Comparison of Patients Receiving Long-Term Metformin Therapy and Vitamin B₁₂ Monitoring

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Abstract

Background: Metformin may cause vitamin B₁₂ deficiency that can present with symptoms of peripheral neuropathy. Lack of vitamin B₁₂ serum concentration monitoring could result in vitamin B₁₂ deficiency progression, worsening of symptoms, and unnecessary medication. **Objectives:** The purpose of this study was to (a) compare the influence of the rate of symptoms consistent with vitamin B₁₂ deficiency on obtaining vitamin B₁₂ serum concentrations in patients using metformin; (b) assess if vitamin B₁₂ serum concentrations were ordered as a routine monitoring parameter. **Methods:** This retrospective case–control study evaluated patients receiving metformin. Patients in the case group had documented symptoms or diagnosis of peripheral neuropathy or macrocytic anemia, while those in the control group did not. The primary outcome was frequency of vitamin B₁₂ serum concentration assessment. The secondary outcomes included frequency of vitamin B₁₂ serum concentration assessment for patients presenting with symptoms or diagnosis of peripheral neuropathy or macrocytic anemia. **Results:** Analysis included 355 patients (116 cases, 239 controls). The cases were 5 times more likely to have a serum vitamin B₁₂ serum concentrations drawn versus controls (odds ratio [OR] = 5.83, 95% confidence interval [CI] = 3.47–9.77, $P < .001$). Patients with a diagnosis of peripheral neuropathy or macrocytic anemia were 4 times more likely to have a serum vitamin B₁₂ concentration drawn than those who did not (peripheral neuropathy: OR = 4.92, 95% CI = 2.95–8.21, $P < .001$; macrocytic anemia: OR = 5.41, 95% CI = 1.30–20.97, $P = .007$). **Conclusions:** Cases were more likely to have vitamin B₁₂ serum concentrations assessed than patients without symptoms. The majority of patients taking metformin did not have routine vitamin B₁₂ serum concentration assessments for medication adverse event monitoring.

Keywords

metformin, vitamin B₁₂ deficiency, peripheral neuropathy, macrocytic anemia

Introduction

The American Diabetes Association and the American Association of Clinical Endocrinologists recommend the use of metformin as first-line treatment for both type 2 diabetes mellitus and prediabetes to prevent progression of the disease.^{1,2} The toxicity that draws the most attention in association with metformin use is lactic acidosis. While this side effect is a very serious concern, the reported incidence of lactic acidosis is markedly low (about 0.03 cases/1000 patient years), and there are currently not any routine monitoring parameters to screen for this event.³ Another adverse effect associated with metformin that has been well documented and has the potential to cause long-term deleterious neurological and hematologic effects is vitamin B₁₂ malabsorption.^{4,7} Approximately 30% of patients taking metformin do not properly absorb vitamin B₁₂.⁸ This effect is most

often seen after the patient has received long-term treatment (ie, ≥ 6 months) and high doses (ie, >1 g/day) of metformin.^{7,9}

The mechanism by which metformin causes decreased vitamin B₁₂ absorption is not wholly understood. It is hypothesized that the effect may be due to impaired calcium-dependent ileal absorption of the intrinsic factor

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vitamin B₁₂ complex caused by metformin.¹⁰ Deficiency in vitamin B₁₂ can manifest as macrocytic anemia, gastrointestinal symptoms, pancytopenia, and neurologic deterioration that usually presents similar to diabetic peripheral neuropathy. Neurologic manifestations may include paresthesias, weakness, gait abnormalities, and changes in behavior or cognition.¹¹ The neurologic damage caused by vitamin B₁₂ deficiency may not be reversible if left undetected for long periods of time. However, it is possible to stop symptom progression through either intramuscular or oral cyanocobalamin supplementation.

It has been recommended that all patients receiving metformin have vitamin B₁₂ serum concentrations monitored annually.^{7-9,12} This monitoring has the capability to prevent neurologic deterioration and lead to a better quality of life for patients taking metformin.

A recent study in the Veterans' population revealed that the rate of assessment of vitamin B₁₂ serum concentrations in patients on long-term (>1 year), high-dose (>2 g/day) metformin is not routinely conducted in clinical practice.¹³ The study results do not indicate if the assessment of vitamin B₁₂ was conducted in response to new onset of symptoms or as routine monitoring for metformin use.

The purpose of this study was to (a) compare the influence of the rate of symptoms consistent with vitamin B₁₂ deficiency on obtaining vitamin B₁₂ serum concentrations in patients using metformin long-term; (b) assess if vitamin B₁₂ serum concentrations were ordered as a routine monitoring parameter or following symptoms suggestive of vitamin B₁₂ deficiency.

Methods

This was a retrospective, case-control study at 2 academic primary care practices (Internal Medicine and Family Medicine) that was conducted in compliance with the University of Tennessee Health Science Center Institutional Review Board requirements. Patients were identified for potential inclusion in the study by searching the electronic medical records for active medications that contain metformin. Adult patients (≥18 years of age) were included in the study if they had been prescribed metformin between January 1, 2010, and February 28, 2014, and had been using metformin for at least 12 months. Patients were excluded if they had documented vitamin B₁₂ deficiency, macrocytic anemia, or peripheral neuropathy prior to the initiation of metformin. Patients were also excluded if they were diagnosed with any of the following conditions: active cancer, end-stage renal disease, diagnosed reason for vitamin B₁₂ malabsorption (alcoholism, atrophic gastritis, celiac disease, Crohn's disease, gastric banding or bypass, partial or complete gastrectomy, *Helicobacter pylori* infection, human immunodeficiency virus, ileal resection, or chronic pancreatitis).

Cases were defined as those taking metformin who had symptoms or diagnosis of peripheral neuropathy or macrocytic anemia documented in the electronic medical record. Controls lacked symptoms or diagnosis of peripheral neuropathy or macrocytic anemia but were taking metformin chronically. All problem lists and progress notes were reviewed to identify patient complaints of symptoms consistent with peripheral neuropathy or macrocytic anemia, to ensure appropriate study group classification.

The primary outcome was frequency of vitamin B₁₂ serum concentration assessment. The secondary outcomes included frequency of vitamin B₁₂ serum concentration assessment for patients presenting with symptoms or diagnosis of peripheral neuropathy or macrocytic anemia. A subgroup analysis was conducted to determine if the vitamin B₁₂ serum concentration assessments were ordered prior to onset of symptoms consistent with vitamin B₁₂ deficiency, or in response to the patient presenting with such symptoms. These symptoms included those consistent with peripheral neuropathy and macrocytic anemia.

Following the initiation of the study, the US Food and Drug Administration released a warning stating that the use of systemic fluoroquinolones carries a potential risk of causing permanent nerve damage.¹⁴ The study protocol was altered to collect additional information about individual patient use of systemic fluoroquinolones to determine if data needed to be controlled for in the statistical analysis.

Descriptive statistics for baseline comparisons between the study groups were assessed using a combination of independent *t* tests for continuous outcomes and χ^2 tests of independence for categorical outcomes. Additional descriptive characteristics of the case group were analyzed using the same methods, and results are displayed as frequencies (%) or means (SD) as well as odds ratios (OR) and 95% confidence intervals (95% CI), as appropriate. Primary outcomes were compared using the same approach, and secondary outcomes were compared using Fisher's exact procedure to account for small cell sizes (ie, <5). All statistical tests were 2-sided and assumed a *P* < .05 as statistically significant. All variables were assessed for missing data and outlying values prior to analysis. Outliers were defined as values that were greater than 3 standard deviations away from the mean for that variable. Subjects with outlier variables were removed from the analysis to preserve the normality of the data. Analyses were performed using SPSS v.22 (IBM Inc, Chicago, IL).

Results

After removing 499 patients due to exclusion criteria, 355 patients were enrolled. Five outlying cases were identified and removed prior to data analysis. Variables that led to subject removal from the study included mean corpuscular volume, mean corpuscular hemoglobin, and hematocrit.

Table 1. Baseline Comparisons of Study Group Characteristics.

Variable	Control (n = 239)	Case (n = 116)	OR (95% CI) ^a	P Value ^b
Age (years) ^c	53.24 (13.85)	56.26 (12.5)	—	.048
Sex, n ^d			1.53 (0.97-2.43)	.066
Male	109 (45.6%)	41 (35.3%)		
Female	130 (54.4%)	75 (64.7%)		
Race, n ^d			0.59 (0.32-1.11)	.102
White	184 (79.7%)	99 (86.8%)		
Non-White ^e	47 (20.3%)	15 (13.2%)		
Indication for metformin, n ^d			0.44 (0.16-1.21)	.103
DM type 2	217 (90.8%)	111 (95.7%)		
Other indication ^{e,f}	22 (9.2%)	5 (4.3%)		
Metformin total daily dose at 1 year (mg) ^c	1404.18 (638.51)	1534.05 (617.06)	—	.070
	Control (n = 34)	Case (n = 56)	OR (95% CI) ^a	P Value ^b
Vitamin B ₁₂ serum concentration ^g (pg/mL) ^c	495.69 (336.16)	456.51 (305.91)	—	.567
Lowest vitamin B ₁₂ serum concentration, n ^h				
≤200 pg/mL	2 (5.9%)	9 (16.1%)	3.06 (0.62-15.13)	.152
≤300 pg/mL	10 (29.4%)	17 (30.4%)	1.05 (0.41-2.56)	.924
≤350 pg/mL	12 (35.3%)	28 (50%)	1.83 (0.76-4.41)	.173
	Control (n = 146)	Case (n = 95)	OR (95% CI) ^a	P Value ^b
Hemoglobin (g/dL) ^c	13.61 (1.67)	12.83 (1.81)	—	.001
Hematocrit (%) ^c	41.81 (4.51)	39.94 (4.97)	—	.003
White blood cells (×10 ³ /μL) ^c	8.36 (2.59)	8 (2.9)	—	.326
Platelets (×10 ³ /μL) ^c	280.11 (87.49)	271.59 (90.32)	—	.471
MCV (fL) ^c	88.01 (5.62)	89.29 (6.47)	—	.110
MCH (pg) ^c	28.7 (2.54)	28.54 (2.5)	—	.641
MCHC (g/dL) ^c	32.47 (1.28)	32.04 (1.15)	—	.009

Abbreviations: OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

^aOdds ratio (95% confidence interval).

^bGroups compared using independent samples *t* test or χ^2 test of independence, as appropriate.

^cMean (standard deviation).

^dFrequency (%).

^eAdditional categories were combined due to low numbers.

^fAdditional categories included prediabetes, metabolic syndrome, and polycystic ovarian syndrome.

^gFor those with multiple vitamin B₁₂ concentration values, the lowest concentration observed during the study period was used for comparison.

^hFrequency (cumulative %).

Removal of these outlying cases was done to prevent bias in the analysis of the results and had no effect on primary or secondary outcomes.

Study subjects that had symptoms or diagnosis of peripheral neuropathy or macrocytic anemia (n = 116) were classified as the case group. The remaining patients (n = 239) were classified as controls. Baseline characteristics of the study population are listed in Table 1. Of note, the majority of patients were Caucasian females. There is a statistically significant difference in age between the case and control groups of 3 years (56.26 vs 53.24, respectively). Additionally, over 90% of patients in each group were prescribed metformin to treat type 2 diabetes mellitus. There was no difference in the average vitamin B₁₂ serum

concentration between the case and control groups. However, a breakdown of the number of study subjects in each group with low vitamin B₁₂ is listed in Table 1. Of the patients who had a serum vitamin B₁₂ concentration drawn, 50% of the case group and 36.4% of the control group had low vitamin B₁₂ concentrations (*P* = .173).

The primary outcome of this study was frequency of vitamin B₁₂ serum concentration assessment (Table 2). Patients in the case group were over 5 times more likely to have a serum vitamin B₁₂ level drawn versus those patients in the control group (OR = 5.83, 95%CI = 3.47-9.77, *P* < .001). A total of 56 (48.3%) patients in the case group had a serum vitamin B₁₂ level drawn compared to 34 (14.2%) patients in the control group. The use of fluoroquinolones

Table 2. Frequency of Vitamin B₁₂ Serum Concentrations Based on Study Group and Diagnosis.

	Vitamin B ₁₂ Serum Concentration		OR (95% CI)	P Value
	Not Drawn	Drawn		
Study group				
Control	205 (85.8%)	34 (14.2%)	5.83 (3.47-9.77)	<.001
Case	60 (51.7%)	56 (48.3%)		
Peripheral neuropathy				
Not present	209 (84.6%)	38 (15.4%)	4.92 (2.95-8.21)	<.001
Present	57 (52.8%)	51 (47.2%)		
Macrocytic anemia				
Not present	150 (67.0%)	74 (33.0%)	5.41 (1.39-20.97)	.007
Present	3 (27.3%)	8 (72.7%)		

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3. Timing of Vitamin B₁₂ Serum Concentration in Relation to Symptom Onset or Diagnosis.

	Peripheral Neuropathy (n = 52)	Macrocytic Anemia (n = 8)
First vitamin B ₁₂ serum concentration <i>before</i> symptom onset ^a	18 (24.6%)	2 (25.0%)
First vitamin B ₁₂ serum concentration <i>same day</i> as symptom onset ^a	11 (21.2%)	1 (12.5%)
First vitamin B ₁₂ serum concentration <i>after</i> symptom onset ^a	23 (44.2%)	5 (62.5%)

^aFrequency (%).

had no statistically significant impact on this outcome and therefore was not controlled for in the statistical analysis.

Patients who were diagnosed with peripheral neuropathy and macrocytic anemia were sorted into their respective categories to assess the secondary study outcomes (Table 2). Compared with patients who did not have a diagnosis of peripheral neuropathy or macrocytic anemia, patients who did have either of these diagnoses were more than 4 times more likely to have a serum vitamin B₁₂ concentration drawn (OR = 4.92, 95% CI = 2.95-8.21, $P < .001$, for peripheral neuropathy and OR = 5.41, 95% CI = 1.30-20.97, $P = .007$, for macrocytic anemia).

A subgroup analysis was conducted to determine if vitamin B₁₂ serum concentration assessments were ordered prior to the onset of symptoms of vitamin B₁₂ deficiency, or in response to the patient presenting with such symptoms. For those patients with peripheral neuropathy, the majority of patients had symptom onset either before or on the same day as the first vitamin B₁₂ laboratory draw. The same is true for those patients with macrocytic anemia (Table 3).

A variety of therapies were used to treat peripheral neuropathy and macrocytic anemia (Table 4). Patients who did not have a vitamin B₁₂ serum concentration drawn were treated with an agent other than oral or intramuscular cyanocobalamin, whereas 33.3% of the patients who had vitamin B₁₂ serum concentration assessed were treated

with cyanocobalamin. Only 3 patients received treatment for macrocytic anemia, one with oral cyanocobalamin, one with intramuscular cyanocobalamin, and one with oral iron.

Discussion

The Glucophage package insert advises that all patients have hematological parameters measured on an annual basis, and specifically states that those patients predisposed to low vitamin B₁₂ levels should have routine serum vitamin B₁₂ measurements drawn every 2 to 3 years.³ Additionally, other articles suggest that vitamin B₁₂ serum concentrations be monitored annually in order to prevent potential neurologic deterioration rather than treat it once it has begun.^{7-9,12} A systematic review of vitamin B₁₂ deficiency among patients with diabetes recommends assessing a vitamin B₁₂ serum concentration prior to starting metformin therapy and then yearly thereafter.¹² The results of this study indicate patients presenting with signs and symptoms of peripheral neuropathy were more likely to have a vitamin B₁₂ serum concentration drawn. Unfortunately, 51.7% of patients presenting with said symptoms did not have a vitamin B₁₂ serum concentration measured. This is similar to prior reports from a recent study in the Veterans' population where 60% of total patients and 42% of patients with newly

Table 4. Medication Treatment for Peripheral Neuropathy and Macrocytic Anemia.

Variable	Vitamin B ₁₂ Serum Concentration	
	Drawn (n = 52)	Not Drawn (n = 57)
Peripheral neuropathy treated with medication ^{a,b}		
Yes	36 (69.2%)	29 (50.9%)
No	16 (30.8%)	28 (49.1%)
Peripheral neuropathy treatment type ^b		
Cyanocobalamin (oral)	7 (19.4%)	—
Cyanocobalamin (intramuscular)	5 (13.9%)	—
Gabapentin	21 (58.3%)	23 (79.3%)
Pregabalin	4 (11.1%)	2 (6.9%)
Serotonin norepinephrine reuptake inhibitor	—	1 (3.4%)
Topical lidocaine	—	2 (6.9%)
Cyclobenzaprine	—	1 (3.4%)

^aOdds ratio = 2.17 (95% confidence interval = 0.99-4.77), *P* = .079.

^bFrequency (%).

diagnosed neuropathy did not have a vitamin B₁₂ serum concentration measured.¹³

Of the total number of patients who were diagnosed with peripheral neuropathy, 47.2% had a vitamin B₁₂ serum concentration drawn to assess for deficiency and 52.8% did not. In comparison to the patients with macrocytic anemia, 72.7% of these patients had a vitamin B₁₂ serum concentration assessed while 27.3% did not. These data suggest that there is a disparity in measuring vitamin B₁₂ serum concentrations favoring macrocytic anemia over peripheral neuropathy. However, these conclusions need to be confirmed due to the low number of patients enrolled in the study with macrocytic anemia.

Based on the results presented in Table 3, we found that patients were not having vitamin B₁₂ serum concentrations ordered for assessment as a medication safety parameter for metformin. Instead, these data suggest that vitamin B₁₂ serum concentrations were monitored in reaction to symptom onset instead of a preventative approach. Only a quarter of the patients in this study appeared to have medication safety monitoring performed in an effort to detect vitamin B₁₂ deficiency prior to symptom onset.

Of the patients being treated with medications for peripheral neuropathy, 44.6% did not have a vitamin B₁₂ serum concentration drawn. Failing to evaluate for vitamin B₁₂ deficiency could lead to progression of symptoms, unnecessary medication use, additional adverse drug reactions, and added treatment expense.

Evidence shows that measuring vitamin B₁₂ serum concentrations may not be the most accurate method of determining the vitamin B₁₂ status of a patient.¹⁵ We acknowledge that measuring both serum homocysteine and methylmalonic acid may be truer indicators of physiologic vitamin B₁₂. However, because this study was retrospective in nature we were not able to include these 2 markers in our data collection due to

their infrequent use at the practice locations being reviewed. Additionally, there was no difference between the case and the control groups in the mean serum vitamin B₁₂ concentration shown in Table 1.

Data included in the study were subject to the limitations of collecting data retrospectively using an electronic medical record. This may have led to some patients being incorrectly classified in the control group instead of the case group. To assist with avoiding misclassification of patients included in the study, all progress notes were reviewed to attempt to identify any mention of patient complaints of symptoms that could be consistent with peripheral neuropathy or macrocytic anemia. Unfortunately, the study population included very few patients with macrocytic anemia. Not all study subjects had a complete blood cell count drawn. In fact, it was only 240 patients of the total 355 that were enrolled. We were therefore unable to evaluate the remaining 115 for macrocytic anemia. Further studies are needed to draw conclusions regarding vitamin B₁₂ serum concentration monitoring in patients with macrocytic anemia.

Conclusion

Our retrospective study found the majority of patients taking metformin did not have routine vitamin B₁₂ serum concentration assessments for medication adverse event monitoring. Patients with symptoms or diagnosis of peripheral neuropathy or macrocytic anemia were more likely to have vitamin B₁₂ serum concentrations assessed than patients without symptoms. Many patients with peripheral neuropathy have not had vitamin B₁₂ serum concentrations assessed and may unknowingly be vitamin B₁₂ deficient. This could progress to worsening of symptoms and unnecessary medication use leading to adverse drug reactions and

added medical expenses. Unnecessary medications or poor medication choices could cause unneeded and unwanted effects. This may be easily avoidable by drawing a yearly B₁₂ level in patients taking metformin and treating them accordingly.

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Declaration of Conflicting Interests

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