part, B₁₂ deficiency–induced neuropathy resulting from the concomitant use of these medications. Health care providers and people with diabetes also should be aware of the many strategies and alternatives that have been shown to improve B₁₂ deficiency and resultant neuropathy.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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