ORIGINAL ARTICLE

Vitamin B12 Deficiency in Relation to Metformin Use in Adults with Type-2 Diabetes Mellitus

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ABSTRACT

Objective: To find the correlation between serum vitamin B12 levels in metformin users among type-2 diabetics.

Study Design: Cross-sectional Study.

Place and Duration of Study: The study was carried out at the Department of Medicine of Combined Military Hospital, Peshawar, Pakistan from April 2021 to September 2021.

Materials and Methods: Using a consecutive sampling technique, patients were selected from both outdoor and indoor medical health facility Blood tests were performed on all patients and serum vitamin B12 level was assessed, a level less than 200 pg/ml was considered deficient. The comparison was made among patients taking metformin and those not on metformin.

Results: 148 patients were enrolled, consisting of an equal proportion of cases and controls i.e. 74 patients in each group, with a mean age of 44.09± 10.61 and 46.15± 10.64 respectively. Vitamin B12 deficiency was found more in metformin user group 34 (45.94%) than in patients not on metformin 11 (14.86%) (p<0.001). The odd ratio was 4.87 (95% CI is 2.22 – 10.69).

Conclusion: Metformin users taking at least 1000mg daily of minimum one-year duration experienced significant reductions in blood vitamin B12 levels as compared to patients not using metformin. A serum vitamin B12 test needs to be performed on regular basis after every three months in type-2 diabetic patients taking metformin of more than 1 gram daily for more than a year.

Keywords: *Metformin Users, Type- 2 Diabetes Mellitus, Vitamin B12 Deficiency.*

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Introduction

Diabetes is a globally widespread disease with more than 400 million affected populations and >700 million people are expected to be affected up to 2045.[1] World Health Organization assigned that in 2016, about 422 million adults (age 18 years and above) were suffering from type-2 diabetes mellitus.[2] In Pakistan, the prevalence of diabetes mellitus is around 17%.[3] According to American Diabetes Association (ADA) guidelines, for the treatment of type-2 diabetes mellitus (T2DM) Metformin is taken as a first-line drug and is also used in the treatment of pre-diabetes, other insulin resistance diseases (like metabolic syndrome) and polycystic ovarian syndrome.[4] Furthermore, metformin demonstrates vessel safety and potential vessel benefits.[5] However, metformin use may increase the risk of deficiency of vitamin B12 in diabetic patients; figures 5.8% to 52% have been reported previously.[6,7]

Vitamin B12 deficiency could have serious consequences. It could lead to or aggravate peripheral neuropathy in case the deficiency is not corrected promptly.[8] Moreover, depression and cognitive impairment had found a link with a deficiency of vitamin B12.[9] As pernicious anaemia

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and gastric atrophy prevalence has increased, the risk of vitamin B12 deficiency is more prominent in elder patients, which decreases the capacity of food protein to release vitamin B12 which is required for absorption.[10]

There have been few studies on the deficiency of vitamin B12 in type-2 diabetics using metformin supplementation. The purpose of the current study was to determine the incidence of low serum vitamin B12 levels in type-2 diabetics who were taking metformin for a prolonged duration without using any other oral hypoglycemic drug or insulin for their diabetic control and compare it with those T2DM who do not use metformin for their diabetic control in patients having age ≥ 18 years. This will help us detect vitamin B12 deficiency and prevent complications of vitamin B12 deficiency especially peripheral neuropathy, by timely initiation of treatment.

Materials and Methods

This cross-sectional study was carried out at the Department of Medicine, Combined Military Hospital Peshawar, Pakistan from April 2021 to Sep 2021 after obtaining ethical approval from the Ethical Committee of Combined Military Hospital Peshawar, Pakistan vide reference number 19. Patients between ages 18 to 60 years, having type-2 diabetes mellitus, on metformin > 1gram daily for more than a year (total duration of study was six months), those with oral consent were enrolled in the study, While those not giving oral consent, having age <18 years and >60 years, type-1 diabetes mellitus, using any other oral hypoglycemic drug or insulin along with metformin, using vitamin B12 supplements and multivitamins, having pernicious anaemia, also patients with iron deficiency anaemia, on thyroxin treatment, malnourished, strict vegetarians, family history of vitamin B12 deficiency, ovarian primary failure, malabsorption such as inflammatory bowel disease, arterial disease, and other causes of neuropathy, previously operated for bariatric surgery, on vitamin D supplementation, using proton-pump inhibitors (PPI) within pregnancy were not included in the study. Patients were divided into metformin users) and non-users. Informed oral consent and short history from each individual were taken. Demographic and other details such as age, gender, diabetes, metformin medication usage duration and average daily dose were recorded. Three milliliters of blood was collected in gel and clot activator tubes. Roche Diagnostic Cobas e411 Immunoassay System was used for analyzing vitamin B12 levels. Levels <200 pg/mL were considered deficient.[11]

Statistical Analysis

For sample size calculation free statistic calculator version 4.0 was used. The total sample size required was 148 using alpha 0.05, beta 0.2, power 0.8 and anticipated incidence of vitamin B12 deficiency 40% in group A (metformin users) and 20% in group B (non- metformin users) (p= 0.001).[12] Data was analyzed using the Statistical Package for Social Sciences (SPSS V.20). Mean age, mean Vitamin B12 levels and vitamin B12 deficiency was calculated in the both groups. Odds ratio with 95% confidence interval was calculated. Chi-square test was applied to check for association between Metformin use and vitamin B12 in type-2 diabetic patients. *P* value of less than 0.05 was considered significant.

Results

There were 148 patients in this study, equally divided between the two groups. The mean age was 45.12 ±10.64 years. The two groups were matched with regard to age. There were 34 patients with lower vitamin B12 levels in user group compared to 11 in non-user group (p<0.001). Mean vitamin b12 levels were 218 ±375 pg/ml and 381.50 ±121.5 pg/ml in users and non-users group respectively. Vitamin B12 levels were significantly low in metformin users (p=0.003), table 1. The odds of low vitamin B12 in metformin users were 4.87 (2.2-10.6) compared to other group (CI: 95%).

Table 1: Comparison of age and Vitamin B12 deficiency in both groups

Variable	Metformin Users	Non-Metformin Users (mean ±SD)	*P*- Value
Age (Years)	44.09± 10.61	46.15± 10.64	0.241
Vitamin 12 levels (pg/ml)	218.00 ± 375 -	381.50 ± 121.5 -	0.003
Vitamin B12 deficiency	34 (45.94%)	11(14.86%)	<0.001

Discussion

This study found that type-2 diabetics (T2DM) with at least 1000 mg daily metformin of minimum one-year duration experienced significantly lower serum vitamin B12 levels. These results are the same as

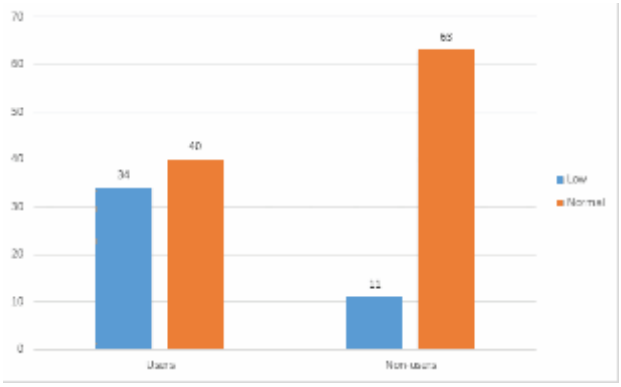

Fig 1: vitamin B12 status among metformin users and non-metformin users

indicated in a study done in 2020 by the American Diabetes Association (ADA) which states that T2DM patients treated with metformin had a higher prevalence of low serum vitamin B12 levels.[13] In contrast, non-users showed significantly higher levels of B12 deficiency than metformin users. Raizada et al. showed that patients with lower vitamin B12 levels had higher VPT and DN4 scores in metformin-users.[14] Reversal of neuropathy has been demonstrated in a study by Miyan et al.[15]

Lower serum vitamin B12 levels in metformin-users is caused by malabsorption such as bacterial overgrowth in the small bowel, intrinsic secretions, calcium levels, and bile acid metabolism which absorbs vitamin B12 in the terminal ileum.[16] Lower serum vitamin B12 levels have been associated with the duration of metformin use.[17] However, Ahmed et al. found no link between the two.[18] In the present study, 34 (45.84%) metformin users had lower serum vitamin B12 levels compared to non-users 11 (14.86%). These findings are consistent with the results published by Olt S et al. who found 38.4% metformin users had lower serum vitamin B12 levels. Besides, they found no link of metformin-associated neuropathy in these patients. Results published by Basit et al. earlier reported positive relation among the two.[17,19]

A substantial relationship has been reported between lower serum vitamin B12 levels in metformin users and parameters such as age, BMI, marital status, gender, and blood pressure.[19] Age has been reported with no significant association with serum vitamin B12 levels by Alharbi et al.[20]

Metformin dose and duration of use have been reported as the prominent risk factor for lower serum vitamin B12 levels.[21] Despite the fact that neuropathy caused by B12 deficiency of metformin-induced has been reported, the pivotal associations are still unknown.[22] There were no differences in neuropathy rate between normal and subnormal B12 groups. Previous research has linked the diabetic neuropathy diagnosis to B12 lower levels.[23] A detailed investigation on monitoring neuropathy and its causes in the diabetic patients should be carried out because early detection and treatment improves prognosis.[24]

Our results are interpreted with caution but still, there are some limitations in our study. One limitation is we have included a minimum number of patients required for our study. Secondly, we collected our data in a single setup; these two limitations make our study unable to apply to the general population. So, a large sample size and data collected from different regions of the country is required. Third, our study is data base so cause and effect relationships are difficult to determine. Fourth, follow-up are not done for the replacement of vitamin B12. A thorough follow-up should be done, which can help us determining of dose and duration required for the replacement of vitamin B12 deficiency. Fifth, Co-morbid can also act as a confounding factor in the determination of vitamin B12 levels in diabetic patients but in our study, we did not segregate patients on basis of co-morbid. Sixth, in this study, we do not measure levels of methylmalonic acid, which can help us in determination of vitamin B_{12} deficiency during their asymptomatic period. Further studies should be done to get better data about vitamin B_{12} deficiency causes and its replacement.

Conclusion

Type-2 diabetes mellitus patients taking a daily dose of metformin > 1 gram for more than a year, have lower levels of vitamin B12 levels than non-metformin users. Type-2 diabetic patients using > 1gram metformin daily for more than a year should check their serum vitamin B12 levels after every three months.

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