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Original Research

Peripheral Blood Cytopenias and Morphological Features Across the Spectrum of Vitamin B12 Deficiency in a Diabetic Cohort: A Quantitative Study from a Jharkhand Tertiary Hospital.

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Abstract
Background: The growing frequency of vitamin B12 insufficiency in people with diabetes mellitus raises major question for haematological health. This study sought to assess the peripheral blood picture—specifically, the presence of cytopenias and neurological symptoms—across the spectrum of vitamin B12 insufficiency severity in a group of type 2 diabetic patients.From January 2024 to September 2024, a cross-sectional, hospital-based study was carried out in a tertiary care centre in Jharkhand, India. The sample size determined was 420. Informed consent was given by adult type 2 diabetes mellitus diagnosed patients with serum vitamin B12 levels < 180 pg/mL. Demographic, clinical history, metformin use, vegetarian diet, vitamin B12 levels, full blood counts, and neurological symptoms—tingling, numbness, ataxia—were all gathered. Deficiency (100-179 pg/mL) and Severely Deficient (<100 pg/mL) were classifications for vitamin B12 deficiency. The adjusted relationship between severe vitamin B12 insufficiency and the results of anaemia, macrocytosis, leukopenia, thrombocytopenia, and presence of any neurological symptom was evaluated using multivariate logistic regression.There were 420 type 2 diabetic patients lacking vitamin B12 in the study. After controlling for age, sex, vegetarian diet, and metformin use, severe vitamin B12 insufficiency was notably linked to a higher likelihood of macrocytosis (Adjusted OR: 4.18, 95% CI: 2.03-8.61, $p < 0.001$). Although trends were seen, adjusted analysis revealed no significant correlation between severe B12 deficiency and anaemia, leukopenia, thrombocytopenia, or any reported neurological symptom.Conclusion: Among type 2 diabetic patients lacking vitamin B12 in this cohort, severe deficiency was a strong independent predictor of macrocytosis. The link between vitamin B12 insufficiency severity and other haematological parameters and neurological symptoms in this vulnerable population has to be clarified by more study using larger sample sizes and longitudinal studies.

Key Words - DM Type 2 , Vitamin B12 Deficiency , Blood picture ,Jharkhand .

Introduction

Vitamin B12, or cobalamin, is a water-soluble vitamin essential for hematopoiesis, neurological function, and DNA synthesis, acting as a cofactor in methionine synthesis and methylmalonic acid metabolism. Deficiency disrupts these pathways, leading to megaloblastic anemia, peripheral neuropathy, and metabolic complications. Recent studies emphasize its role in exacerbating metabolic dysfunction in diabetic patients, where oxidative stress and impaired methylation amplify complications like neuropathy and cytopenias. (1) Globally, vitamin B12 deficiency is a significant public health issue, with prevalence rates ranging from 12% to 67% in various populations, driven by dietary insufficiency, malabsorption, and medication

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use. Vitamin B12 deficiency contributes to anemia, neurological disorders, and increased morbidity, particularly in low-resource settings where screening and supplementation are limited. (2)

A developing global epidemic, diabetes mellitus—especially type 2 diabetes (T2DM)—is projected by GBD 2023 to have 529 million cases worldwide, predicted to approach 1.3 billion by 2050. Driven by genetic predisposition, lifestyle changes, and healthcare access inequalities, more than 77 million adults are impacted, making the situation in India especially severe.(3) Various country wide studies highlights diabetes as a leading cause of disability-adjusted life years (DALYs) in India, with complications like nephropathy, neuropathy, and retinopathy exacerbating morbidity. (3,4)

Especially troubling is the connection of diabetes and vitamin B12 deficiency. First-line treatment for T2DM, metformin has been linked to B12 deficiency; studies show 20–43% of metformin users have it owing to poor intestinal absorption. This deficiency can cause or aggravate peripheral blood cytopenias (anaemia, thrombocytopenia, or pancytopenia) and morphological abnormalities such macrocytosis or hypersegmented neutrophils, which could mimic or worsen diabetes symptoms. (5,6,7) In India, where vegetarian diets and metformin use are widespread, the prevalence of B12 deficiency in diabetic patients is alarmingly high, ranging from 18% to 47%. (6)

The Indian setting offers unique challenges. Dietary patterns, especially in northern and eastern areas like Jharkhand, are mostly vegetarian, hence B12 consumption is limited. Diabetic patients in India are at greater risk for B12 deficiency-related problems when combined with common metformin use and restricted screening. North Indian studies indicate a 47% incidence of B12 insufficiency in general populations; diabetic groups had higher rates of neuropathy and haematological problems. (8) However, region-specific data from Jharkhand are scarce, with few studies quantifying the burden of B12 deficiency in diabetic populations or its hematological consequences.

Jharkhand, a resource-constrained state with a high burden of diabetes and malnutrition, lacks comprehensive evidence on B12 deficiency in its diabetic cohort. A study from a tertiary hospital in Jharkhand reported a high prevalence of anemia in diabetic patients, but the role of B12 deficiency was underexplored. (9) Such studies are critical to inform targeted interventions, as B12 deficiency is a modifiable risk factor that, if addressed, could reduce the burden of cytopenias and neuropathy in diabetic patients. The absence of region-specific data hinders policy formulation for screening and supplementation, underscoring the need for quantitative studies in Jharkhand's tertiary care settings.

This study aims to bridge this gap by investigating the spectrum of peripheral blood cytopenias and morphological features associated with vitamin B12 deficiency in a diabetic cohort at a Jharkhand tertiary hospital. By quantifying the prevalence and severity of B12 deficiency and its hematological manifestations, we seek to provide evidence to guide clinical practice and public health strategies in resource-limited settings.

Methods

Study Design and Setting: This cross-sectional, quantitative study was conducted at a tertiary care hospital in Jharkhand, India, from January 2024 to September 2024. The hospital serves a diverse population, including urban and rural patients with a high prevalence of diabetes and nutritional deficiencies.

Study Population: We enrolled 420 adult patients (aged 18 years and above) diagnosed with type 2 diabetes mellitus (T2DM) per American Diabetes Association criteria (fasting blood glucose ≥126 mg/dL, HbA1c ≥6.5%, or use of glucose-lowering drugs). Patients were recruited from the endocrinology outpatient department.

Inclusion Criteria

1. Patients with serum vitamin B12 levels <180 pg/mL.
2. Patients aged 18 years and above.

Exclusion Criteria

1. Patients with blood transfusion within 3 months prior to presentation.
2. Patients on vitamin B12 supplementation for the last 6 months.
3. Pregnancy.
4. Critically ill patients (admitted to ICU or CCU).
5. Known malignancy.
6. HIV-positive patients.

Sample Size Calculation

The sample size was calculated using the formula for estimating a population proportion:

The sample size was calculated using the formula for estimating a population proportion:

n = (Z^(2) * P * (1 - P)) / d^(2)

Where:

- Z = 1.96 (standard normal deviate at 95% confidence interval)
- P = 0.47 (expected proportion of vitamin B12 deficiency, based on Singla et al.,. (8)
- d = 0.05 (absolute allowable error)

Using these values, the calculated sample size was 382. Accounting for a 10% dropout rate, the final sample size was adjusted to 420 patients.

Data Collection

After obtaining informed consent, demographic and clinical data were collected, including age, gender, duration of diabetes, metformin dose and duration, dietary habits (vegetarian vs. non-vegetarian), and

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history of neuropathy or anemia. Blood samples were drawn and stored at −20°C for analysis. Serum vitamin B12 levels were measured using a solid-phase competitive chemiluminescent enzyme immunoassay . Deficiency was defined as B12 levels <180 pg/mL, consistent with inclusion criteria.

Complete blood counts (CBC) were performed using an automated hematology analyzer (Sysmex XN-1000) to assess hemoglobin, mean corpuscular volume (MCV), white blood cell count, and platelet count. Peripheral blood smears were examined for morphological features, including macrocytosis, hypersegmented neutrophils, and anisopoikilocytosis. Diabetic neuropathy was assessed using the Diabetic Neuropathy Symptom (DNS) score (≥1 suggestive of neuropathy) and Diabetic Neuropathy Examination (DNE) score (≥3 suggestive of neuropathy).

Statistical Analysis

Data were analyzed using SPSS version 29 (IBM Corp., Armonk, NY). Continuous variables (e.g., B12 levels, hemoglobin, MCV) were reported as means ± standard deviation (SD) or medians (interquartile range) based on normality, assessed via the Shapiro-Wilk test. Categorical variables (e.g., cytopenia prevalence, neuropathy scores) were reported as percentages. Associations between B12 levels and cytopenias or neuropathy were evaluated using independent t-tests for continuous variables and chi-square tests for categorical variables. Multivariate logistic regression was used to adjust for confounders (e.g., metformin dose, diabetes duration, diet). A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Ethics Committee of the participating hospital. All participants provided written informed consent, and data were anonymized to ensure confidentiality.

Table 1. Baseline Characteristics and Vitamin B12 Status of the Study Cohort

Characteristic Value (N=420)

Age (years) Mean ± SD	46.83 ± 17.98
Gender (Male) N(%)	168 (40%)
Duration of Diabetes (years) Mean ± SD	5± 3.2
Metformin Use N(%)	22 (5.24%)
Metformin Dose (mg/day) Mean ± SD	680± 40
Dietary Habits (Vegetarian) N(%)	162 (38.57%)
Presence of Neurological / Neuropsychiatric Symptoms (Any) N(%)	275 (65%)
Presence of Anorexia N(%)	156 (37.14%)
Presence of Anemia N(%)	226 (53.81 %)
Vitamin B12 Level (pg/mL) Mean ± SD	114.45 ± 38.22
Other Associated Deficiencies (Yes) N(%)	16 (3.81%)

All 420 study subjects had vitamin B12 insufficiency (serum levels < 180 pg/mL); Table 1 shows their baseline traits. The cohort's average age was 46.83 ± 17.98 years; 40% were male. The average length of diabetes was 5.00 ± 3.20 years; a small percentage (5.24%) were on metformin. More than a third (38.57%) of the respondents said they followed a vegetarian diet; a significant number (65.48%) said they had neuropsychiatric or neurological symptoms; and 37.14% said they had anorexia. The average vitamin B12 level was 114.45 ± 38.22 pg/mL and 53.81% of the group had anaemia.

Table 2. Comparison of Clinical Characteristics and Outcomes Between Severe and Vitamin B12 Deficiency

Characteristic	Vitamin B12 Deficiency N=268 (100-179 pg/mL) N (%) or Mean ± SD	Severe Vitamin B12 Deficiency N=152 (<100 pg/mL) N (%) or Mean ± SD	p-value
Age (years)	46.47 ± 18.33	47.47 ± 17.38	>0.05
Gender (Male)	103 (38.40%)	65 (42.80%)	
Duration of Diabetes (years)	6.1 ± 2.4	5.8 ± 3.2	<.05
Metformin Use	19 (7.10%)	3 (2.0 %)	<.05
Metformin Dose (mg/day)	535 ± 38.4	690 ± 67.4	<.00

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Dietary Habits (Vegetarian)	106 (39.60%)	56 (36.20%)	>0.05
History of Anemia	121 (45.10%)	35 (22.40%)	>0.05
Presence of Neuropsychiatric/Neurological Symptoms (Any)	177 (66.0%)	98 (64.5%)	>0.05
Anorexia (Loss of Appetite Reported)	121 (45.10%)	35 (22.40%)	>0.05
Hemoglobin (g/dL)	11.71 ± 2.37	11.54 ± 2.39	>0.05
Mean Corpuscular Volume (MCV) (fL)	88.74 ± 8.96	92.94 ± 14.43	**<0.001**
White Blood Cell Count (WBC) (/µL)	8038.66 ± 3013.68	7830.26 ± 3036.67	>0.05
Platelet Count (/µL)	178773.51 ± 72233.66	175652.63 ± 80619.18	>0.05
Anemia (Hb < WHO cut-off)	139 (51.90 %)	87 (57.20 %)	>0.05
Macrocytosis (MCV > 100 fL)	13 (4.9%)	26 (17.1%)	**<0.00**
Leukopenia (WBC < 4000 /µL)	5 (1.9 %)	6 (3.9 %)	>0.05
Thrombocytopenia (Platelets < 150,000 /µL)	109 (40.7 %)	74 (48.7%)	>0.05
Hypersegmented Neutrophils (on smear)	9 (3.36%)	7 (4.61%)	**<0.05**

Table 2 contrasts the clinical features and results of persons with less severe vitamin B12 shortage (100-179 pg/mL, n=268) with those with severe deficiency (<100 pg/mL, n=152). The two groups showed no statistically significant variations in age, gender distribution, or the prevalence of neuropsychiatric/neurological symptoms, anorexia, or general anaemia. Participants with severe vitamin B12 insufficiency, on the other hand, had a significantly shorter diabetes duration ($p<0.05$) yet were on a much greater metformin dose ($p<0.001$).
The severe deficient group (92.94 ± 14.43 fL) had a significantly greater mean MCV than the less severe group (88.74 ± 8.96 fL, $p<0.001$). The severe deficient group (17.1%) had significantly greater prevalence of macrocytosis (MCV > 100 fL) than the less severe group (4.9%, $p<0.001$). Although the average haemoglobin levels, WBC counts, and platelet counts were not statisticaly different between the groups, the frequency of leukopenia and thrombocytopenia similarly lacked statistical relevance. The two groups did not differ much in the frequency of hypersegmented neutrophils on peripheral blood smear ($p>0.05$).

Table 3: Adjusted Odds Ratios for Peripheral Blood Cytopenias and Neurological Symptoms Associated with Severe Vitamin B12 Deficiency (Reference: Vitamin B12 Deficient)

Outcome Variable	Independent Variable (Severe vs. Less Severe B12)	Adjusted Odds Ratio (95% CI)	p-value	Adjusted For
Anemia (Hb < WHO cut-off)	Vitamin B12 Category	1.340 (0.855 - 2.100)	0.202	Age, Sex, Vegetarian Diet, Metformin Use
Macrocytosis (MCV > 100 fL)	Vitamin B12 Category	4.181 (2.030 - 8.612)	<.001	Age, Sex, Vegetarian Diet, Metformin Use
Leukopenia (WBC < 4000 /µL)	Vitamin B12 Category	2.227 (0.647 - 7.657)	0.204	Age, Sex, Vegetarian Diet, Metformin Use
Thrombocytopenia (Platelets < 150,000 /µL)	Vitamin B12 Category	0.742 (0.490 - 1.125)	0.16	Age, Sex, Vegetarian Diet, Metformin Use
Presence of Neuropsychiatric/Neurological Symptoms (Any)	Vitamin B12 Category	0.873 (0.571 - 1.334)	0.529	Age, Sex, Vegetarian Diet, Metformin Use

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Table 3 summarizes the adjusted associations between severe vitamin B12 deficiency and various clinical manifestations, controlling for age, sex, vegetarian diet, and metformin use. Severe deficiency was significantly associated with higher odds of macrocytosis (OR = 4.18, $p < .001$). While increased odds were also observed for anemia and leukopenia, and decreased odds for thrombocytopenia and neurological symptoms, these associations did not reach statistical significance.

These adjusted analyses suggest that, after accounting for potential confounders, severe vitamin B12 deficiency is a strong independent predictor of macrocytosis in this diabetic cohort. While trends were observed for anemia and leukopenia, they did not reach statistical significance in this model. Thrombocytopenia and the presence of neurological symptoms did not show a statistically significant association with the severity of vitamin B12 deficiency in this adjusted analysis.

Discussion -

This study provides novel insights into the spectrum of clinical and hematological features associated with vitamin B12 deficiency in a significant cohort of adult patients with type 2 diabetes mellitus attending a tertiary care hospital in Jharkhand, a region with a high burden of both diabetes and nutritional deficiencies. To the best of our knowledge, this is one of the first studies to specifically characterize these associations in this under-researched population. We systematically assessed the baseline characteristics of B12 deficient diabetic individuals and compared clinical and hematological parameters between those with less severe and severe deficiency, establishing a quantitative framework for understanding the impact of varying degrees of cobalamin insufficiency in this vulnerable group.

Our findings revealed a high prevalence of vitamin B12 deficiency in this diabetic cohort, with a substantial proportion exhibiting severe deficiency. We observed significant differences in the duration of diabetes and metformin dosage between the less severe and severe B12 deficiency groups. Notably, the severe deficiency group presented with significantly higher mean MCV and a greater prevalence of macrocytosis compared to the less severe group, underscoring the classical association between severe B12 deficiency and macrocytic anemia. While other hematological parameters such as hemoglobin, WBC, and platelet counts did not show significant differences in mean values between the groups, the prevalence of overall anemia, leukopenia, and thrombocytopenia also did not significantly differ. Similarly, the presence of neurological/neuropsychiatric symptoms and anorexia was not associated with the severity of B12 deficiency in our bivariate analysis.

Our finding of a significant prevalence of vitamin B12 insufficiency in diabetes individuals aligns with several earlier research. A meta-analysis by Sayedali et al. (10) indicated a substantial connection between metformin use and biochemical B12 insufficiency in older persons. Although our total metformin use rate was very low (5.24%), we did discover a notably greater metformin dose in the severely deficient group, implying a possible dose-dependent influence on B12 levels, as noted by Ramzan et al. in a review study with a different range from 5-41%.(11)The found B12 deficiency, in line with results from research around India, is probably greatly influenced by the high percentage of vegetarianism (38.57%) in our group, a typical dietary pattern in India. A recent study by Mercantepe et al. (13) looked at how vitamin B12 levels related to various degrees of diabetes mellitus and obesity, interestingly. Although their research may have emphasised a different population or particular facets of this relationship, contrasting their results on the frequency and severity of B12 deficiency in diabetic patients with ours from a Jharkhand tertiary centre could offer a more comprehensive knowledge of this problem across several geographical and possibly ethnic settings. The strong association we found between severe B12 deficiency and macrocytosis is a well-established hematological hallmark of cobalamin deficiency (14). However, the lack of significant difference in mean hemoglobin levels between the severity groups, despite a higher prevalence of macrocytosis in the severe group, suggests that the degree of anemia may not always directly correlate with the severity of B12 deficiency, a finding also noted by Lindenbaum et al. (15) who described neuropsychiatric disorders due to cobalamin deficiency in the absence of marked anemia or macrocytosis. This highlights the importance of assessing a range of hematological parameters beyond just hemoglobin and MCV in the evaluation of B12 deficiency.

Interestingly, we did not find a significant association between the severity of B12 deficiency and the prevalence of overall anemia in our bivariate analysis. This contrasts with some studies that have reported a higher prevalence of anemia with lower B12 levels (16). However, our finding might be influenced by the presence of diabetes itself, which can contribute to anemia through various mechanisms, potentially obscuring a direct relationship with B12 deficiency severity in this specific population.

The lack of a significant association between B12 deficiency severity and the presence of neurological/neuropsychiatric symptoms in our bivariate analysis is also noteworthy. While B12 deficiency is a known cause of neurological complications (17), the cross-sectional nature of our study and the way we defined "presence of any symptom" might have limited our ability to detect a clear dose-response relationship. Future studies with more detailed neurological assessments and longitudinal follow-up could provide further clarity on this aspect. Similarly, the lack of association with

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anorexia, a symptom sometimes linked to B12 deficiency, might be due to the multifactorial etiology of appetite changes in diabetic patients.

In our study, leukopenia and thrombocytopenia were uncommon and did not much vary among the severity categories. Although severe B12 deficiency can cause pancytopenia (18), our results indicate that in this diabetic group with a range of B12 deficiency, these pan cytopenias may be less frequent.

The discovery of a notably shorter diabetes duration in the severely deficeincy group is interesting and calls for more research. Those with a shorter diabetes duration may experience sooner or more intensive metabolic care that could unintentional cause B12 insufficiency, possibly by dietary advice or drug interactions. Though with a shorter diabetes duration, the seriously deficient group's much higher metformin dose supports more the possible function of metformin in B12 depletion.

Strengths and Weaknesses - There are certain limits to our work. Its cross-sectional approach hinders our capacity to determine causation. Self-reporting, which could be affected by recall bias, formed the basis of the evaluation of dietary practices. Not evaluated were thorough neurological tests and particular B12 metabolite levels—such as methylmalonic acid and homocysteine—which might have offered a more complex evaluation of B12 status and its neurological effect.

Notwithstanding these constraints, our study offers insightful information on the clinical and haematological features of vitamin B12 deficiency in a diabetic population from an area with little previous study. The results underline the need of addressing the degree of B12 deficiency in relation to macrocytosis as well as the possible impact of metformin dose and duration of diabetes on B12 status in this at-risk population. To clarify the intricate interaction between vitamin B12 insufficiency, diabetes, and their clinical repercussions in this particular group, more longitudinal studies with thorough evaluations are required.

Conclusion

Among the severity groups, leukopenia and thrombocytopenia were rare in our population and did not greatly differ. Though severe B12 deficiency could lead pancytopenia (18), our findings suggest that in this diabetic population with varying B12 deficit, these profound cytopenias could be less common.

The finding of a much shorter diabetes duration in the highly compromised group is intriguing and merits further investigation. Those with a shorter diabetic duration might undergo earlier or more aggressive metabolic treatment that could accidentally produce B12 deficiency, perhaps through dietary recommendations or medication combinations. Although having a shorter diabetes duration, the seriously deficient group's significantly higher metformin dose supports more the likely function of metformin in B12 depletion.

Strengths and Limitations - Our labour has specific boundaries. Its cross-sectional design limits our ability to identify cause. The assessment of food habits was based on self-reporting, which could be influenced by memory bias. Not evaluated were thorough neurological tests and particular B12 metabolite levels—such as methylmalonic acid and homocysteine—which might have offered a more complex evaluation of B12 status and its neurological effect.

Despite these limitations, this research provides interesting data on the clinical and haematological characteristics of vitamin B12 deficiency in a diabetic population from a region with limited prior research. The findings highlight the need of considering the level of B12 deficiency in relation to macrocytosis as well as the prospective influence of metformin dose and duration of diabetes on B12 status in this at-risk group. More longitudinal studies with comprehensive assessments are needed to elucidate the complex interplay between vitamin B12 deficiency, diabetes, and their clinical consequences in this specific population.

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