

Evaluating the Association between Vitamin B12 Deficiency and Peripheral Neuropathy in Patients with Diabetes

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Abstract

Objective: The objective of this study is to ascertain if there is an association between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes. **Methods:** We identified 7,929 patient records from January 2009 to July 2013 with a serum vitamin B12 concentration and a diagnosis of diabetes only (DO) or diabetes and peripheral neuropathy (DPN). **Results:** Of the 5,709 patients included (4,650 in DO and 1,059 DPN), 447 patients had a documented vitamin B12 concentration ≤ 250 pg/ml (361 in DO and 86 in DPN). Neither the mean vitamin B12 concentration nor incidence of vitamin B12 deficiency was significantly different between the DO and DPN groups (683 pg/ml vs. 693 pg/ml, $p=0.77$) (361 (7.8%) vs. 86 (8.1%), $p=0.70$). Those patients who used metformin and those patients age ≥ 55 were found to have an increased incidence of vitamin B12 deficiency (96 (12.3%) vs. 351 (7.1%), $p<0.0001$) (384 (8.2%) vs. 63 (6.0%), $p=0.02$). Yet, only patients age ≥ 65 were found to have an increased incidence of neuropathy with vitamin B12 deficiency (242 (8.2%) vs. 70 (11.0%), $p=0.02$). **Conclusions:** Metformin and age ≥ 55 were associated with decreased vitamin B12 concentrations. In addition, vitamin B12 deficiency was not found to be associated with neuropathy in patients with diabetes. However, in a subgroup analysis, vitamin B12 deficiency was associated with an increased likelihood of neuropathy in patients with diabetes age ≥ 65 .

Keywords: vitamin B12, B12, peripheral neuropathy, neuropathy, diabetes

1. Background

Vitamin B12 or cobalamin is a water soluble vitamin principally obtained through the dietary intake of animal proteins.^{6,9}

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Vitamin B12 is essential for DNA synthesis, red blood cell production, and neurological function.^{6,9}The National Health and Nutrition Examination Survey (NHANES) defined biochemical vitamin B12 deficiency as ≤ 148 pmol/L (200 pg/ml) with borderline deficiency as $\geq 148-221$ pmol/L ($\geq 200-300$ pg/ml).¹³Yet, the serum vitamin B12 concentration at which a person is considered to be deficient in clinical research is set anywhere from $<100-350$ pg/ml.^{4-7,11-12,14}In clinical practice, vitamin B12 deficiency is diagnosed with a serum B12 concentration <100 pg/ml or between 100 and 400 pg/ml with confirmatory testing. Confirmatory testing includes either an elevated serum methylmalonic acid or homocysteine concentration.^{6,9-10}Elevated levels of methylmalonic acid are as sensitive but more specific to vitamin B12 deficiency than homocysteine.^{9-10,15}

Causes of vitamin B12 deficiency can include insufficient dietary intake due to age, alcohol use, or a vegetarian diet, gastric abnormalities, small bowel disease, and pancreatic insufficiency.^{6,9-10}Medications such as metformin, proton pump inhibitors, and histamine-2 antagonists can also contribute to vitamin B12 deficiency.^{6,9-10}Due to extensive hepatic stores there may be a five to ten year delay between the onset of deficiency and the appearance of clinically overt symptoms.^{6,9}

In addition to the broad definition of vitamin B12 deficiency, there is also disparity in the prevalence of vitamin B12 deficiency.⁶In patients with type 2 diabetes the incidence can range from 2.4% to 33%.^{6,11-13}While in patients with type 1 diabetes the incidence has been reported as 45.5% to 54%.⁷Metformin is the preferred initial pharmacological agent for type 2 diabetes and metformin induced vitamin B12 deficiency has been described extensively in the literature.^{1,3-7,9-15}While proton pump inhibitors and histamine-2 receptor antagonists have also been associated with vitamin B12 deficiency there is less data.^{8,9-10}

Although the exact mechanism is unknown, common neurological manifestations of vitamin B12 deficiency include peripheral neuropathy, weakness, gait abnormalities, and cognitive or behavioral changes.⁹Studies describing the link between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes are lacking and have produced conflicting results.^{3-4, 14-15}Moreover, there are no guidelines on screening or providing supplementation for vitamin B12 deficiency in patients with diabetes.^{6,9}The objective of this study is to ascertain if there is an association between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes.

2. Methods

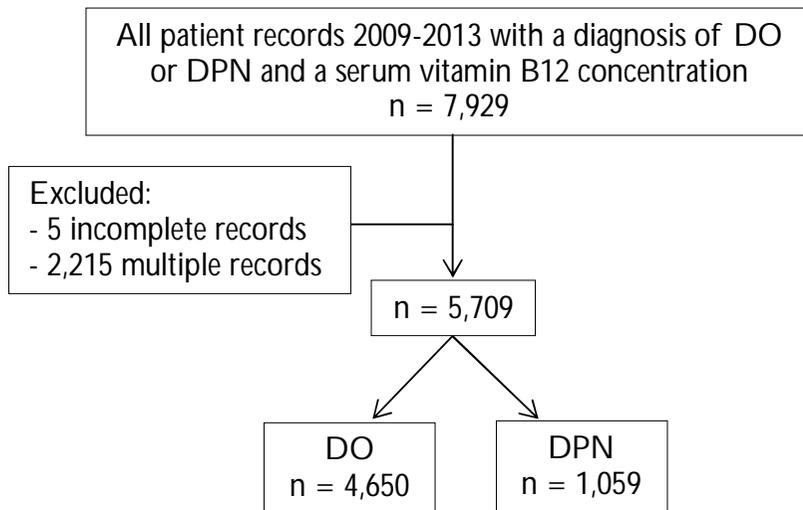
2.1 Study Design

The investigation was conducted as a case-control study. All patient records were obtained from a multi-hospital health network after the protocol was deemed exempt by the network's Institutional Review Board. Medical record data from January 1, 2009 to July 3, 2013 was reviewed for diagnosis codes from the *International Classification of Diseases, Ninth Revision* (ICD-9) indicating a diagnosis of diabetes with or without peripheral neuropathy. Included patients must also be >18 years of age and have a recorded serum vitamin B12 concentration.

Seven thousand nine hundred and twenty nine patient records were identified with a diagnosis of diabetes only (ICD-9 code 250.XX excluding 250.6X and 250.7X) or diabetes plus peripheral neuropathy (ICD-9 code 250.XX and 337.XX, 356.XX, 250.6X, 250.7X, or 357.2) and a serum vitamin B12 concentration. The results were then evaluated for duplicate records, incomplete records, or for patients with records in both groups. In the event a patient had multiple records in one group, the record with the lowest vitamin B12 serum concentration was kept. If a patient had records in both evaluation groups, we only included the record for the diabetes plus peripheral neuropathy group.

After identification, we evaluated each patient record for vitamin B12 concentration, methylmalonic acid concentration (when available), presence of medications that may induce vitamin B12 deficiency, and age. Although the concentration at which a person is considered to be vitamin B12 deficient varies, for the purpose of this analysis vitamin B12 deficiency was evaluated as both ≤ 250 pg/ml, which is consistent with the NHANES definition of borderline deficiency, and ≤ 100 pg/ml, which is consistent with deficiency in clinical practice.³

Among the medications that may induce vitamin B12 deficiency, those evaluated in this study are metformin, proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), and histamine-2 receptor antagonists (cimetidine, famotidine, ranitidine). The primary outcome was differences in vitamin B12 concentration and incidence of neuropathy. In addition, we performed subpopulation analyses based on concurrent medication use.

Figure 1

DO= diabetes only; DPN= diabetes plus peripheral neuropathy

2.2 Statistical Analyses

For the purposes of this study, a two-tailed alpha of 0.05 was used to establish significance. For continuous variables such as vitamin B12 concentration, a Student t-test was used to test for significance. For categorical variables such as presence or absence of B12 deficiency or peripheral neuropathy, a Chi-squared or Fisher's exact was employed. All statistical evaluations were conducted using SPSS (IBM, Armonk, New York).

3. Results

Seven thousand nine hundred and twenty nine patient records were identified with a diagnosis of diabetes only (DO) or diabetes plus peripheral neuropathy (DPN) and a serum vitamin B12 concentration. Five patients were excluded due to incomplete records and 2,215 patients were excluded due to multiple records leaving 5,709 patients (4,650 in DO and 1,059 DPN) to be included in the final analysis.

Four hundred forty seven (7.8%) patients had a documented vitamin B12 concentration ≤ 250 pg/ml (361 in DO and 86 in DPN). Of these only 70 (15.7%) patients had a documented methylmalonic acid concentration.

Thus, for the purpose of this study, we chose to include all patients with a sole vitamin B12 concentration <250 pg/ml, regardless of confirmatory testing. We did not conduct an analysis for patients with a vitamin B12 concentration <100 pg/ml as planned because the number of included patients meeting this criteria was too low. Seven patients in the DO group and three patients in the DPN group had recorded vitamin B12 concentrations <100 pg/ml.

For patients with a vitamin B12 ≤ 250 pg/ml, the mean concentration did not differ significantly between the DO and DPN groups (683 pg/ml vs. 693 pg/ml, $p=0.77$). In addition, the likelihood of having B12 deficiency did not differ between the DO and DPN groups (361 (7.8%) vs. 86 (8.1%), $p=0.70$).

In patients who used metformin, the incidence of vitamin B12 concentrations <250 pg/ml was significantly higher compared to those who did not take metformin (96 (12.3%) vs. 351 (7.1%), $p<0.0001$), but they were not at an increased risk of neuropathy (70 (11.6%) vs. 26 (14.3%), $p=0.34$). The data did not find a difference in incidence of vitamin B12 deficiency or neuropathy in the proton pump inhibitor or histamine-2 antagonist groups.

Patients age ≥ 55 were found to have an increased incidence of vitamin B12 concentrations <250 pg/ml (384 (8.2%) vs. 63 (6.0%), $p=0.02$). However, it was not until ages 65 and older that patients with a B12 concentration <250 pg/ml were found to have an increased incidence of neuropathy (242 (8.2%) vs. 70 (11.0%), $p=0.02$).

Table 1: Average Vitamin B12 Concentration (pg/ml)

	DO n=4,650	DPN n=1,059	p value
All Patients	683	693	0.77
Metformin	577	579	0.98
Proton pump inhibitors	713	751	0.39
Histamine-2 antagonists	763	817	0.60

DO= diabetes only; DPN= diabetes plus peripheral neuropathy

Table 2: Average Vitamin B12 Concentration (pg/ml)

	DO n=4,650	DPN n=1,059	p value
Age ≥ 70	710	696	0.82
Age ≥ 65	711	672	0.45
Age ≥ 60	705	699	0.90
Age ≥ 55	696	695	0.97
Age ≥ 50	693	691	0.95

DO= diabetes only; DPN= diabetes plus peripheral neuropathy

Table 3: Incidence of Vitamin B12 Deficiency Based Upon Medication Usage

	No. (%) of Patients		p value
	Use	No Use	
Metformin	96/783 (12.3)	351/4926 (7.1)	<0.0001
Proton pump inhibitors	168/2226 (7.5)	279/3483 (8.0)	0.53
Histamine-2 antagonists	22/372 (5.9)	425/5337 (8.0)	0.15

Table 4: Incidence of Vitamin B12 Deficiency Based Upon Age

	No. (%) of Patients		p value
	Yes	No	
Age ≥ 70	252/2921 (8.6)	195/2788 (7.0)	0.02
Age ≥ 65	312/3581 (8.7)	135/2128 (6.3)	<0.01
Age ≥ 60	355/4188 (8.5)	92/1521 (6.0)	<0.01
Age ≥ 55	384/4662 (8.2)	63/1047 (6.0)	0.02
Age ≥ 50	404/5037 (8.0)	43/672 (6.4)	0.14

Table 5: Incidence of Vitamin B12 Deficiency and Peripheral Neuropathy

	No. (%) of Patients			p value
	DO	DPN	Total	
Vitamin B12 ≤ 250 pg/ml	361 (7.8)	86 (8.1)	447 (7.8)	0.70
Metformin	70 (11.6)	26 (14.3)	96 (12.3)	0.34
Proton pump inhibitors	127 (7.5)	41 (7.6)	168 (7.5)	0.97
Histamine-2 antagonists	15 (5.3)	7 (7.9)	22 (5.9)	0.37

DO= diabetes only; DPN= diabetes plus peripheral neuropathy

Table 6: Incidence of Vitamin B12 Deficiency and Peripheral Neuropathy

	No. (%) of Patients			
	DO	DPN	Total	p value
Age ≥ 70	196 (8.0)	56 (11.5)	254 (8.7)	0.01
Age ≥ 65	242 (8.2)	70 (11.0)	312 (8.7)	0.02
Age ≥ 60	280 (8.2)	75 (9.9)	355 (8.5)	0.12
Age ≥ 55	306 (8.0)	78 (9.1)	384 (8.2)	0.30
Age ≥ 50	323 (7.9)	81 (8.8)	404 (8.0)	0.36

DO= diabetes only; DPN= diabetes plus peripheral neuropathy

4. Discussion

Vitamin B12 concentrations were not found to be associated with neuropathy in the general population with diabetes. Neither the mean vitamin B12 concentration nor incidence of vitamin B12 deficiency was significantly different between the DO and DPN groups at any level presented. Similarly, two studies in patients with type 2 diabetes found no difference in neuropathy while investigating the impact of metformin use on vitamin B12 deficiency.³⁻⁴ Conversely, studies have produced results conflicting with our findings as well. Two studies found that in patients with type 2 diabetes, metformin exposure was associated with decreased vitamin B12 concentration and higher neuropathy scores.¹⁴⁻¹⁵ Although these studies add to the body of evidence describing the link between vitamin B12 deficiency and peripheral neuropathy, they are not entirely applicable to our results. These studies compared neuropathy scores, but did not assess incidence of neuropathy as in our study. Moreover, there are no guidelines on providing vitamin B12 supplementation, and further investigation is warranted. A Cochrane review conducted in 2008 showed inconsistent evidence regarding vitamin B supplementation for the treatment of peripheral neuropathy.²

Metformin was associated with decreased vitamin B12 concentrations, but this did not translate into a higher incidence of neuropathy in this study. Those patients who used metformin were found to have an increased incidence of vitamin B12 deficiency, but not an increased incidence of neuropathy. Metformin induced vitamin B12 deficiency has been extensively described in the literature, yet only two studies suggested that metformin may exacerbate peripheral neuropathy in patients with diabetes.^{1,3-7,9-15}

One study even found that patients who used metformin developed neuropathies less often, and in logistic regression only the duration of diabetes was found to predict the chances of neuropathy.⁴

A difference was not found in the incidence of vitamin B12 deficiency or neuropathy in the proton pump inhibitor or histamine-2 antagonist groups. Limited data is available on the association between vitamin B12 deficiency and these agents; however, one study showed that a two or more year supply of proton pump inhibitor or histamine-2 antagonist was significantly associated with an increased risk for vitamin B12 deficiency.⁸ Our study was only able to obtain medication data from inpatient records which accounted for 73% of the data. Thus, medication use was only a snapshot and not necessarily representative of chronic use. We feel confident that the metformin use rates in this study were consistent with outpatient use, but given the liberal use of proton pump inhibitors in hospitalized and acutely ill patients, the data may not reflect the true impact of this medicine class on vitamin B12 concentrations and deficiency.

Data from NHANES suggests vitamin B12 concentration decreases with age as 3.2% of U.S. adults older than 50 are estimated to have a serum vitamin B12 <200 pg/ml.⁹ Similarly, our data found that patients ≥ 55 years of age had an increased incidence of vitamin B12 deficiency. However, only patients ≥ 65 years of age had an increased incidence of neuropathy. The reason we found no difference in the incidence of vitamin B12 deficiency and peripheral neuropathy except in those patients those ≥ 65 years of age is unclear. We can speculate the increased likelihood of neuropathy may be due to the duration of diabetes or vitamin B12 deficiency.

It is unfortunate that the number of patients with a vitamin B12 concentration <100 pg/ml was so few, as this is the absolute for diagnosing vitamin B12 deficiency without secondary or confirmatory testing. In addition, the low rates of confirmatory testing with serum methylmalonic acid concentrations brings into question the true rate of vitamin B12 deficiency in this patient population. Though previous publications have cited prevalence as high as 33% in patients with type 2 diabetes and higher in patients with type 1 disease, our cohort only found 7.8% of the patient records with a vitamin B12 concentration <250 pg/ml. It is unclear if this low rate is because other studies have used smaller population samples to derive prevalence or the population in this study was not representative of a true type 2 diabetes population.

Despite the above limitations, this study adds to the literature describing the link between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes.^{3-4, 14-15} It provides useful information in that vitamin B12 levels are not associated with peripheral neuropathy in the general population with diabetes. Studies that found a link between vitamin B12 deficiency and neuropathy were only in severity and not incidence of neuropathy.¹⁴⁻¹⁵

The question still remains regarding the utility of serum vitamin B12 concentration in patients with diabetes with or without neuropathy. Based on these findings, serum vitamin B12 concentrations are not associated with developing neuropathies in the general population with diabetes and should not be used routinely evaluated as a cause. However, patients ≥ 65 years of age may benefit from screening. Our study does not answer if vitamin B12 supplementation has any effect on neuropathies in patients with diabetes with or without vitamin B12 deficiency. The next logical step will be to conduct research that investigates the efficacy of vitamin B12 supplementation in patients with diabetes stratified by vitamin B12 concentration and peripheral neuropathy.

5. Conclusions

Findings of this study add to the body of evidence describing the link between vitamin B12 deficiency and peripheral neuropathy in patient with diabetes.^{3-4,14-15} Metformin and age ≥ 55 were associated with decreased vitamin B12 concentrations similarly to previous studies and data. Vitamin B12 deficiency was not found to be associated with neuropathy in the general population with diabetes. There are no guidelines on screening or providing supplementation for vitamin B12 deficiency in patients with diabetes; however, based upon these results we do not recommend screening for vitamin B12 deficiency in the general population with diabetes.^{6,9} Screening may however be warranted in patients with diabetes ≥ 65 years of age. Further studies are needed to assess whether or not patient with diabetes and peripheral neuropathy should receive vitamin B12 supplementation, especially those patients taking metformin and age ≥ 55 .

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