Journal of Endocrinology, Metabolism and Diabetes of South Africa 2024; 29(2):43–47
https://doi.org/10.1080/16089677.2024.2325810

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

RESEARCH ARTICLE

Interrelations between metformin administration and vitamin B12 concentrations in a black South African diabetic cohort: a retrospective cohort analysis

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Background: Metformin, widely used in diabetes treatment, is linked to reduced cobalamin (vitamin B12) levels, potentially exacerbating diabetic peripheral neuropathy (PN) and increasing the risk of lower limb amputations. Studies suggest that black individuals might be less prone to vitamin B12 deficiency, but the impact of metformin on vitamin B12 levels in this group is unclear.
Objective: This study investigated the prevalence of vitamin B12 deficiency in diabetics on metformin and examined the relationship between metformin use and PN.
Methods: A retrospective review of patient records from Edendale Hospital's diabetes clinic in Pietermaritzburg (January 1, 2017, to December 31, 2018) was conducted. Patients over 18 years of black descent with documented vitamin B12 levels were included. The study extracted data on diabetes treatment, vitamin B12 levels, and PN indicators.
Results: Of 668 patients, 558 met the criteria. Metformin was used by 341 patients (61.1%), alone or with other treatments, while 217 (38.9%) did not use metformin. Glycaemic control was similar in both groups (median HbA1C 9.4% (IQR 7.8–11.0) in metformin users vs. 9.46% (IQR 7.1–11.0) in non-users, $p = 0.80$). Absolute vitamin B12 deficiency was equally rare in both groups (6 [1.8%] in metformin users vs. 4 [1.8%] in non-users, $p = 1.0$), but metformin users had significantly lower median vitamin B12 levels (299.0 pmol/l vs. 340.0 pmol/l in non-users, $p < 0.05$). PN prevalence was similar in both groups (31.7% in metformin users vs. 25.1% in non-users, $p = 0.12$). However, those with borderline-low vitamin B12 levels ($\leq$ 269 pmol/l) had a higher risk of PN (OR 1.6; 95% CI: 1.1–2.3, $p = 0.015$).
Conclusion: Metformin users showed lower median serum vitamin B12 levels than non-users, with an association between metformin use and borderline-low vitamin B12 levels. Higher metformin doses correlated with lower vitamin B12 levels, yet a direct link between metformin use and PN was not established.

Keywords: metformin; vitamin B12; peripheral neuropathy

Background

Type 2 diabetes mellitus (T2DM) is a significant global health issue, being a major source of morbidity and mortality worldwide.[1] Peripheral neuropathy (PN) is a prevalent complication associated with diabetes mellitus and poses a substantial risk for lower limb amputations.[2] In the region of KwaZulu-Natal alone, over 20 000 individuals are diagnosed annually with diabetes and begin treatment.[3] Metformin is universally recommended as the primary treatment option for T2DM, as per both international and national guidelines.[4,5]

Myriad studies have linked the use of metformin with vitamin B12 deficiency.[6–12] However, the exact incidence of vitamin B12 deficiency among people living with diabetes remains uncertain, as does its contribution to the development of PN. Research from high-income countries indicates that vitamin B12 levels might inherently vary among different ethnic groups, with studies suggesting that individuals of black race may have higher vitamin B12 levels.[13,14] A specific study in South Africa reported that approximately 28% of patients on metformin therapy exhibited vitamin B12 deficiency.[6] Interestingly, this study also indicated that black race might confer a degree of protection against metformin-induced vitamin B12 deficiency, though the study included only 89 black participants.

Both vitamin B12 deficiency and diabetes mellitus are recognised as potential causes of PN, with their clinical manifestations often being indistinguishable from each other.[15,16] Vitamin B12 deficiency can be diagnosed through laboratory-based assays and is treatable with either oral or intramuscular supplementation.[17,18]

Given these observations, and considering the unique biochemical profile of the demographic, our study investigates the prevalence of vitamin B12 deficiency in an outpatient cohort of black adults attending the diabetes clinic at Edendale Hospital. This research is crucial for understanding the interplay between T2DM, metformin usage, and vitamin B12 levels within this specific population group.

Methods

Study design and patient selection

This retrospective analysis was conducted at the regional diabetes clinic of Edendale Hospital, Pietermaritzburg, KwaZulu-Natal, over a two-year span from January 1, 2017, to December 31, 2018. A consecutive sampling approach was employed. Patient files were identified from the clinic's registry, screened for eligibility, and pertinent data were collated for statistical

examination. Data capture focused on each patient's initial visit within the study timeframe.

Inclusion criteria:

- Age: 18 years or older.
- Race: Self-identified as black.
- Requirement: At least one documented vitamin B12 level.

Exclusion criteria:

- Age: Below 18 years.
- Race: Non-black individuals.
- Requirement: Absence of a documented vitamin B12 level.

Variables and data collection

Data were meticulously extracted from each patient's medical record, encompassing sex, age, race, diabetes type, body mass index (BMI), glucose-lowering therapy, haemoglobin A1c (HbA1c) percentage, serum vitamin B12 level (pmol/l), HIV status, antiretroviral therapy (ART) use, alcohol consumption, symptoms indicative of distal sensory neuropathy, and estimated glomerular filtration rate (eGFR). All laboratory data were obtained from a singular blood sample collected during the patient's initial visit in the study period. Vitamin B12 levels were measured using the Siemens ADVIA Centaur CP System immunoassay (Siemens Healthineers AG, Forchheim, Germany), while HbA1c was determined through the Siemens Dimensions Atellica CH enzymatic assay. The eGFR was calculated employing the Cockcroft–Gault formula. Racial classification was based on self-declaration by the patients.

In the context of this investigation, we employed a specific operational definition for Vitamin B12 concentrations, acknowledging that the precise threshold values delineating Vitamin B12 deficiency exhibit global variability:

- Absolute deficiency: serum vitamin B12 level < 148 pmol/l.
- Borderline-low levels: serum vitamin B12 levels ranging between 148 and 296 pmol/l.[17–19]

Table 1: Patients' demographic, clinical and biochemical characteristics

Patient characteristics	*n* (%)
Female, *n** (%)	403 (72.2)
Age, median (IQR**), years	59 (49–66)
Type 2 diabetes mellitus, *n* (%)	517 (92.8)
Type 1 diabetes mellitus, *n* (%)	40 (7.2)
Body mass index, median (IQR), kg/m^2	32 (27–37)
Prescribed metformin, *n* (%)	341 (61.1)
Haemoglobin A1c (HbA1c), median (IQR), %	9.2 (7.5–11.0)
Vitamin B12, median (IQR), pmol/l	319 (242.3–422.3)
HIV seropositive, *n* (%)	91 (16.3)
Alcohol use, *n* (%)	26 (4.7)
Peripheral neuropathy, *n* (%)	162 (29.0)
Glomerular filtration rate, *n* (%):	
• > 60 ml/minute	353 (63.3)
• 45–59 ml/minute	76 (13.6)
• 30–44 ml/minute	68 (12.2)
• 15–29 ml/minute	42 (7.5)
• 0–14 ml/minute	19 (3.4)

*n – number; **IQR = interquartile range.

Table 2: Medication combinations used by overall patient cohort

Therapy	*n* (%)
Metformin monotherapy	22 (3.9)
Insulin monotherapy	215 (38.5)
Metformin PLUS insulin	171 (30.6)
Metformin PLUS sulphonylurea PLUS insulin	80 (14.3)
Metformin PLUS sulphonylurea without insulin	68 (12.2)
Untreated	1 (0.2)
Insulin and sulphonylurea	1 (0.2)

Peripheral neuropathy screening and assessment

Patients were evaluated for peripheral neuropathy (PN) by medical practitioners during their clinic visits. PN presence was determined based on the patient's history of paraesthesia and clinically diminished sensation, ascertained through monofilament testing.

Statistical analysis

Sample size calculation was determined using statistical power analysis and yielded a total of 436 patients, which when allowing for a further 4% for attrition, set the total patients needed at 454 (95% confidence interval [CI]). A total of 558 files were used for the statistical analysis and a p-value < 0.05 was considered statistically significant. Data were analysed using Analyse-it® for Excel version 5.56 (Microsoft Corp, Redmond, WA, USA). Data distribution was assessed using the Shapiro–Wilk test. Groups of non-parametric data nominal or ordinal data were analysed using the Wilcoxon–Mann–Whitney test, or the Kruskal–Wallis test (for more than two groups). The Pearson chi-square test was used to compare more than two groups of categorical data, and Fisher's exact test to compare proportions and calculate odds ratios. Percentages were reported to one decimal point.

Results

The study evaluated medical records of 668 patients for potential inclusion. Of these, 100 patients (15.0%) were excluded due to unrecorded vitamin B12 results, 6 patients (0.9%) for not being of black race, and 4 patients (0.6%) for being under 18 years of age. Consequently, 558 patients were included in the analysis.

Table 1 encapsulates the demographic, clinical, and biochemical characteristics of the patient cohort. A substantial majority, nearly three-quarters, were female (403 out of 558, or 72.2%). Type 2 diabetes mellitus was prevalent in 93% of the patients (517 out of 558). The median HbA1c for the entire cohort was recorded at 9.2% (interquartile range [IQR], 7.5–11). Notably, 16% (91 patients) were living with HIV, of whom 95% (86 patients) were undergoing antiretroviral therapy (ART). The cohort's median vitamin B12 level was 319 pmol/l (IQR, 242.3–422.3). Peripheral neuropathy (PN) was identified in 162 patients, accounting for 29% of the cohort (Table 1).

Among the patients included in the study, 341 (61%) were on a regimen involving metformin, used either as a standalone medication or in conjunction with other glucose-lowering therapies, as detailed in Table 2.

The analysis did not reveal any substantial differences in median age, gender distribution, HbA1c levels, HIV prevalence, or the incidence of peripheral neuropathy between the two subgroups.

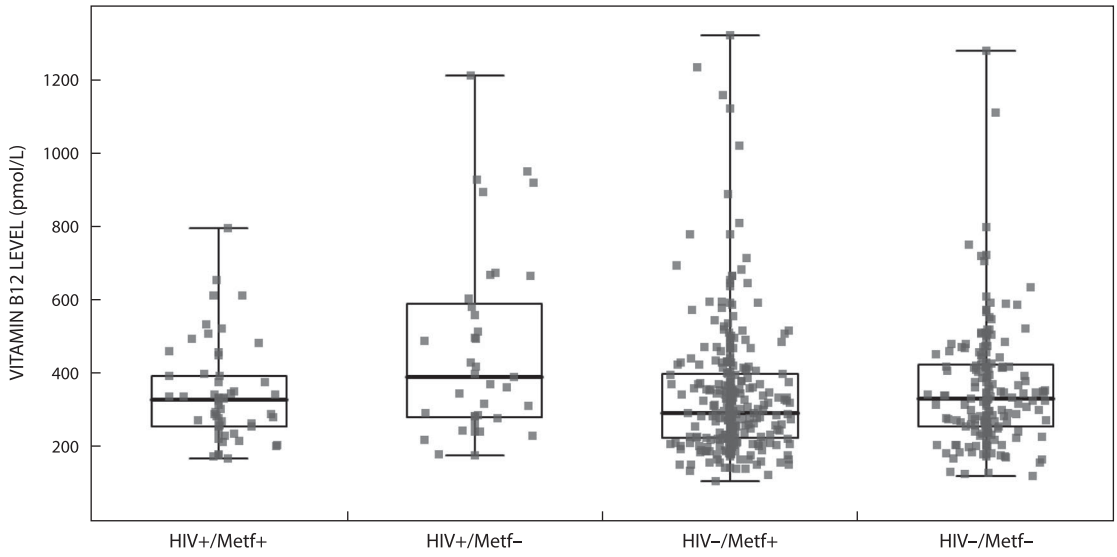

Figure 1: Median serum vitamin B12 levels stratified by metformin use and HIV serostatus.
Note: *p-value for trend 0,0006; Metf = metformin; HIV = human immunodeficiency virus; +ve = positive; -ve = negative.

Notably, among the metformin cohort, the median daily dosage was identified as 3.0 g (IQR, 2.0–3.0 g). The prevalence of type 2 diabetes was significantly higher in the metformin group (334 versus 5, $p < 0.001$), as was the proportion of patients with a glomerular filtration rate (GFR) exceeding 60 ml/minute (66.0%, $p < 0.001$).

Absolute vitamin B12 deficiency was observed in 1.8% of patients across both subgroups (6 of 341 in the metformin group and 4 of 217 in the non-metformin group, $p = 1.0$). However, patients on metformin had a notably lower median vitamin B12 level (299.0 pmol/l vs. 340.0 pmol/l in the non-metformin group, $p = 0.004$). Furthermore, 49.3% of the metformin group exhibited borderline-low vitamin B12 levels, compared with 38.7% in the non-metformin group (odds ratio [OR] 1.54; 95% CI: 1.10–2.17, $p = 0.015$).

Among patients with borderline-low vitamin B12 levels, 35% had PN, whereas this figure was 25% in patients with normal vitamin B12 levels (OR 1.6; 95% CI: 1.1–2.3, $p = 0.015$). Patients with borderline-low vitamin B12 levels were also on higher total daily doses of metformin (2.0 g [IQR, 2.0–3.0] vs. 1.0 g [IQR, 0.0–3.0], $p = 0.02$), and had lower HbA1c levels (8.7% [IQR, 7.2–10.2] vs. 9.9% [IQR, 7.8–11.3], $p = 0.0001$). Nevertheless, no direct association was found between PN and either metformin use (OR 1.37, 95% CI: 0.92–2.04, $p = 0.13$) or HIV status (OR 0.69, 95% CI: 0.38–1.18, $p = 0.17$).

HIV seropositivity correlated with higher vitamin B12 levels irrespective of metformin use when compared with HIV seronegative patients, as depicted in Figure 1 ($p_{trend} = 0.0006$) (Table 3).

Discussion

This retrospective cohort analysis of black adults attending a diabetes clinic in Pietermaritzburg reveals a significant correlation between metformin administration and decreased median vitamin B12 concentrations, as well as a heightened incidence of borderline-low vitamin B12 levels. Notably, absolute vitamin B12 deficiency was infrequent and exhibited no substantial variation between patient subgroups either on or off metformin. Importantly, patients exhibiting borderline-low vitamin B12 levels were predominantly those receiving higher dosages of metformin.

Interestingly, the occurrence of peripheral neuropathy (PN) was comparable across patients regardless of metformin usage. Nevertheless, a noteworthy association was detected between borderline-low vitamin B12 levels and PN. This suggests the potential utility of measuring methylmalonic acid levels in patients with borderline-low vitamin B12 concentrations presenting with clinical symptoms indicative of bona fide B12 deficiency. The parallel prevalence of PN in both metformin and non-metformin cohorts likely reflects diverse aetiologies underlying PN. In the metformin group, borderline-low vitamin B12 levels, a consequence of metformin use, likely contributed substantially to PN prevalence. Conversely, the non-metformin group, exhibiting significantly impaired renal function, likely represents a segment of diabetic patients with pre-existing target organ damage, including PN. This study's findings, aligning borderline-low vitamin B12 levels with metformin use rather than absolute deficiency, diverge from previous studies,[6–12] and may be attributed to inherently higher vitamin B12 levels in individuals of black race.

In South Africa, the management of diabetes, particularly achieving optimal glycaemic control, remains a challenge,[20,21] potentially leading to the observed trend of maximum dose metformin administration in this study. This practice is concerning given the identified link between higher metformin doses and borderline-low serum vitamin B12 levels.

Contrary to previous research,[22–24] which identified HIV as a risk factor for vitamin B12 deficiency, this study observed higher vitamin B12 levels in HIV-positive individuals, regardless of metformin use. This could be attributed to vitamin B12 supplementation in this demographic.[25]

Conclusion

Future research should delve deeper into the role of borderline vitamin B12 levels, utilising methylmalonic acid or homocysteine levels to more accurately assess the impact of metformin use in this population. Additional studies are warranted to explore the combined effects of HIV and diabetes on vitamin B12 levels and PN. Prospective studies with larger cohorts of diabetic patients with PN are necessary to conclusively

Table 3: Characteristics of patient subgroups taking metformin versus those not taking metformin

Characteristics	Taking metformin *n = 341*	Not taking metformin *n = 217*	*p-value*
Age, median (IQR**), years	58.0 (51.0–66.0)	60.0 (43.0–67.3)	0.97
Female, *n* (%)	255 (63.3)	148 (36.7)	0.11
Type 2 diabetes mellitus, *n* (%)	334 (98.2)	183 (84.3)	< 0.001
Metformin daily dose, median (IQR), g	3.0 (2.0–3.0)	0.0 (0.0–0.0)	< 0.001
Metformin daily dose categories, *n* (%)			
• 1.0 g	40 (11.7)		
• 1.5 g	11 (3.2)		
• 2.0 g	88 (28.8)		
• 2.5 g	9 (2.6)		
• 3.0 g	193 (56.6)		
BMI, median (IQR), kg/m^2	32.0 (27.1–37.0)	31.0 (26.0–37.0)	0.1
HbA1C, median (IQR), %	9.4 (7.8–11.0)	9.0 (7.1–11.0)	0.2
HIV seropositive, *n* (%)	54 (15.8)	37 (17.1)	0.776
Alcohol use, *n* (%)	15 (4.4)	11 (5.1)	0.863
Peripheral neuropathy, *n* (%)	108 (31.7)	54 (25.1)	0.119
Vitamin B12 level, median (IQR), pmol/l	299.0 (231.0–400.8)	340.0 (261.2–455.5)	0.004
Vitamin B12 categories, *n* (%)			0.046***
• < 148 pmol/l	6 (1.8)	4 (1.8)	
• 148 pmol/l – 296 pmol/l	168 (49.3)	84 (38.7)	
• > 296 pmol/l	167 (49.0)	183 (84.3)	
GFR, median (IQR), ml/minute	46.0 (37.3; 53.3)	34.0 (24.0; 46.0)	< 0.001
GFR categories, *n* (%)			< 0.001***
• > 60 ml/minute	225 (66.0)	79 (36.4)	
• 45–59 ml/minute	61 (17.9)	45 (20.7)	
• 30–44 ml/minute	23 (6.7)	48 (22.1)	
• 15–29 ml/minute	5 (1.5)	14 (6.5)	
• 0–14 ml/minute	0 (0.0)	9 (4.1)	
Missing Data, *n* (%)	27 (7.9)	22 (10.1)	

**IQR = interquartile range; ***p-value for trend.

determine the need for routine vitamin B12 level screening in black individuals with diabetes.

Limitations

The study has several limitations, primarily due to its retrospective nature. The duration of metformin therapy, an influential factor in vitamin B12 levels as indicated in prior studies,[6–12] was not recorded. Additionally, the retrospective design precluded assessment of treatment adherence. Including patients from other racial groups could have provided a control to account for ethnic variations in vitamin B12 levels, although only a small number of non-black patients were treated at this clinic during the study period. Methylmalonic acid levels were not available for patients with borderline-low vitamin B12 levels, and data on dietary habits, vitamin B12 supplementation, and use of proton pump inhibitors (PPI), all of which can affect vitamin B12 levels, were not captured.[26] Furthermore, the absence of nerve conduction studies meant that the diagnosis of PN relied on subjective clinical assessment, potentially leading to underdiagnosis.

Disclosure statement – No potential conflict of interest was reported by the authors.

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Received: 29-11-2023 Accepted: 28-02-2024