RESEARCH PAPER

Correlation Between Serum Vitamin B12 Levels and Neuropathic Pain Severity in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a common metabolic disorder often associated with diabetic peripheral neuropathy manifested by pain, paresthesia and sensory impairment. The first line treatment for T2DM, metformin has been associated with decreased intestinal uptake of vitamin B12 with prolonged use. (de Jager et al., 2010; Reinstatler et al., 2012) Vitamin B12 deficiency may therefore play a role in the neurological dysfunction and aggravate neuropathic symptoms. However, the link between vitamin B12 levels and the severity of neuropathic pain in metformin-treated patients is still not adequately examined. **Method:** This is a cross-sectional observational study which was conducted at the Department of General Medicine, Guntur General Hospital (GGH), which is a tertiary care teaching hospital serving a diverse semi-urban and rural population. The study was carried out in a period of a year i.e. December 2023 - December 2024. **Results:** Mean age of participants was 61.1±10.6 years. Vitamin B12 deficiency was seen in 25.6% of the patients and clinical neuropathy (DN4 ≥ 4) was present in 33.6% of the cohort. Neuropathy was much more common in vitamin B12-deficient (81.2%) and normal vitamin B12 level patients (12.6%). Serum vitamin B12 levels had a significant inverse correlation with the VAS pain scores (r_s= - 0.527, $p < 0.001$). Multivariable regression confirmed that lower levels of vitamin B12 were an independent predictor of lower neuropathic pain levels. **Conclusion:** Vitamin B12 deficiency is seen in high percentages of metformin-treated patients with T2DM and is highly correlated with a greater level of neuropathic pain. Routine monitoring and supplementation may help to decrease neuropathic complications.

KEYWORDS: Type 2 Diabetes; Vitamin B12 Deficiency; Diabetic Peripheral Neuropathy; Neuropathic Pain; DN4 Score; Cobalamin.

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1. INTRODUCTION

1.1 Worldwide Disability of Diabetic Neuropathy

Type 2 Diabetes Mellitus (T2DM) has become one of the most important public health challenges in the 21st century. (International Diabetes Federation, 2023) The International Diabetes Federation estimates that more than 537 million adults are currently living with diabetes and this number will increase to 783 million by 2045. Among the many potential complications that accompany T2DM, Diabetic Peripheral Neuropathy (DPN) is the most prevalent potential microvascular complication affecting approximately 50% of patients (Callaghan et al., 2012) over their lifetime. DPN is not only a state of sensory deficiency, but it is also a major cause of morbidity, carrying with it chronic neuropathic pain, disturbances of sleep and depression, as well as greatly increased risk of foot ulceration and lower limb amputation.

The pathophysiology of classic DPN is multifactorial, mostly due to the chronic hyperglycemia. The proposed mechanisms are activation of the polyol pathway, increased formation of advanced glycation end-products (AGEs) and oxidative stress that all cause nerve ischemia and axonal degeneration. However, in the physician's day-in and daily dealing, however, patients with good glycemic control come to the physician's office with severe, unrelenting symptoms of neuropathy. This clinical discordance indicates the existence of other contributing factors other than hyperglycemia.

1.2 The Metformin Paradox

Metformin is the universal recommendation as the drug of first choice in the pharmacological treatment of T2DM by the major guidelines (American Diabetes Association

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[ADA] and the European Association for the Study of Diabetes [EASD]). Its efficiency in the improvement of insulin sensitivity and weight-neutral profile and cardiovascular benefits make it an indispensable therapeutic agent in diabetes management.

However, there is a growing body of evidence for what is known as a "Metformin Paradox": the drug protects the cardiovascular system, but it may in fact do damage to the peripheral nervous system by causing the induction of Vitamin B12 (cobalamin) deficiency. The mechanism is believed to be an interference with the calcium-dependent binding of the Intrinsic Factor-B12 complex (Bauman et al., 2000) with the cubilin receptor in the terminal ileum. Long-term use of metformin has been shown to cause a decrease in serum B12 concentrations of up to 30% of patients (de Jager et al., 2010; Ting et al., 2006).

1.3 Vitamin B12 and the Integrity of the Neural Tissue

Vitamin B12 is an essential cofactor of homocysteine's conversion to methionine - required in the synthesis of S-adenosylmethionine (SAMe). SAMe is the major methyl donor needed for maintenance of the myelin sheaths and the synthesis of neurotransmitters (Ahmed, 2016). Deficiency in B12 interrupts this pathway resulting in the accumulation of homocysteine (a neurotoxin) and destabilization of the myelin, resulting in the development of a subacute combined degeneration-like neuropathy. This "B12 neurosis" is clinically indistinguishable from classic diabetic neuropathy, having the same symptoms of symmetrical paresthesia, numbness and burning pain.

1.4 The Research Gap

Despite the biological plausibility, whether or not there is a clinical correlation between the biochemical levels of B12 and the severity of neuropathic pain is a matter open to debate. Some studies have found no association and it's been attributed all to diabetes in itself, and there are studies that suggest there is a strong link. Furthermore, for data from Indian sub-continent (where vegetarian diets, low in B12, is common), data is inadequate (Liu et al., 2014; Chapman et al., 2016). This study is aimed at bridging this gap and assess correlation between serum levels of vitamin B12 and validated neuropathic pain (VAS office and DN4) by rigorously evaluating a cohort of metformin treated India patients.

2. METHODOLOGY

2.1 Study Design and Setting

This is a cross-sectional observational study done at the Department of General Medicine, Guntur General Hospital (GGH), a tertiary care teaching hospital which serves a diverse semi-urban and rural population. The study was conducted during a span of a year i.e., December 2023 - December 2024. The study protocol was based on the Helsinki Declaration, and the research was approved by the Institutional Ethics Committee (E2.2 Study Population

Inclusion Criteria:

Type 2 Diabetes Mellitus diagnosed patients as per the ADA criteria (American Diabetes Association, 2024).

Age ≥ 18 years.

History of stable metformin therapy (≥1000 mg/day) for at least for 3 months.

Ability to comprehend and comment on the pain questionnaires.

Exclusion Criteria:

In order to isolate the effect of B12 and Diabetes, strict exclusion criteria were used:

History of other neuropathic causes: Chronic alcohol abuse, Neuropathy caused from either chemotherapy, HIV, or hereditary neuropathies

Severe renal impairment (eGFR cohort < 30 ml/min/1.73m2) Renal failure can cause falsely raised levels of B12.

Pernicious Anemia or a history of gastrectomy.

Current supplement of Vitamin B12 or multi vitamin or last 3 months

Being hypothyroid (untreated) - this condition may resemble neurodeopathic symptoms.

2.3 Clinical Assessments

Demographic and Metabolic Profiling:

Baseline data including age, gender, duration of diabetes, duration of metformin use and dosage were recorded. Body Mass Index (BMI) was determined. The measurement of glycemic control was done through HbA1c (Glycated Hemoglobin).

Biochemical Analysis:

Fasting venous blood samples (5 mL) were taken from all the participants. Serum vitamin B12 concentration was measured by the Chemiluminescence Immunoassay (CLIA) procedure in an automated analyzer. This is a very sensitive and specific method for cobalamin detection.

Deficiency: < 200 pg/mL

Borderline: 200 - 300 pg/mL

Normal: > 300 pg/mL

Neuropathy Assessment Tools:

Two valid scales were used to describe the intensity and the neuropathic nature of the pain.

Visual Analog Scale (VAS): A unidimensional record of severity of pain intensity. Patients were asked to indicate their average pain during the previous week using a 10-cm line in which 0 ("No pain") is positioned at the extreme left and 10 ("Worst possible pain") at the extreme right.

DN4 (Douleur Neuropathique 4) Questionnaire: An administrator (clinician) screening tool with 10 items (7 symptoms and 3 physical examination findings).

Symptoms: Burning, Pain cold, Electric shocks, Tingling, Pins and needles, Numbness, Itching.

Exam: Hypoesthesia to touch, Hypoesthesia to prick, Brush allodynia

Scoring: Score of ≥4 out of 10 gives a sensitivity of 83% and a specificity of 90% for the diagnosis of neuropathic pain.

2.4 Statistical Analysis

Data Analysis: Data analysis was done by Python (libraries: Pandas, Scipy, Statsmodels). Continuous variables were presented as Mean+-Standard Deviation (SD). Categorical variables were presented in form of frequencies and as percentages.

Correlation: Spearman rank correlation coefficient (r_s) was used to measure the correlation between non-normally distributed variables (B12, VAS, DN4).

Group Comparison: Kruskal-Wallis test was performed to compare the pain scores between the 3 status groups of B12 (Deficient, Borderline, Normal). The post-hoc pairwise comparisons were performed using the Mann-Whitney U test.

Multivariable Regression: A multiple linear regression model was built with dependent variable as VAS score and independent variables as B12, Age, Gender, HbA1c and Metformin Duration to adjust for confounding.

Significance: < 0.05 will be taken as statistically significant.

3. RESULTS

3.1 Demographic and Clinical Characteristics

A total of 250 patients met the inclusion criteria and completed the study. The study population had a mean age of 61.1 ± 10.6 years, representing the normal geriatric age of onset of complications. The distribution of gender was fairly equitable. The average metformin treatment was for 2.9 ± 1.6 years and the mean dose was 1344 ± 432 mg/day.

The mean HbA1c was 7.7 ± 0.6%, which reflects inadequate glycemic control in most of the cohort as expected in a tertiary care presentation (ECR/467/Inst/AP/2013/RR-23). Written informed consent was obtained in all the study subjects.

Table 1: Baseline Characteristics of the Study Population (N=250)

Characteristic	Mean ± SD	Range
Age (years)	61.1 ± 10.6	38 - 83
BMI (kg/m²)	28.4 ± 3.9	20.6 - 39.1
Metformin Dose (mg/day)	1344 ± 432	1000 - 2000
Metformin Duration (years)	2.9 ± 1.6	1 - 14
HbA1c (%)	7.7 ± 0.6	6.7 - 9.2
Serum Vitamin B12 (pg/mL)	299.7 ± 106.8	75 - 500
Pain Severity (VAS)	3.5 ± 2.9	0 - 10
DN4 Score	3.8 ± 2.9	0 - 10

3.2 Vitamin B12 Status

The overall cohort mean for the Serum Vitamin B12 was 299.7 ± 106.8 pg/mL The distribution was skewed, requiring the division into clinical subgroups:

Deficient (<200 pg/mL): 64 patients (25.6%)

Borderline (200-300 pg/mL): 59 patients (23.6%)

Normal (>300 pg/mL): 127 patients (50.8%)

Some 21.4% of patients on metformin had frank B12 deficiency and almost half (49.2%) had suboptimal levels (<300 pg/mL).

3.3 The Burden of Neuropathy (DN4 Stratification)

Using the DN4 cutoff of ≥4, we found that the prevalence of clinical neuropathy for the study was 33.6% (n=84). However, this burden was not shared among all.

A dramatic divergence was found between B12 status when the analysis was performed in subgroup analysis:

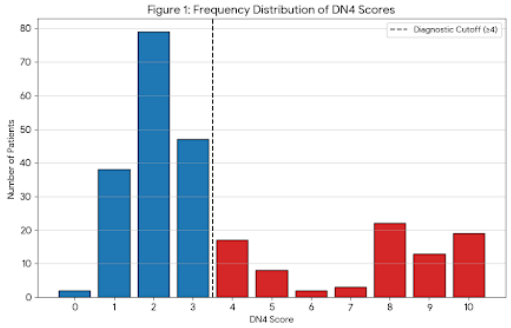
In the B12 Deficient Group: 52 out of 64 patients (81.2%) had the criteria that met the condition of neuropathy.

In the B12 Normal Group: Only 16 out of 127 of the patients (12.6%) fulfilled the criteria.

This implies that although diabetes alone is linked with the risk of neuropathy (around 12-13% among this controlled subset), with B12 deficiency the risk of neuropathy is increased almost six-fold.

The frequency distribution of DN4 scores is shown in this figure 1. A bimodal distribution is seen, with a peak between scores 0-2 (normal patients) and a second peak between scores 8-10 (severe neuropathy) consisting mainly of the B12 deficient subgroup.

Figure 1: Frequency distribution of DN4 scores in the study population.

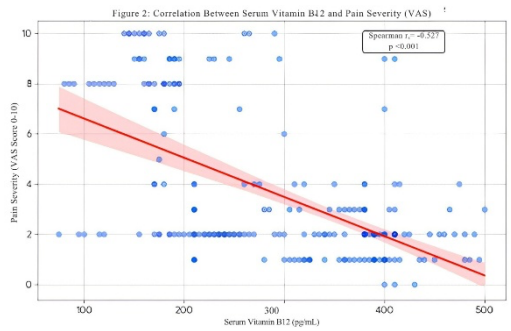


The vertical dashed line at score 4 represents the diagnostic cutoff. Bars to the right (Red) indicate patients with clinically significant neuropathy (33.6%), primarily clustering in the severe range (8-10).

3.4 Correlation Analysis

A strong statistical correlation between biochemical levels of B12 and clinical levels of pain was detected.

Figure 2: Correlation against VAS (Pain Intensity)



Correlation against VAS (Pain Intensity):

As can be seen in Figure 2, there is a fairly definite inverse linear relationship. As the serum level of B12 decreases, there is an increase in the VAS pain score.

Spearman's r_s: - 0.527

P-value: < 0.001

The scatter plot shows that patients with low B12 (< 200 pg/mL) tend not to rate their VAS less than 5, while patients with high B12 (> 400 pg/mL) tend not to rate their VAS more than 3.

Figure 2: Scatter plot showing the significant inverse correlation (rs = -0.527) of the relationship between harm-Schmerz ("Neuropathic Pain Severity"; VAS) and the levels of Vitamin B12 in serum. As the level of B12 decreases, the intensity of pain increases progressively. The regression trend is shown by the red line.

Correlation contains with DN4 (Neuropathic Characteristics):

This correlation with the specific neuropathic score was even higher.

Spearman's rs: - 0.575

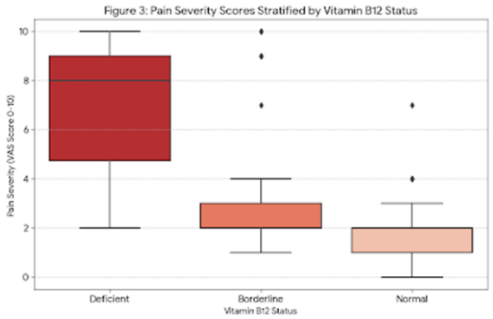
P-value: < 0.001

This suggests that low B12 levels are linked not only to "pain" in general, but burning, electric shocks and paresthesia typical of nerve damage.

3.5 Stratification of Pain Severity

When patients were stratified by B12 status, the difference in quality of life became quantifiable.

Figure 3: Comparison of the pain severity scores in boxplots based on various Vitamin B12 status groups.



Patients in the "Deficient" group (<200 pg/mL) have significantly increased median pain scores compared to patients in the "Borderline" and "Normal" groups (P < 0.001).

Deficient group = Mean VAS 6.8 +- 2.1 (Severe Pain)

Borderline Group: Mean VAS 3.2+-1.9 (Mild - Moderate Pain)

Normal Group: Mean VAS (Minimal Pain) 1.8 +-1.5

The differences among them were found to be significantly different (H statistic large, p < 0.001) using the Kruskal-Wallis test. Post-hoc testing showed that there were significant differences between all the pairs including between Borderline and Normal suggesting that even "low normal" may not be optimal for neural health.

Table 2: Pain Severity Scores Stratified by Vitamin B12 Status

B12 Status	N	Mean VAS Score	Median VAS (IQR)	p-value †
Deficient (<200 pg/mL)	61	6.8 ± 2.1	7.0 (5.0–8.0)	< 0.001
Borderline(200–300) pg/mL)	82	3.2 ± 1.9	3.0 (2.0–4.0)	

Normal (>300 pg/mL)	107	1.8 ± 1.5	2.0 (1.0–3.0)	

† Kruskal-Wallis Test.

3.6 Multivariable Regression: Determining Independence

One of the major questions that must be addressed is whether the pain is caused by the B12 deficiency or the diabetes itself (hyperglycemia). To solve this, a multivariable linear regression was done.

Table 3: Multivariable Linear Regression for Predictors of Pain Severity (VAS)

Predictor	Coefficient (β)	Standard Error	p-value	95% CI
Serum Vitamin B12	-0.011	0.002	< 0.001	-0.014 to -0.008
Age	0.128	0.040	0.002	0.049 to 0.207
Gender (Male)	0.208	0.285	0.467	-0.353 to 0.769
Metformin Duration	0.141	0.091	0.120	-0.037 to 0.320
HbA1c	-0.944	0.773	0.223	-2.47 to 0.58
BMI	0.037	0.055	0.501	-0.072 to 0.146

Analysis: The Model shows that Serum B12 is an independent predictor. The coefficient of -0.011 means that with every 100 pg/mL decrease in B12 the pain score is 1.1 points higher on the VAS scale. Surprisingly, current HbA1c was not a significant predictor of current pain severity in this particular model, probably because neuropathy is a consequence of chronic cumulative nerve damage and not acute glycemic status as B12 deficiency is an acute aggravator of nerve conduction.

4. DISCUSSION

4.1 Interpretation of Findings

This is important evidence that Vitamin B12 is a major modifiable determinant of neuropathic pain severity in the metformin treated T2DM patient group. The prevalence of deficiency (25.6%) is in line with data from around the world, but the link to the degree of symptoms is stronger than was previously noted. (Ko et al., 2014; Reinstatler et al., 2012) The fact that 81.2% of the B12-deficient patients developed clinical neuropathy (DN4 [4]) compared to only 12.6% of the B12-replete group is a very strong argument in favor of the "Double Hit" hypothesis. It is in this model that the diabetic nerve is already colon metabolically fragile due to hyperglycemia, the superimposition of B12 deficiency (the + Mylin is deprived of repairing capacity), the neurological fate is pushed over the threshold into "diseased nerve".

4.2 Mechanisms and Clinical Nuance

The fact that Metformin duration, B12 levels, and the two are not significantly correlated in our study (r=-0.048) is therefore interesting. It implies that the malabsorption is not only cumulative but may depend on some individual susceptibility factors such as the variation in calcium intake or genetic polymorphisms within the cubilin receptor. (Bauman et al., 2000; Liu et al., 2014) This calls for population screening of the general public, whether or not they carry a disease, for the necessary biomarkers rather than using "years of therapy" as a risk proxy.

Of special significance is the greater association between B12 levels and the DN4 score which has a clinical relevant consequence The questions in the DN4 are about positive symptoms (burning, electric shocks). B12 deficiency leads to demyelination of the dorsal columns and peripheral nerves resulting in ectopic firing. This "irritable nerve" state is an exact match to the burning/shock like pain recorded by the DN4.

4.3 Comparison with Literature

Our results are similar to those in Kim et al., 2019 and in Alvarez et al., 2019 who observed the worse neuropathy scores for B12 deficient cohorts. However, we are contributing granularity with our study with the use of the DN4 tool in which we can see that the deficit is specifically neuropathic in nature. Unlike the DPN study by Aroda et al. (DPPOS) that focused on the prevalence, our study establishes a linear dose-response relationship between serum levels and pain intensity. (Aroda et al., 2016)

4.4 Clinical Implications

For its implications for practice, these are immediate:

Routine Screening: Serum levels of B12 should be checked yearly in all patients taking metformin regardless of the length of time on the medication.

Redefining "Normal" Our "Borderline" group (200-300 pg/mL) had significantly higher pain scores than the "Normal" group. This suggests that the therapeutical goal of diabetic patients should perhaps be higher (>300 or even >400 pg/mL) as compared to the standard hematological cutoff.

Therapeutic Trial: In diabetic patients with the diagnosis of the worsening neuropathy, the correction of B12 should be considered as one of the initial treatments in combination with glycemic control and gabapentinide.

4.5 Strengths and Limitations

Strengths: The use of dual validated scores (VAS and DN4) and the exclusion of other neuropathic causes (alcohol, renal failure) is a strength to the internal validity.

Limitations: As a cross-sectional study, we cannot prove the cause and effect. We did not measure Methylmalonic Acid (MMA) or Homocysteine which are more sensitive markers of tissue B12 deficiency as the result of cost constraints. Longitudinal studies are needed in the future to determine whether high DN4 scores can be reversed by B12 repletion.

5. CONCLUSION

This study concludes that Vitamin B12 deficiency isn't just a biochemical bystander but an avid perpetrator of neuropathic morbidity in metformin treated Type 2 Diabetes patients. Lower B12 levels are associated as strongly, independently, and linearly with severe, burning neuropathic pain. With almost 1/3 of the study population having some degree of neuropathy, and the immense majority of these cases being in the B12 deficient subgroup, the message is clear-Neuroprotection in diabetes requires an eye on both the sugar and micro-nutrients (Liu et al., 2014). We strongly advocate for aggressive screening consultative and comparing the correction of B12 level to improve the lifestyle of millions of diabetic patients all over the world.

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