

## Evaluation of Vitamin B12 Monitoring in Patients on Concomitant Metformin and Proton Pump Inhibitors

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### ABSTRACT

**Background:** Type 2 diabetes mellitus and gastroesophageal reflux disease are highly prevalent in the United States. First-line therapies for these disease states include metformin and proton pump inhibitors, respectively. Both of these medications have been associated with a decreased absorption of vitamin B12.

**Objective:** The objective of this study was to assess the prevalence of B12 monitoring and supplementation in patients receiving concomitant metformin and PPI therapy.

**Methods:** A retrospective data analysis was performed at a single federally qualified health center. Patients receiving concomitant metformin and PPI therapy (specifically omeprazole and pantoprazole) over the past year were included. Data collected included demographics, dosing, therapy duration, and vitamin B12 level. Data were analyzed using descriptive statistics.

**Results:** A total of 104 patients met the inclusion criteria for this study. Metformin 1000 mg immediate release tablets was the most common dose and formulation prescribed. Omeprazole and pantoprazole were the most commonly prescribed PPIs. The most frequent duration of therapy was 1 to 4 years. Fourteen patients had a documented B12 level and no patients were categorized as deficient. Seven patients were prescribed a B12 supplement during the study period.

**Conclusion:** In this single center, retrospective chart review of patients receiving concomitant metformin and PPI therapy, the average duration of therapy for both agents was 1-4 years. Only 13.5% of patients had a documented B12 level. Of those patients, none were categorized as deficient. Though routine monitoring of B12 levels may be important for patients on long-term therapy with both agents or who present with symptoms of B12 deficiency, this study does not support routine monitoring of B12 levels for patients with duration of therapy of 4 years or less.

**Keywords:** vitamin B12, metformin, proton pump inhibitors

### BACKGROUND

Type 2 diabetes mellitus and gastroesophageal reflux disease (GERD) are two prevalent disease states in the United States affecting approximately 10% and 20% of the population, respectively.<sup>1,2</sup> First line therapies for these disease states include metformin and proton pump inhibitors (PPIs), both of which have been associated with a decreased absorption of vitamin B12 (B12).<sup>3,4</sup>

B12 is a water-soluble vitamin obtained through ingestion of certain meat and dairy products as well as fortified cereals. The proenzyme pepsinogen is released from gastric chief cells and converted by gastric acid to active pepsin, a digestive enzyme responsible for releasing B12 from food protein.<sup>5</sup> In the small intestine, B12 forms a complex with intrinsic factor (IF), a glycoprotein excreted by gastric parietal cells in response to histamine, gastrin, and acetylcholine.<sup>6</sup> This B12-intrinsic factor complex binds transmembrane receptors on cells in the ileum and is taken into the cell by endocytosis. Intrinsic factor is degraded, leaving free vitamin B12 which is then released into portal circulation, bound to the transport protein transcobalamin, and distributed throughout the body.<sup>5</sup>

B12 is necessary for proper neurologic function, erythropoiesis, and DNA synthesis. B12 deficiency may result in complications ranging from mild fatigue to severe neurological impairments.<sup>6</sup>

Metformin is thought to decrease B12 levels by interfering with calcium-dependent binding of B12-intrinsic factor complex to its receptor.<sup>7</sup> The risk of metformin induced B12 deficiency increases with dose and duration of metformin therapy.<sup>8,9</sup> Patients treated with metformin, particularly those with poor dietary intake of B12 or who are predisposed to malabsorption (eg, after bariatric surgery), should have B12 levels monitored annually.<sup>10</sup>

PPIs decrease B12 levels by reducing the production of gastric acid thereby reducing the release of B12 from food protein.<sup>5</sup> Though there is substantial evidence that PPI therapy reduces B12 levels, the clinical significance of this reduction is unclear.<sup>11-13</sup>

Patients receiving concomitant metformin and PPI therapy would seem to be at greater risk of B12 deficiency as the problem of decreased release of B12 from food protein is compounded by the decreased ability of the B12-intrinsic factor complex to bind its receptor. Research testing this hypothesis is lacking.

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**OBJECTIVE**

The objective of this study was to assess the prevalence of B12 monitoring and supplementation in patients receiving concomitant metformin and PPI therapy.

**METHODS**

A retrospective data analysis was performed at a single location of a multisite Federally Qualified Health Center (FQHC) with a 340B dispensing pharmacy. Patients 19 years of age and older receiving concomitant therapy with metformin and either omeprazole or pantoprazole from July 1, 2018 to July 1, 2019 were included. Included PPIs were those most commonly prescribed at the study location. Data was collected by generating a report from the electronic medical record (EMR), Athenahealth.

Patients were excluded if they were 19 years of age or younger, had a glomerular filtration rate of less than 30 mL/min, pregnant, or diagnosed with pernicious anemia, peripheral neuropathy, Crohn's disease, Celiac disease, atrophic gastritis, or tapeworm infection. Additionally, patients seen at a clinic site other than the study location were excluded.

Once patients on dual therapy were identified, charts were reviewed and the following data was collected: age, gender, race, prescriber, insurance status, metformin dose, metformin dosage form, metformin years of exposure, prescribed PPI, PPI dose, PPI years of exposure, and vitamin B12 level.

Data were analyzed using descriptive statistics (e.g. averages) with Microsoft Excel 2016. This study was approved by the Institutional Review Board of Samford University.

**RESULTS**

Patient demographics are provided in Table 1. A total of 138 patients were identified for this study, of which 104 met the inclusion criteria (Figure 1). The average age was 53 years. Seventy-seven (74%) were female. Approximately half of the patients self identified as black; one patient identified as Asian, while all the remaining patients identified as white. Eighty-four percent (n=87) of patients had some form of insurance.

Metformin 1000 mg immediate release tablets was the most common dose and formulation prescribed. The majority of patients had a duration of metformin therapy of 1 to 4 years; 21 patients had a duration of less than 1 year, while the remaining 8 had a duration of use longer than 4 years.

Omeprazole 40 mg capsules was the most commonly prescribed PPI, followed by omeprazole 20 mg capsules and pantoprazole 40 mg tablets. The most prevalent duration of PPI therapy was also 1 to 4 years (n=79). Of the remaining patients, 17 had a duration of therapy less than one year and the remaining 8 had a duration greater than 4 years.

Only 14 patients (13.5%) had a documented B12 level. Based upon laboratory reference values, no patients were categorized

as deficient. Despite the lack of a documented deficiency, 7 patients had been prescribed a B12 supplement during the study period.

**Discussion**

This study aimed to assess the prevalence of B12 monitoring and supplementation in patients receiving concomitant metformin and PPI therapy. The majority of patients did not have documented B12 levels. For those patients with documented levels, B12 was within the normal range according to the laboratory reference range currently in use at the study location (200-1100 pg/mL) when B12 supplementation was initiated.

A small number of patients had been prescribed a supplement during the study period despite having a documented B12 level within the currently used laboratory reference range. Upon further investigation of visit notes, 4 patients were prescribed B12 for cobalamin deficiency / non anemic B12 deficiency and 1 for biotin deficiency; however, these problems were not included in the patients' problem list in the EMR. No indication for B12 supplementation was listed for the remaining 2 patients. The prescription for 2 of the patients appears to have only been entered, not prescribed by our system. It is unknown if a written prescription was provided for these patients. Four of the patients seem to have currently active prescriptions for B12. All patients with a B12 supplement had insurance of some form; therefore it is reasonable to assume that access to coverage was not a limiting factor, but prescription coverage of B12 supplements for these patients was not able to be determined.

Other studies recommend routine monitoring of B12 levels for patients who have been on metformin long term (> 5 years). Aroda et al<sup>9</sup> demonstrated that years of metformin use was associated with an increased risk of B12 deficiency in patients taking metformin 850 mg twice daily for at least 5 years. Ko et al<sup>14</sup> found that patients taking metformin  $\geq 2000$  mg daily for  $\geq 10$  years had a 4 fold higher risk for developing B12 deficiency compared to patients taking  $\leq 1000$  mg for  $\leq 4$  years. Of the patients in our study with a B12 level, all have been on metformin therapy for less than 4 years; only one patient had been on PPI therapy for longer than 4 years (8 year therapy duration). Only 3 patients in the study have been on both metformin and a PPI for longer than 4 years; unfortunately, despite receiving higher doses of each medicine, none of those patients had a B12 level available.

Although studies examining the association between PPI use and B12 deficiency have yielded conflicting results, a study that assessed B12 deficiency in patients taking metformin with a proton pump inhibitor found that, of 123 patients taking concomitant metformin and a proton pump inhibitor, 42 were found to have a B12 deficiency, defined for the purposes of that study as  $< 300$  pg/mL.<sup>15</sup>

This study is not without limitations. Our clinic serves a high proportion of Hispanic patients, yet none of the patients included in the study were of this race. Given the prevalence of

type 2 diabetes and GERD in this patient population,<sup>16,17</sup> it was surprising the final study sample did not include any Hispanic patients. The accuracy and completeness of historical data was limited as our EMR system changed during the spring of 2017. The low number of patients with a recent documented B12 level could be the result of lack of provider knowledge of the need to monitor B12 levels, or obtaining and processing the laboratory sample could have been cost prohibitive. Future studies might assess the impact of educating providers about the need to monitor B12 levels in patients taking concomitant metformin and PPI therapy.

Another limitation of this study was its failure to identify those patients who would have been at increased risk of B12 deficiency despite the concomitant use of metformin and a PPI; for example, patients with pernicious anemia or GI disorders like Celiac disease or Crohn's disease, patients who have had GI surgery, and vegetarians. It would have been helpful to know whether those conditions and not the concomitant use of metformin and a PPI prompted monitoring of B12 levels.

## CONCLUSION

In this single center, retrospective chart review of patients receiving concomitant metformin and PPI therapy, the average duration of therapy for both agents was 1-4 years. Only 13.5% of patients had a documented B12 level. Of those patients, none were categorized as deficient. Though routine monitoring of B12 levels may be important for patients on long-term therapy with both agents or who present with symptoms of B12 deficiency, we did not observe a need to routinely monitor B12 levels for patients with a duration of therapy of 4 years or less.

## CREDIT

Chappell L: Conceptualization, Methodology, Data curation, Writing-Original draft preparation.

Brown SA: Writing-Reviewing and Editing.

Wensel TM: Conceptualization, Methodology, Writing-Reviewing and Editing.

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## REFERENCES

- Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.Pdf>. Accessed May 18, 2020.
- National Institute of Diabetes and Digestive and Kidney Diseases. Definition and Facts for GER & GERD. <https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-adults/definition-facts>. Accessed May 18, 2020.
- de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010;340:c2181. PMID:20488910
- Lam JR, Schneider JL, Zhao W, et al. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA*. 2013;310(22):2435-2442. PMID:24327038
- Miller JW. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B-12 deficiency: clinical implications. *Adv Nutr*. 2018;9(4):511S-518S. PMID:30032223
- Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. *Am Fam Physician*. 2017 Sep 15;96(6):384-389. PubMed PMID: 28925645.
- Festen HPM. Intrinsic factor secretion and cobalamin absorption: physiology and pathophysiology in the gastrointestinal tract. *Scand J Gastroenterol*. 1991;26(suppl 188):1-7.
- Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patient receiving metformin. *Arch Intern Med*. 2006;166(18):1975-1979. PMID:17030830
- Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab*. 2016;101(4):1754-1761. PMID:26900641
- Wexler DJ. Metformin in the treatment of adults with type 2 diabetes mellitus. In: Nathan DM, ed. *UpToDate*. Waltham, MA: UpToDate; 2019. [www.uptodate.com](http://www.uptodate.com). Accessed May 19, 2020.
- Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12). *Ann Intern Med*. 1994;120(3):211-5.
- Schenk BE, Festen HP, Kuipers EJ, Klinkenberg-Knol EC, Meuwissen SG. Effect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin. *Aliment Pharmacol Ther*. 1996;10(4):541-5.
- Linder L, Tambou C, Clements JN. Drug-induced vitamin B12 deficiency: a focus on proton pump inhibitors and histamine-2 antagonists. *J Pharm Pract*. 2017;30(6):639-42.
- Ko SH, Ko SH, Ahn YB, et al. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. *J Korean Med Sci*. 2014;29(7):965-972. doi:10.3346/jkms.2014.29.7.965
- Long AN, Atwell CL, Yoo W, Solomon SS. Vitamin B(12) deficiency associated with concomitant metformin and proton pump inhibitor use. *Diabetes Care*. 2012;35(12):e84. doi:10.2337/dc12-0980
- Centers for Disease Control and Prevention. Hispanic/Latino Americans and Type 2 Diabetes. <https://www.cdc.gov/diabetes/library/features/hispanic-diabetes.html>. Accessed June 10, 2020.
- Yuen E, Toner RW, Cobb NM, Katz P, Spodik M, Goldfarb NI. Prevalence, knowledge and care patterns for gastro-oesophageal reflux disease in United States minority populations. *Aliment Pharmacol Ther*. 2010;32(5):645-54. PMID:20629972

Table 1: Patient Demographics

		n; %
Age, years	20-30	4
	31-39	13
	40-49	16
	50-59	34
	60-69	25
	70 and older	11
Gender	Male	27
	Female	76
Race	Asian	1
	Black	55
	White	47
Insured	Yes	86
	No	17
Prescribed Metformin Formulation	Extended Release	20
	Immediate Release	83
Prescribed PPI	Omeprazole	71
	Pantoprazole	32
Duration of Therapy (metformin; PPI, respectively)	< 1 year	20; 17
	1 to 4 years	77; 81
	> 4 years	6; 5

Figure 1: Patient is the study based on inclusion and exclusion criteria

