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Long-term metformin treatment and risk of peripheral neuropathy in older Veterans

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Abstract

Aim: Our objective was to assess whether increased duration of metformin therapy is associated with incident peripheral neuropathy (PN) in older Veterans with diabetes.

Methods: Using national Veterans Affairs registry data from 2002 to 2015, we examined Veterans (50 + years) with diabetes. Long-term metformin therapy was defined as prescription 500 mg/day, filled for ≥ 6 consecutive months. Metformin therapy duration was examined both as continuous and categorical measures. Incident PN was defined by medical chart review. We estimated unadjusted and adjusted (variables selected *a priori*) odds ratios (OR) and 95% confidence intervals (CI) using logistic regression.

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Disclosure statement

Dr. Phillips declares that there is no duality of interest associated with this manuscript. With regard to potential conflicts of interest, Dr. Phillips has served on Scientific Advisory Boards for Boehringer Ingelheim and Janssen, and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, and the Cystic Fibrosis Foundation. Dr. Phillips is also a cofounder and Officer and Board member and stockholder of a company, Diasyst, Inc., which is developing software aimed to help improve diabetes management. The other authors have nothing to disclose.

Results: The study included $n = 210,004$ individuals (mean \pm SD: age: 66.2 ± 8.4 yrs, 96% male) prescribed metformin for 47.0 ± 34.0 months. Nineteen percent developed PN during follow-up. After adjusting for age, body mass index, duration of time receiving health care within the VA, smoking status, alcohol abuse, and vitamin B12 testing and treatment, the number of months of metformin treatment was associated with elevated odds for incident PN (aOR (metformin treatment - continuous) = 1.009 (95% CI = 1.009, 1.010); aOR (metformin treatment - categorical (ref: 6- $<$ 18 months): 18- $<$ 44.1 months = 1.57 (1.51-1.63), 44.1- $<$ 61 months = 2.05 (1.97-2.14), 61 + months = 2.69 (2.58-2.79), all p-values $<$ 0.0001).

Conclusion: Our study suggests that Veterans treated for at least 18 months with metformin are approximately 2-3 times more likely to develop PN than those treated at least six, but $<$ 18 months. Future studies are needed to determine whether the association we found may be due to a decline in vitamin B12 status following metformin initiation.

Keywords

Aging; Metformin; Type 2 diabetes; Veteran; Vitamin B12

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in aging adults in the U.S. has risen dramatically, particularly among U.S. Veterans, where it currently affects over 20% of the Veteran population [1]. Metformin is recommended as a first line treatment for individuals with T2DM and normal kidney function, resulting in nearly 70% of all U.S. Veterans receiving metformin to treat their T2DM [2].

Older adults are at greater risk of vitamin B12 deficiency than their younger counterparts [3], but this risk may be magnified in older adults with T2DM. We [4] and others [5-7] have shown that long-term metformin therapy is associated with lower serum vitamin B12 concentration. Though the clinical impact of long-term metformin therapy and low B12 is currently unknown, it could have implications for exacerbation of peripheral neuropathy since prolonged vitamin B12 deficiency may have deleterious effects on peripheral nerves, leading to irreversible nervous system damage [8]. Peripheral neuropathy is among the most common complication of T2DM, affecting approximately 50% of patients [9]. Despite these links, to date, few studies have assessed the impact of metformin directly on peripheral neuropathy [10-12].

The present study aimed to examine whether long-term (six or more months) metformin therapy was associated with the development of peripheral neuropathy in older Veterans. We hypothesized that a longer duration of metformin treatment in older Veterans with T2DM would be associated with a greater incidence of peripheral neuropathy. The findings from this study may be useful to formulate best practices for diabetes management among older adults.

2. Subjects

The study was approved by the Emory University Institutional Review Board and the participating VA Research and Development Committee. We conducted a retrospective cohort study using existing national Veterans Affairs (VA) data for Veterans receiving care at any VA medical center (VAMC) between January 2002 and December 2015. Veterans aged 50 years or older receiving long-term metformin only drug therapy for their T2DM management were identified from outpatient records. Those using other antihyperglycemic agents, including insulin, were excluded due to their associations with more advanced T2DM and the potential for co-existing peripheral neuropathy. Those without complete age, sex, and race/ethnicity data or having an International Classification of Diseases code from the ninth revision (ICD-9) code diagnosis of pernicious anemia (ICD 9: 281.0) or end-stage renal disease (ICD-9: 585.6) at baseline also were excluded (Fig. 1).

T2DM was defined as use of at least one T2DM code (ICD-9: 250.00–250.92) at a primary care location or use of at least two T2DM codes at a non-primary care location and at least one outpatient prescription of diabetes medication during the study period. Long-term metformin therapy was defined as a dose of 500 mg/day and refilled for at least six consecutive months during the study period.

3. Materials and methods

3.1. Study variables

We examined the following demographic variables as co-factors: age, race/ethnicity, and sex. We also examined body mass index (BMI), the number of years treated at a VAMC during the study period, and clinical factors, including estimated glomerular filtration rate (eGFR) and hemoglobin A1c. Serum vitamin B12 concentrations measured any time after six consecutive months of metformin prescription and hemoglobin A1c and creatinine concentrations from the test closest to the vitamin B12 test date or closest to metformin initiation date when vitamin B12 testing was not available using VAMC laboratory records were examined. Creatinine was used to calculate estimated glomerular filtration rate eGFR [13]. Outliers (vitamin B12 values > 2,000 pg/dL and creatinine values > 25 mg/dL) were recoded as missing. Serum B12 concentrations were classified as deficient (<170 pg/dL), borderline low (170–<300 pg/dL), or adequate (≥ 300 pg/dL) based on previously established cut-points among older Veterans [14]. Peripheral neuropathy was defined as receiving any of the following (ICD)-9 diagnosis codes during the study period: 356.8, 356.9 and 250.6. Smoking history was identified using previously validated methods [15] and patients were classified as “ever” having smoked (past or present) vs. “never” having smoked. The presence of alcohol abuse was defined as receiving any of the following ICD-9 diagnosis codes related to alcohol use disorder or alcohol-related end organ damage during the study period: 291.0–291.8, 291.82–291.9, 303.90–303.93, 305.00–305.03, 357.5, 425.5, 535.30–535.31, 571.0, and 571.2–571.3.

3.2. Statistical analysis

Data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC). Descriptive statistics including means and standard deviations, or frequency and percents, were calculated for selected variables stratified by those who developed peripheral neuropathy and those who did not and compared using t-tests for continuous variables and chi-squared tests for categorical variables. Significance was set at $P < 0.05$. We used unadjusted and adjusted logistic regression to examine the association between duration of metformin therapy and the development of peripheral neuropathy. Duration of metformin therapy was examined as both continuous and categorical variable. For categorical measure of metformin therapy duration, we created quartiles of months of metformin use from the distribution of those who did not develop peripheral neuropathy. Based on this distribution, the cut-offs for categorical metformin use durations were: quartile 1: 6–<18 months, quartile 2: 18–<44.1 months, quartile 3: 44.1–<61 months, and quartile 4: 61 + months. Quartile 1 was used as a reference level in logistic regression analysis. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression models. Co-variables in multivariable models were selected using backward logistic regression and a 10% change-in-estimate criterion. Covariates included age, BMI, duration of time treated within the VA Health Care System, eGFR, race/ethnicity, sex, smoking status, alcohol abuse, vitamin B12 concentration, testing, and treatment status.

4. Results

4.1. Subject Selection

A total of 2,114,838 Veterans had ICD-9 codes indicating T2DM on at least one outpatient visit at the VAMC during the study period. Of these, 63,598 were excluded due to ICD-9 codes for ESRD and pernicious anemia and an additional 397,740 were excluded due to incomplete age, race, or sex data. Among the remaining patients, 228,137 had a prescription filled for metformin for at least six consecutive months, and received no other antihyperglycemic agents. Of these patients, 210,004 were over the age of 50 years and included in the final analyses (Fig. 1).

4.2. Demographic data

Overall, patients (mean age: 66.2 years) were majority male (96%), non-Hispanic white (84%), and past or current smokers (79%). Alcohol abuse was reported in 9% of patients. On average, they were treated at the VAMC for 11.4 years and had been on metformin therapy for 47.0 months. During the study duration, 58.8% received a serum vitamin B12 assessment, of which, 3.0% were deficient, 20.5% borderline low, and 76.5% adequate. After a duration of at least six months of metformin prescription, only 27.8% of patients received vitamin B12 treatment and 19.3% developed peripheral neuropathy during the study period. Comparison of demographic and clinical variables between the two groups, those with and without the development of peripheral neuropathy during the study period, are presented in Table 1. The average time to develop peripheral neuropathy after metformin initiation was 28.1 ± 30 months. Of those developing peripheral neuropathy, 26.9% did not have a vitamin B12 assessment and only 39.3% received vitamin B12 treatment.

Duration of metformin use among those who developed peripheral neuropathy was on average 59.2 ± 36.7 months and for those who did not develop peripheral neuropathy was 44.1 ± 32.7 months. Those who developed peripheral neuropathy were, on average, younger compared to those who did not (65.8 ± 8.1 vs. 66.3 ± 8.5 years).

4.3. Regression analyses

Our unadjusted analysis showed a significant association between duration of metformin use (both continuous and categorical measures) and peripheral neuropathy (Table 2). For the continuous measure of duration of metformin use, there was 1% increase in the odds for each month increment in use. For categorical measure, unadjusted ORs showed a positive association with peripheral neuropathy, with estimates 1.78, 2.45, and 3.99 for quartiles 2, 3, and 4 of duration of metformin use, respectively, compared to the lowest quartile. These associations remained significant after controlling for potential confounders. In our univariate analysis, the development of peripheral neuropathy does not appear to be influenced by hemoglobin A1c; therefore, we did not include it in the multivariate model (OR (95% CI): 0.997 (0.973–1.020), p-value = 0.78). For continuous measure of duration of metformin use, adjusted estimate was 1.009 (95% CI = 1.009–1.01); and for categorical measure, the adjusted estimate was 1.57, 2.05, and 2.69 for quartiles 2, 3, and 4 of duration of metformin use, respectively, compared to the lowest quartile. These results show that as the duration of metformin use increases, there is an increase in the odds of developing peripheral neuropathy in the target population.

5. Discussion

We find that Veterans treated for at least 18 months with metformin are approximately 2–3 times more likely to develop peripheral neuropathy than those treated at least six, but <18 months. Our data support the need to monitor serum vitamin B12 concentrations in older patients with T2DM treated long-term with metformin by demonstrating that the duration of metformin therapy is a risk factor for the development of new peripheral neuropathy at a rate of approximately 1% per month and slightly >10% per year of treatment. However, studies suggest that older persons prescribed metformin are two to three times less likely to receive vitamin B12 testing compared to those without metformin treatment [4]. In line with other studies of long-term metformin treatment [4,16,17], we find that despite being on metformin treatment for at least six months, only slightly more than half of the Veterans had a serum vitamin B12 assessment indicating that healthcare providers often fail to order a vitamin B12 assessment for their patients on long-term metformin therapy. Though it may take years to deplete physiologic reserves of vitamin B12, declines in circulating vitamin B12 concentrations have been observed within four weeks after initiation of metformin [18], signifying the need for early monitoring.

Since diabetic neuropathy is the most common complication associated with diabetes mellitus [19], healthcare providers may overlook other contributing factors for peripheral neuropathy resulting in unnecessary and potentially harmful pharmacological treatments. Similar to other studies [5,20], we find that ~25% of long-term metformin users have serum vitamin B12 concentrations that are deficient or borderline low. The mechanism by which

vitamin B12 deficiency may lead to and/or exacerbate peripheral neuropathy in patients with T2DM treated with long-term metformin therapy remains to be explored. It is believed that metformin interferes with vitamin B12 absorption in the gastrointestinal tract [21]. Vitamin B12 is involved in the conversion of methylmalonyl-CoA to succinyl-CoA and homocysteine to methionine; therefore, metformin-induced vitamin B12 deficiency may have a deleterious impact on the macrovascular system, including hematological and neurological manifestations, via increased concentrations of methylmalonic acid and homocysteine [22].

Only ~ 30% of Veterans on long-term metformin received vitamin B12 treatment during the duration of this study. It remains to be seen whether repletion or supplementation of vitamin B12 will prevent or slow the progression of diabetic peripheral neuropathy, with the majority of current research finding no evidence that oral vitamin B12 supplements improve the clinical symptoms of neuropathy [23]. While vitamin B12 deficiency is reversible, the progress of the neuropathy may not be reversible with initiation of vitamin B12 therapy, highlighting the need for early vitamin B12 monitoring and intervention.

Strengths of this analysis include the large sample size, which allowed for adjustment of several confounders [24], and the ability for long-term (over 10 years) follow-up using nationally representative, longitudinal data from the VA clinical data warehouse. Our study also has certain practical limitations. Data to quantify alcohol use were not available in the VA database. A limited number of women were included in the analyses, limiting generalizability. Since prior studies have suggested that men are more susceptible to vitamin B12 deficiency [25,26], similar studies in women are needed. Further, vitamin B12 prescribed from outside of the VA or the use of over-the-counter vitamin supplements was not collected during the study. Lastly, the use of clinical encounter data did not allow us to systematically examine the decline in B12 status following metformin initiation because nearly half of the study population did not receive serum B12 assessment and differential testing rates between those with and without peripheral neuropathy were present..

In summary, our findings show that there is an elevated risk for the development of new peripheral neuropathy with longer duration metformin treatment in older Veterans with T2DM. Despite this finding, only about half of the Veterans receiving long-term metformin were evaluated for serum vitamin B12 concentrations; therefore, more research is needed to determine factors affecting vitamin B12 monitoring among older adults who are prescribed metformin. Further, future studies are needed to determine whether the risk for peripheral neuropathy may be altered with concomitant B12 supplementation following metformin initiation. As first line therapy for T2DM management, these results may inform clinical guidelines regarding serum vitamin B12 testing among the growing number of older adults with T2DM who are treated with metformin.

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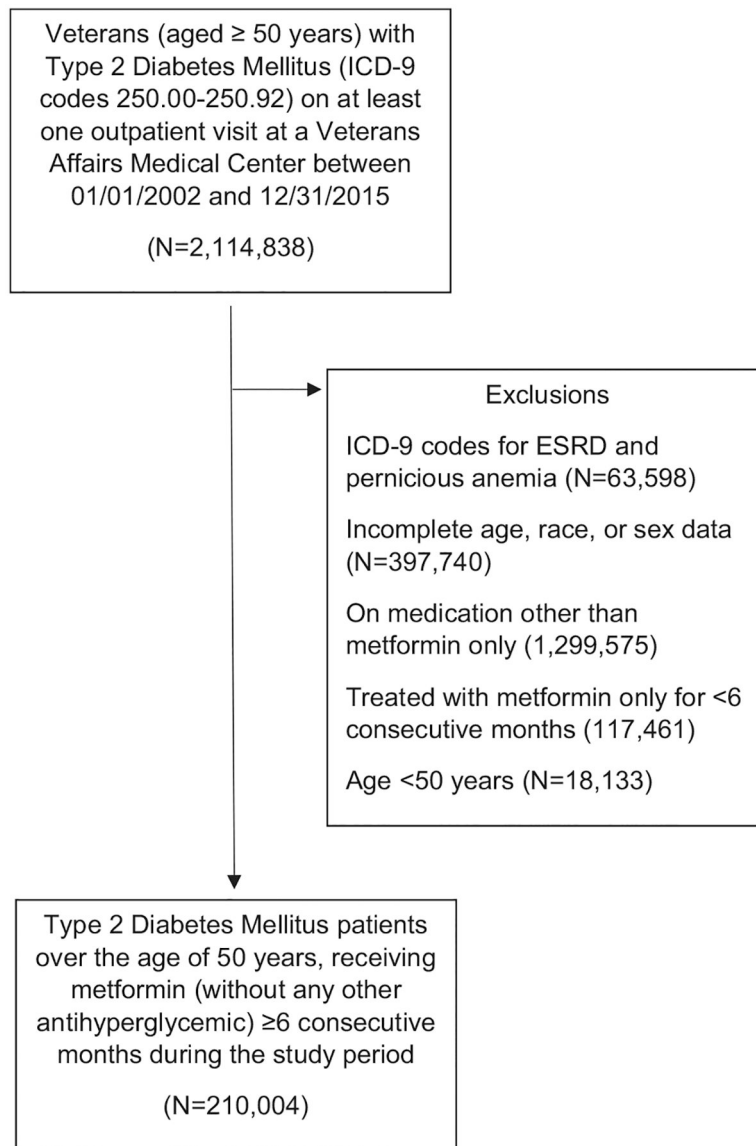


Fig. 1 -.
Subject Selection Criteria.

Subject characteristics, total and stratified by the development of peripheral neuropathy, among older adults with Type 2 Diabetes Mellitus seeking outpatient care at U.S. Veterans Affairs Medical Centers, 2002–2015.

Table 1 –

	Total		Developed Peripheral Neuropathy		Did Not Develop Peripheral Neuropathy		P-value
	Mean	SD	Mean	SD	Mean	SD	
	N = 210,004		N = 40,534		N = 169,470		
Age (years)	66.2 ± 8.4	65.8 ± 8.1	66.3 ± 8.5	<0.0001			
BMI (kg/m ²)	29.6 ± 9.7	31.3 ± 8.0	29.2 ± 10.0	<0.0001			
Duration of metformin treatment (months)	47.0 ± 34.0	59.2 ± 36.7	44.1 ± 32.7	<0.0001			
Duration treated at the VAMC (years)	11.4 ± 4.0	12.3 ± 3.6	11.2 ± 4.1	<0.0001			
eGFR (mL/min/1.73 m ²)	77.1 ± 20.8	78.7 ± 17.2	76.7 ± 21.5	<0.0001			
Hemoglobin A1c (%)	5.8 ± 2.0	6.0 ± 1.7	5.8 ± 2.1	<0.0001			
Hemoglobin A1c (mmol/mol)	40 ± 13	42 ± 12	40 ± 14	<0.0001			
Race and Ethnicity	N	%	N	%	N	%	
Non-Hispanic White	175,646	84	34,747	86	140,899	83	<0.0001
Non-Hispanic Black	29,316	14	5,047	12	24,269	14	
Other	5,042	2	740	2	4,302	3	
Sex (N, % male)	201,357	96	39,248	96.8	162,109	95.7	<0.0001
Smoker (N, % yes)	165,705	78.9	32,906	81.2	132,799	78.4	<0.0001
Alcohol abuse (N, % yes)	19,665	9.4	5,329	13.1	14,336	8.5	<0.0001
Received vitamin B12 assessment (N, % yes)	123,463	58.8	29,641	73.1	93,822	55.4	<0.0001
Serum vitamin B12 (pg/dL)							<0.0001
<170	3,750	3.0	872	2.2	2,878	1.7	
170–<300	25,262	20.5	5,970	14.7	19,292	11.4	
300	94,451	76.5	22,799	56.3	71,652	42.3	
Received vitamin B12 treatment (N, % yes)	58,429	27.8	15,943	39.3	42,486	25.1	<0.0001

BMI: body mass index; VAMC: U.S. Veterans Affairs Medical Centers; eGFR: estimated glomerular filtration rate

Unadjusted and adjusted analysis to examine the association between duration of metformin use and development of peripheral neuropathy among older adults with Type 2 Diabetes Mellitus seeking outpatient care at U.S. Veterans Affairs Medical Centers, 2002–2015.

Table 2 –

	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Months of metformin use				
Continuous	1.01 (1.01–1.01)	<0.0001	1.009 (1.009–1.01)	<0.0001
Categorical				
6–<18	Ref		Ref	
18 –<44.1	1.78 (1.73–1.83)	<0.0001	1.57 (1.51–1.63)	<0.0001
44.1 –< 61	2.45 (2.37–2.54)	<0.0001	2.05 (1.97–2.14)	<0.0001
61+	3.19 (3.09–3.29)	<0.0001	2.69 (2.58–2.79)	<0.0001
Age (years)	0.99 (0.99–0.99)	<0.0001	1.00 (0.99–1.00)	0.4218
BMI (kg/m ²)	1.02 (1.02–1.03)	<0.0001	1.02 (1.017–1.02)	<0.0001
Duration treated at the VAMC (years)	1.07 (1.07–1.08)	<0.0001	1.02 (1.01–1.02)	<0.0001
eGFR (mL/min/1.73 m ²)	1.005 (1.004–1.005)	<0.0001	1.00 (0.99–1.00)	0.3540
Race and Ethnicity				
Non-Hispanic White	Ref		Ref	
Non-Hispanic Black	0.84 (0.82–0.87)	<0.0001	0.82 (0.79–0.85)	<0.0001
Other	0.69 (0.64–0.76)	<0.0001	0.73 (0.67–0.79)	<0.0001
Sex				
Female	Ref		Ref	
Male	1.38 (1.30–1.47)	<0.0001	1.34 (1.26–1.43)	<0.0001
Smoking				
Never Smoker	Ref		Ref	
Ever Smoker	1.17 (1.14–1.21)	<0.0001	1.02 (0.99–1.05)	0.1931
Unknown smoking status	0.90 (0.84–0.97)	0.004	1.07 (1.00–1.15)	0.0605
Alcohol abuse				
Absent	Ref		Ref	
Present	1.64 (1.58–1.69)	<0.0001	1.34 (1.29 – 1.39)	<0.0001
Received vitamin B12 assessment				

	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
No	Ref		Ref	
Yes	2.19 (2.14–2.25)	<0.0001	1.69 (1.64–1.73)	<0.0001
Serum vitamin B12 (pg/dL)				
Unknown	0.45 (0.44–0.46)	<0.0001	–	–
<170	0.95 (0.88–1.03)	0.21	0.72 (0.67–0.78)	<0.0001
170–<300	0.97 (0.94–1.01)	0.09	0.86 (0.83–0.89)	<0.0001
≥300	Ref		Ref	
Received vitamin B12 treatment				
No	Ref		Ref	
Yes	1.94 (1.89–1.98)	<0.0001	1.53 (1.49–1.57)	<0.0001

BMI: body mass index; VAMC: U.S. Veterans Affairs Medical Centers; eGFR: estimated glomerular filtration rate.

* Each variable is adjusted for all other variables in the model.