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Comparison of Vitamin B12 Deficiency Among Diabetics with Peripheral Neuropathy Taking Metformin Versus Non-Metformin Therapies

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ABSTRACT

Objectives: 1). To assess the frequency of low vitamin B12 levels in diabetics having peripheral neuropathy 2). To compare frequency of vitamin B12 deficiency among diabetics with peripheral neuropathy who are taking metformin Vs non-metformin therapies.

Methodology: This descriptive, cross-sectional study was conducted in the Medicine department POF hospital Wah, Pakistan from 1st march 2023 to 31st August 2023. A total number of 215 patients with diabetes mellitus aged 12-70 years of either gender who fulfilled the selection criteria were selected. The data was filled on the Proforma. Serum vitamin B12 was calculated by chemiluminescence immunoassay in the POF hospital laboratory

Results: Frequency of vitamin B-12 deficiency among diabetics presenting with peripheral neuropathy was 11.63%(n=25). Vitamin B-12 deficiency among diabetics on metformin was n=18(13.95%) and among diabetics on non-metformin therapy was n=07(8.14%). The p value was calculated that was 0.193, therefore statistically insignificant.

Conclusion: No significant difference in vitamin B12 levels was observed between diabetics on metformin and those on non-metformin therapies, suggesting that diabetic neuropathy itself is the primary contributor to peripheral neuropathy in these patients.

Keywords: Diabetes mellitus, Metformin, Vitamin B12 deficiency

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

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Introduction

The number of diabetic patients has rapidly increased worldwide from approximately 150 million in the year 1990 to more than 200 million in the year 2022 and this increase is more in those countries with low or poor socioeconomic status.[1] According to the region wise statistical data revealed by IDF Diabetes atlas 2021, China ranks first worldwide and has the topmost number of diabetes cases with approximately more than 140 million patients with diabetes. The second highest number of cases are from India who is in the first position from South east Asia having more than 70 million patients with diabetes. Pakistan stands at third position with 33 million diabetics, whereas United

States of America has approximately more than 30 million diabetes cases.[2] The comparative diabetes prevalence rate in 2021 was highest in Pakistan which is alarming situation and indicates that we need to review our management strategies.[3] Peripheral neuropathy is among the frequently observed complications of diabetes. In a meta-analysis conducted by Sohail et al prevalence of peripheral neuropathy due to diabetes in Pakistan was about 43.16%.[4] Risk factors for development of neuropathy include duration of diabetes, HBA1c level, smoking, alcohol abuse and old age.[5] The pathophysiological basis of neuropathy in diabetics is multi factorial with involvement of genetic factors, lipids metabolism, formation of advanced glycosylation end products (AGEs), these disturbances occurred because of vasculopathy involving both the micro and macro-vessels in diabetic patients.[5] The prolonged use of metformin, which is most widely used drug has been associated with vitamin B12 deficiency.[6] Though the exact mechanism is not fully understood. Among the several mechanisms considered include impaired B12 absorption, delayed small bowel motility, bacterial over growth.[6] A study in South Africa found that approximately 28% of patients on metformin therapy revealed vitamin B12 deficiency[7]. Metformin users show lower median serum vitamin B12 levels than non-users.[7] Another observational research, including over 162 patients revealed reduced B12 levels in 7.3% (95% CI: 4.0–12%) among diabetics presenting with peripheral neuropathy.[8] Liver has sufficient B12 stores that may take years to get depleted, B12 levels start to fall by 4 months of initiation of metformin therapy, though the symptomatology takes as long as 3-5 years due to the significant body storage but this may be affected by the metformin dose using and the elderly age.[9] This study was carried out with an aim to determine the frequency of low vitamin B12 or its deficiency among diabetics on Metformin therapy who present with peripheral neuropathy at POF Hospital Wah Cantt, Pakistan, so that it would be helpful to assess, whether most of neuropathy in diabetics is because of diabetic neuropathy itself or because of reduced levels of vitamin b12 particularly in Pakistani population.

Methodology

This descriptive cross-sectional study was conducted in the Department of Medicine, POF Hospital Wah, from 1st March to 31st August 2023. A total of 215 diabetic patients, aged 12–70 years, with clinical features of neuropathy and previously normal vitamin B12 levels were included using a WHO sample size calculator (confidence interval: 95%; power: 80%; significance level: 5%; expected prevalence: 7.3%; margin of error: 3.5%). Non-probability consecutive sampling was employed. Exclusion criteria were liver disease, malabsorption, and prior vitamin B12 deficiency. Data were recorded on a structured proforma. Serum vitamin B12 levels were measured using chemiluminescence immunoassay at the hospital laboratory, and results were verified by a pathologist. Qualitative variables (e.g., gender, vitamin B12 deficiency, drug therapy) were expressed as frequencies and percentages, while quantitative variables (e.g., age, duration of diabetes) were summarized as means with standard deviations. Effect modifiers such as age, sex, and duration of diabetes were controlled through stratification. Post-stratification, chi-square test was applied, with $p < 0.05$ considered statistically significant.

Ethical approval for the study was obtained from the institutional review board of POF Hospital, Wah Medical College, NUMS (IRB/POFH/02-2023/MED/11) on 08-02-2023.

Results

Of the 215 participants, 127(59.07%) were male and 88(40.93%) were females. The average length or duration of diabetes mellitus was 7.80 ± 3.22 years.

Table I: Comparison of the frequency of low B12 levels in diabetics taking metformin Vs non-metformin-based therapies			
Drug Therapy	**Vitamin B12 deficiency**		**P-value**
	Present	**Absent**	
Metformin (n=129)	18(13.95%)	111(86.05%)	**0.193**
Non-metformin (n=86)	07(8.14%)	79(91.86%)	

Table II: Low B12 levels related to age, gender and duration of diabetes			
Age groups	**Low Vitamin B12 levels**		**P-value**
	Present n (%)	**Absent n (%)**	
12-45	12(13.04)	80(86.96)	**0.576**
46-70	13(10.57)	110(9.43)	
Gender			**O.444**
Male	13(10.24)	114(89.76)	
Female	12(13.64)	76(86.36)	
Duration of Diabetes			**0.804**
≤10 years	19(11.95)	149(88.05)	
>10 years	06(10.91)	50(89.09)	

The overall frequency of vitamin B-12 deficiency among diabetics presenting with peripheral neuropathy was 11.63% (n=25). Vitamin B-12 deficiency among diabetics on metformin was 13.95%(n=18) and among diabetics on non-metformin therapy was 8.14%(n=7) as highlighted in table 1. Stratification of low levels of vitamin b12 with respect to age, gender and duration of diabetes have been highlighted in table 2. Our results showed that 18 patients (13.95%) who were on metformin showed low vitamin b12 levels, whereas 07 patients (8.14 %) of those with non-metformin-based treatment also had vitamin B12 deficiency with p value of 0.193, that was not statistically significant. We also found no statistical difference with respect tsso the factors like age, gender and duration of diabetes.

Discussion

Metformin is the most widely prescribed oral drug for type 2 diabetes due to its efficacy and low risk of hypoglycemia.[10] While generally well tolerated, gastrointestinal side effects such as abdominal discomfort and diarrhea are common but usually self-limiting. Long-term use of metformin, however, has been consistently associated with reduced serum vitamin B12 levels. This effect is believed to result from impaired calcium-dependent absorption and dose- and durationdependent effects.[11]

Use of metformin for longer duration has been found to be linked with low vitamin B12 levels or deficiency of this important vitamin in the body likely related to the impairment in the calcium-dependent absorption of vitamin B12.[12] There is negative or inverse relationship between the levels of vitamin B12 with dose and length of metformin use.[12,13] Our study showed that there was no significant difference in vitamin B-12 deficiency among diabetics on metformin and non-metformin therapy. A multi-center cross-sectional study at Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, Karachi, Pakistan revealed that vitamin B12 insufficiency was more frequent in the non-metformin group than the metformin group.[14] This alarming finding of inadequate vitamin B12 levels in Pakistani population could be due to lack of a balanced diet and eating habits. The low vitamin B12 levels may not be clinically apparent or undetectable unless symptoms develop and the patient seeks medical care for evaluation. The low vitamin B12 levels or the deficiency of this vitamin was found to be more pronounced in those patients who were on metformin therapy which highlights the fact that metformin use can make the underlying vitamin B12 worse which may cause symptoms and complications.[15] Review of literature showed that use of metformin for longer duration is linked with low B12 levels.[16,17] Serum vitamin B12 levels should be monitored in people taking metformin for longer duration.[18] A very high prevalence of low vitamin

B12 or deficiency of this vitamin has been observed in various studies.[19,20] In a study from Pakistan, Vitamin B12 deficiency was quite high among diabetics particularly those taking Metformin and they suggested that supplementation may improve the outcomes as well whereas our study showed no significant difference in metformin Vs non metformin groups hence we need further studies with larger sample size and participants from all over the country to see such co relation and effects of vitamin B12 supplementation in diabetics prior to and after starting metformin treatment.[21]

One limitation of our study was its single-center design which may limit generalizability. Larger multi-center studies across Pakistan are needed to clarify the association between metformin use and vitamin B12 deficiency and to evaluate the potential benefits of supplementation.

Conclusion

This study did not demonstrate a significant difference in vitamin B12 deficiency between diabetic patients with peripheral neuropathy on metformin versus non-metformin therapies. Future large-scale, multi-center studies are recommended to further explore this relationship and to assess the role of vitamin B12 supplementation in improving outcomes.

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