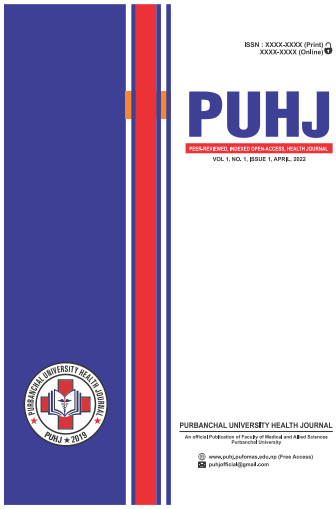

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Prevalence of Vitamin B12 Deficiency in Patients with Type II Diabetes Mellitus in Morang District

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Abstract

Introduction: Type II Diabetes Mellitus is a significant global health concern that has become prevalent worldwide, and its impact on morbidity and mortality is substantial. Metformin is a commonly prescribed medication for type II diabetes that interferes with the absorption of vitamin B12 in the gastrointestinal tract, which leads to neurological issues in patients.

Objective: The aim of this study was to evaluate the vitamin B12 levels in Type II diabetic patients taking metformin at the Purbanchal University Teaching Hospital medical OPD.

Method: A quantitative, descriptive cross-sectional study was done from May 2022 to April 2023 at the medical outpatient department of Purbanchal University Teaching Hospital, Gothgaun, Morang. Non-probability purposive sampling was done to select 385 Type II diabetic patients on metformin for 12 months. A structured questionnaire was used for data collection, which was validated with the consultation of experts.

Result: It was found that the mean age (in years) with SD was 55.2±11.3; most of the respondents were female. The prevalence of low vitamin B12 was 21.8% among the study respondents. Diabetic patients on low vitamin B12 taking metformin were significantly associated with age over 50 years, a higher metformin dosage, a longer duration of use, and vegetarian dietary patterns.

Conclusion: These findings emphasize the importance of regular monitoring of vitamin B12 levels in Type II diabetes mellitus and prolonged metformin treatment to prevent potential complications.

Keywords: Diabetes mellitus; Metformin; VitaminB12

Introduction

Diabetes Mellitus is a metabolic disease caused by high blood sugar (hyperglycemia) due to insu fficient insulin, insulin resistance, or both. Insuli n is a substance produced by the pancreas that pl ays an important role in controlling blood sugar by promoting the uptake of glucose into cells.[1]

The prevalence of diabetes in Southeast Asia, including countries like Nepal, is substantial. With an estimated 436,000 people currently affected and projections suggesting a rise to 1.3 million by 2030, there is an urgent need for effective strategies in prevention, early detection, and management of diabetes.[2] The Nepalese Diabetes Association reports that in urban areas, approximately 15% of people over 20 years of age and 19% of people over 40 years of age have diabetes.[3]

Metformin is widely recognized as an effective cornerstone in managing Type II diabetes and is recommended by various guidelines for its safety and tolerability. However, many long-term metformin users are unaware of the risk of vitamin B12 deficiency and its symptoms.[4] Cobalamin is an important water-soluble B-complex vitamin, which plays an important role in brain function (central and internal nervous system), DNA synthesis, and red blood cell (RBC) synthesis[5]. Non-vegetarian foods are naturally rich in vitamin B12, and the recommended daily allowance (RDA) is 2.4 micrograms per day. The average level of vitamin B12 in the human body is over 221 mmol/L.[6]

It has been reported that vitamin B12 deficiency may develop in an average of 6% to 30% of patients due to metformin use. Recently, large st udies have clarified this relationship, and 2017 American Diabetes Association guidelines now recommend monitoring vitamin B12 levels in pe ople with diabetes taking metformin.[7]

In Nepal, limited patient knowledge about diabetes due to factors like poverty and lack of education makes it difficult for doctors to explain the disease's consequences. To address this knowledge gap and potential health risk, this study aims to assess the prevalence of vitamin B12 deficiency among Type II diabetic patients currently undergoing metformin treatment in Morang District.

Method

The cross-sectional study was conducted between May 2022 and April 2023 at the outpatient department of the Purbanchal University Teaching Hospital. The sample size of 385 was calculated using Cochran's formula to estimate the prevalence of vitamin B12 deficiency with Type II diabetes mellitus on metformin therapy. We assumed a prevalence of 50.95% based on a previous study in Nepal, a desired confidence interval (CI) of 95%, and an acceptable margin of error of 5%.[8] The final sample size included 385 participants.

Non-probability purposive sampling was employed to recruit participants with T2DM who had been taking metformin for more than a year. Informed consent was obtained from all participants before data collection.

A semi-structured questionnaire was used to collect information on social practices, metformin use, diabetes history, lifestyle factors, anthropometric measurements, and past medical history through interviews. The questionnaire's validity was ensured through literature review and consultation with experts. Preliminary testing of the questionnaire was conducted on 10% of the samples at Nobel Medical College and Teaching Hospital, Morang, a similar outpatient setting.

Following informed consent, a detailed medical history was recorded, and a blood sample was drawn for biochemical analysis for those patient with inclusion criteria for study purpose. Serum B12 levels were quantified using a chemi luminescent enzyme immunoassay (CLIA) (Access Immunoassay Systems, Beckman Coulter Inc, CA, USA). Biochemical B12 deficiency was defined as serum B12 levels $\leq$ 200 pmol/L, which aligns with the cut-off adopted by the National Public Health Laboratory, Teku.

Patients with type I diabetes, patients with Type II diabetes mellitus and receiving combination therapy (metformin with insulin or other hypoglycemic drugs), pregnant women, patients with anemia, or patients with liver disease and hypothyroidism were not included in this study. Patients with Type II diabetes mellitus and receiving insulin therapy were also excluded from the study because insulin works differently than metformin to control blood sugar. Metformin is believed to interfere with vitamin B12 absorption in the gut, whereas insulin

directly affects blood sugar levels. Including patients on insulin could introduce a confounding variable, making it difficult to isolate the effect of metformin on vitamin B12 levels.

Data entry was made into Microsoft Excel and analyzed using SPSS v.17. Descriptive and analytic statistics were employed, including frequencies, percentages, means, and standard deviations for demographic and clinical data. Chi-square tests were used to assess associations between categorical variables. Statistical significance was set at a p value ≤0.05.

This study received approval from the Institutional Review Committee of Purbanchal University School of Health Sciences (reference number: 091-07980) and Purbanchal University Teaching Hospital before confidentiality was maintained throughout the study. Data were anonymized and stored securely.

Result

About 47.5 % of the samples were aged 51–60 years, with an average of 59.62±14.06 years. Females comprised 54.3%, while males were 45.7%. Approximately 42.08% were illiterate, and 26.1% were unemployed. Homemakers, unskilled, and semi-skilled workers made up 56.3%, 16.1% were retired, and 39.5% had sufficient income for 6–12 months. (Table1)

Table 1: Socio demographic Characteristics of Respondents n=385

Variables	Frequency (f)	Percentage (%)
Age		
20- 40years	34	8.83
41-50 years	168	43.64
51-60yrs	183	47.5
Mean ± SD:59.62±14.06		
Sex		
Male	176	45.7
Female	209	54.3
Marital status		
Married	205	53.24
Single	125	32.47
Unmarried	55	14.29
Education status		
Illiterate	162	42.08
Literate	223	57.92
Occupation		
Government	68	17.7
Non-government	72	18.7
Self-employed/Business	82	21.3
Homemaker	101	26.2
Retired	62	16.15
Family Income		
Income sufficient for less than 6 months	136	35.3
Income sufficient for 6-12 months	152	39.5
Income sufficient for more than 12 months and surplus	97	25

Around 75.6% of respondents are taking metformin less than 5 years and 58.7% are consuming metformin dose more than 1000mg/day. In our study 55.97% are vegetarian as shown in Table no 2.

Table 2: Variables related to duration of metformin intake, doses, and dietary habits n=385

Variables	Frequency (f)	Percentage (%)
Duration of metformin		
≤5 years	291	75.6
>5 years	94	24.4
Dose of Metformin		
≤1000mg/day	159	41.3
>1000mg/day	266	58.7
Dietary Habit		
Vegetarian	215	55.9
Non vegetarian	170	44.1

Our study shows that 78.2 % respondents had normal vitamin B12 and 21.8% had low vitamin B12 (Table 3).

Table 3: Level of vitamin B12 among respondents n=385

Variables	Frequency (f)	Percentage (%)
Low Vitamin B12	84	21.8
Normal Vitamin B12	301	78.2

Our study reveals that there was a significant association between the ages of respondents with low vitamin B12 in diabetic patients on metformin (OR=0.27, 95% CI =0.16-0.46) as shown in Table 4.

Table 4: Association between Level of Vitamin B12 and selected Sociodemographic Variables (n=385

Variables	Level of Vitamin B12		Chi square	p value	OR 95%CI
	Low	Normal			
Age					
≤50years	24 (6.2%)	178 (46.3%)	26.51	<0.001	0.27
>50years	60 (15.6%)	123 (31.9%)			(0.16-0.46)
Sex					
Male	39 (10.1%)	137 (35.6%)	0.22	0.882	1.03
Female	45 (11.7%)	164 (42.6%)			(0.63-1.68)
Educational Status					
Illiterate	33 (8.6%)	129 (33.5%)	0.334	0.558	0.86
Literate	51 (13.2%)	172 (44.7%)			(0.52-.41)
Marital Status					
Married	39 (10.1%)	166 (43.1%)	0.009	0.925	0.41
Single	45 (11.7%)	80 (20.8%)			(0.25-0.69)
Unmarried	20 (5.2%)	35 (9.1%)			

p value ≤0.05

In our study, we found statistically significant associations between being vegetarian (OR=6.93, 95%CI=3.97-12.12), the duration of metformin intake (OR=0.1495%CI= 0.08-0.24), and the dose of metformin (OR=0.26, 95%CI=0.15-0.44) among variables related to

diabetes mellitus and vitamin B12 deficiency. The association between these variables and vitamin B12 deficiency among study respondents is detailed in Table 5.

Table 5: Association between level of vitamin B12 with metformin intake and dietary habits n=385

Variables	Level of Vitamin B12		chi square	p value	OR 95%CI
	Low	Normal			
Dose of metformin					
≤1000mg/day	64 (16.6%)	95 (24.7%)	53.95	<0.001	6.93
>1000mg/day	20 (5.2%)	206 (53.5%)			(3.97-12.12)
Duration of metformin intake					
≤5years	36 (9.3%)	255 (66.3%)	57.90	<0.001	0.14
>5years	47 (12.2%)	47 (12.2%)			(0.08-0.24)
Dietary Habits					
Vegetarian	26 (6.7%)	189 (49.1%)	26.99	<0.001	0.26
Non Vegetarian	58 (15.1%)	112 (29.1%)			(0.15-0.44)

p value ≤0.05

Discussion

The findings of our study revealed a prevalence of vitamin B12 deficiency of 21.8% among Type II diabetes mellitus (T2DM) patients on long-term metformin therapy. This aligns with other research indicating a prevalence range of 6% to 30% for vitamin B12 deficiency in metformin users, varying based on demographic and methodological differences.[8] Notably, our study identified significant associations between vitamin B12 deficiency and factors such as age over 50 years, higher doses of metformin, longer duration of metformin use, and vegetarian dietary patterns.

Age was a significant factor, with respondents over 50 years showing a higher prevalence of vitamin B12 deficiency. This is consistent with previous studies suggesting that age-related physiological changes may contribute to decreased absorption and increased risk of deficiency.[9-10] Moreover, the association between higher metformin dosage and vitamin B12 deficiency underscores the impact of metformin on gastrointestinal absorption mechanisms. Our findings indicated that a daily dose of metformin over 1000 mg significantly increased the risk of deficiency, which concurs with earlier research highlighting the dose-dependent effect of metformin on vitamin B12 absorption.

Interestingly, our study also found that the duration of metformin use was significantly associated with vitamin B12 deficiency. This contrasts with some studies where duration was not a significant factor, suggesting that both dose and duration are critical in assessing the risk. Our results showed that patients on metformin for more than five years had a higher prevalence of deficiency, emphasizing the need for long-term monitoring.[11-12]

Dietary habits also played a crucial role in vitamin B12 status. Vegetarians in our study were more likely to be deficient, likely due to the lack of animal-based sources of vitamin B12 in their diet. This is consistent with other research indicating that dietary patterns significantly influence vitamin B12 levels.[13]

The clinical implications of vitamin B12 deficiency are significant, particularly concerning neuropathy and anemia. In our study, vitamin B12 deficiency was associated with higher rates of anemia, supporting the role of B12 in red blood cell synthesis. However, unlike some studies, we did not find a strong association between vitamin B12 deficiency and neuropathy after adjusting for confounding factors. This may be due to the difficulty in distinguishing between diabetic neuropathy and neuropathy caused by B12 deficiency.[14]

The mechanism by which metformin induces vitamin B12 deficiency is thought to involve interference with calcium-dependent membrane action responsible for vitamin B12 absorption in the ileum. Our study supports this hypothesis; as higher doses of metformin were linked to greater deficiencies. Although multivitamin supplementation appeared to mitigate the risk, our data was not detailed enough to confirm the specific impact of multivitamin use on B12 levels. Further research is needed to explore the potential benefits of supplementation in preventing metformin-induced B12 deficiency.[15]

This study's strength lies in its sizable sample of T2DM patients on metformin, providing robust data on the prevalence and risk factors of vitamin B12 deficiency in this population. Additionally, the study's inclusion of various

sociodemographic and clinical variables offers a comprehensive view of the factors influencing B12 status.

However, the study also had limitations. The cross-sectional design precludes causal inferences, and reliance on patient recall for metformin use duration may introduce recall bias. Additionally, the lack of detailed dietary intake data and the reliance on self-reported neuropathy symptoms without objective neurological assessments could affect the accuracy of our findings. Future studies should aim to address these limitations by incorporating longitudinal designs, detailed dietary assessments, and objective clinical evaluations.

Conclusion

The study revealed that prolonged and higher daily metformin intakes were risk factors for vitamin B12 deficiency. It highlighted gaps in identifying and treating B12 deficiency, often left undiagnosed, which can worsen diabetic neuropathy. Regular monthly B12 monitoring is essential for long-term, high-dose metformin users, with supplementation as a preventive or therapeutic measure to address this issue.

Recommendation

This study findings could be reinforced by replicating it with a larger sample size in diverse settings, ensuring the validity and broader applicability of the results. It's crucial to enhance health awareness initiatives and provide counseling for diabetic patients using metformin, aiding in better understanding and management of potential vitamin B12 deficiency issues.

Conflict of interest

The author declares no conflict of interest.

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References

1. Nandeshwar S, Jamra V, Pal D. Indian diabetes risk score for screening of undiagnosed diabetic subjects of Bhopal city. Natl J Community Med. 2010, 1:176-7. https://njcmindia.com/index.php/file/article/view/2025
2. World Health Organization. Non-communicable Diseases in the South East Asia Region, World Health Organization, Geneva, Switzerland, 2021.
3. Poudel RR. Diabetes and endocrinology in Nepal. Indian journal of endocrinology and metabolism.vol. 18,1 (2014): 118-9. DOI:10.4103/2230-8210.126593.
4. Chelsea B, Stahr CR, Singh V, Plomondon R, Anderson V, Rasouli N. Should metformin remain the first-line therapy for treatment of Type II diabetes? Ther Adv Endocrinol Metab. 2021 Jan 13;12:2042018820980225.. DOI:10.1177/2042018820980225
5. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. Food Nutr Bull. 2008, 29:S126-31. DOI:10.1177/15648265080292S117
6. Medical NewsToday. Vitamin B12 deficiency: Symptoms, complications, and more. 2023.https://www.medicalnewstoday.com/articles/172774.
7. American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care. 2017;42:S90–S102.
8. Yadav A, Jyoti S, Mehta RK, Parajuli SB. Vitamin B12 Deficiency among Metformin Treated Type II Diabetic Mellitus Patients Visiting the Department of Medicine of a Tertiary Care Centre. J Nepal Med Assoc 2023;61(266):861-3. DOI:10.31729/jnma.8340
9. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021;12(7):916-931. DOI:10.4239/wjd.v12.i7.916
10. Ts R, Ranganathan RS, Raja MS, Srivastav PSS. Prevalence of vitamin B12 deficiency in Type II diabetes mellitus patients on metformin therapy. Cur□us.2023.12;15(4):e37466. DOI: 10.7759/cureus.37466
11. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes study.Journal of Clinical Endocrinology and Metabolism/Journal of Clinical Endocrinology & Metabolism 2016 . 1;101(4):1754–61. DOI:https://doi.org/10.1210/jc.2015-3754
12. Raizada N, Jyotsna VP, Sreenivas V, Tandon N. Serum vitamin B12 levels in Type II diabetes patients on metformin compared to those never on metformin: A cross-sectional study. Indian Journal of Endocrinology

and Metabolism. 2017. 1;21(3):424. DOI: https://doi.org/10.4103/ijem.ijem_529_16
13. Verma VK, Nim RK, Singh PS, Kumar M. Vitamin b12 deficiency among vegetarian and non vegetarian iabetic population receving prolonged metformin based oral hypoglycemic agents therapy. Int J Adv Med. 2017 Aug; 4(4): 1150-1154. DOI: https://doi.org/10.18203/2349-3933.ijam20173249
14. Miyan Z, Waris N, MIBD. Association of vitamin B_{12} deficiency in people with Type II diabetes on metformin and without metformin: a multicenter study, Karachi, Pakistan. BMJ open diabetes research & care. 2020; *8*(1), e001151. DOI: https://doi.org/10.1136/bmjdrc-2019-001151
15. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012;35(2):327-333. DOI: 10.2337/dc11-1582