

ORIGINAL ARTICLE

ASSOCIATION OF VITAMIN B12 DEFICIENCY WITH INTAKE OF ORAL METFORMIN IN DIABETIC PATIENTS

Najam Ul Hasan, Mujeeb Ullah Makki*, Izza Abid, Mujeeb Ur Rehman Abid Butt

Medicine Department, Shalamar Hospital Lahore, *Medicine Department, Services Hospital Lahore-Pakistan

Background: It is estimated that 450 million people worldwide have diabetes mellitus. Objective of the study was to determine effect of Metformin on vitamin B12 level among patients with type 2 diabetes mellitus. It is a cross sectional study conducted at Medicine department, Shalamar Hospital Lahore. **Methods:** Seventy-two patients of diabetes mellitus were included in the study. All patients who could have any other disease process that can lead to Vitamin B12 deficiency were excluded from the study. They were segregated into two groups, first one was getting metformin for the last 2 years and the second group was not taking metformin. Vitamin B12 levels were checked in all the patients and value of 150 pmol/L was taken as normal. **Results:** Out of 72 patients who participated in our study, 40 patients (55.5%) were taking metformin for more than two years while 32 patients (44.5%) were not taking metformin for the last two years. Mean age of patients taking metformin and not taking metformin was 59±9.12 years and 60±5.47 years respectively. Mean vitamin B12 level was 360±185.2 pg/ml in patients taking metformin while among non-metformin group mean vitamin B12 level was 619±176 pg/ml (p value=0.0001). Furthermore, HbA1c and MCV were significantly different among metformin group and non-metformin group, i.e., $p=0.034$ and 0.039 respectively. Among metformin group, age and MCV were also significantly different in those having vitamin B12 deficiency and those having normal Vitamin B12 levels, i.e., $p=0.042$ and 0.001 respectively. **Conclusion:** It was concluded from our study that long term (>2 years) use of metformin is significantly associated with vitamin B12 deficiency.

Keywords: Metformin; Vitamin B12, Diabetes, HbA1c

Citation: Hasan N, Makki MU, Abid I, Butt MRA. Association of vitamin B12 deficiency with intake of oral metformin in diabetic patients. J Ayub Med Coll Abbottabad 2019;31(1):72-5.

INTRODUCTION

Diabetes Mellitus is an important health problem worldwide. It is considered to be sixth leading cause of death in USA.¹ It is prevalent throughout the world and its prevalence varies differently in different age groups. It is estimated that 450 million people worldwide have diabetes mellitus and out of these, 35.4 million people are from middle-east and North Africa region.² In Pakistan it was estimated that prevalence of diabetes was 10.6% in urban 7.7% in rural population.³ According to International diabetes federation this figure has reached 7 million in 2015. Metformin is a widely used drug in the management of type-II diabetes and is recommended as first choice for its treatment. It is relatively well tolerated by the patients, so patients continue to use it for a long period of time. Metformin is known to cause dyspepsia and lactic acidosis among patients with chronic kidney disease.⁴ Vitamin B12 deficiency has also been reported in number of studies but there is a wide variation among the values of vitamin B12 among different ethnic groups.⁵⁻⁷

This study was carried out to investigate the frequency of vitamin B12 deficiency in diabetic patients taking metformin. Furthermore, if significant

vitamin B12 deficiency is noted with metformin, then guidelines have to be formulated for proper follow up of patients taking metformin so that vitamin B12 replacements can be made early to avoid its deficiency. The objective of the study was to see the effect of metformin on vitamin B12 level among patients with type 2 diabetes mellitus.

MATERIAL AND METHODS

This was observational cross-sectional study. Patients of diabetes mellitus, whether taking metformin or not, who presented to Medical Outdoor department of Shalamar Hospital Lahore were informed about the study. Sampling technique was non-probability convenience. Patients of age 30-70 already diagnosed with type II diabetes mellitus that were willing to participate in study were included. Informed consent was taken from each patient. Patients were included in metformin group if they have been taking metformin since for 2 years. Patients who had not taken metformin for 2 years were included in non-metformin group. Patients with history of any type of anaemia, alcohol intake, renal insufficiency, prior gastric surgery, patients on current parenteral or enteral nutritional support, prior transfusion and

thyroid illness, patients of malabsorption syndrome, patients using vitamin supplements especially B12 or proton pump inhibitors and who are vegetarians as assessed on history or previous record were excluded. Patients with any neoplastic disorder or unstable cardiopulmonary, neurological or psychiatric diseases as assessed on history, clinical examination or previous medical records were also excluded from the study.

Data was collected at Medical OPD Shalamar Hospital Lahore after taking prior institutional review board approval. Serum vitamin B12 levels were sent to Shalamar Hospital laboratory along-with other tests. Serum vitamin B 12 levels were measured by Chemiluminescence Technique using Abbot Architect 1000 SR 239-930. Patients were requested to follow after vitamin B12 levels. Serum B 12 levels were noted along with other laboratory results on predesigned proforma. Patients with vitamin B12 levels <220 pmol/l were labelled as vitamin B12 deficient whereas vitamin B12 levels >220 pmol/l were considered as normal. All the data collected was analysed in a computer-based program SPSS-21 and different tables, results and calculations were made accordingly. Descriptive statistics were applied to summarize the data. Mean and standard deviation (\pm SD) was calculated for all the quantitative variables, i.e., age, duration of metformin use and serum vitamin B12 levels. One-way ANOVA test was applied to compare the means among different groups. Chi square test was applied to determine the significant association between different variables by keeping p -value <0.05 as significant.

RESULTS

Total seventy-two (72) patients who fulfilled the criteria were included in this study. Forty patients (55.5%) were taking metformin for more than two

years while thirty-two patients (44.5%) were not taking metformin in the last 2 years. Mean age of patients taking metformin and not taking metformin was 59 ± 9.12 and 60 ± 5.47 respectively. Regarding gender distribution, 45% of the patients taking metformin were male while 65% of control group were males. Mean duration of diabetes was 7 years among metformin and 7.6 years among non-metformin group. It was noticed that there was statistically significant difference in serum vitamin B12 levels and MCV among two groups. In metformin group, mean vitamin B12 level was 360 ± 185.2 while among non-metformin group, mean vitamin B12 level was 619 ± 176 (p -value <0.0001). Mean MCV level among metformin and non-metformin group was 80.19 ± 7.01 and 76.6 ± 7.47 respectively (p -value=0.039). In addition to that statistically significant difference was found for HbA1C among two groups (p -value=0.034). There was no significant difference for duration of disease and serum creatinine levels among two groups (p -value= 0.395 and 0.109 respectively). Details of patients among the two groups are shown in table-1.

When we stratified our data for normal and low Vitamin B12 levels among metformin group, it was seen that 11 (27.5%) patients had vitamin B12 deficiency (Table-2). There was significant difference between ages of vitamin B12 deficient group and normal vitamin B 12 group, i.e., vitamin B12 deficiency was common among elderly patients (p -value=0.042). Among metformin patients, mean MCV was different for normal and vitamin B12 deficient patients (p =0.001). There was no statistically significant correlation for duration of disease, HbA1C, and serum creatinine levels among two groups.

Table-1: Demographic characteristics of study group

	Patients on Metformin (n=40)	Patients not on Metformin (n=32)	p -value
No. of patients (%)	40 (55.5%)	32 (44.5%)	
Age	56 (± 9.12)	60 (± 5.47)	0.49
Duration of Disease	7 (± 3.54)	8 (± 4.7)	0.395
Vitamin B12 Level	360.3 (± 185.2)	619.4 (± 176)	0.0001
HbA1C Level	8.9 (± 1.31)	8.3 (± 0.99)	0.034
MCV (fL)	80.19 (± 7.01)	76.6 (± 7.47)	0.039
S. Creatinine (mg/dl)	0.96 (± 0.01)	0.99 (± 0.06)	0.109

Table-2: Demographic characteristics of patient on metformin

	Normal >200 pmol/L (Mean \pm SD)	Deficient (< 200 pmol/L) (Mean \pm SD)	p -value
No. of patients (%)	29 (72.5%)	11 (27.5%)	
Age (years)	54 (± 9.83)	61 (± 9.11)	0.042
Duration of Disease (years)	6.5 (± 3.5)	7.64 (± 3.64)	0.379
HbA1c (%)	9 (± 1.44)	8.8 (± 0.94)	0.672
MCV (fL)	77.6 (± 4.6)	87.7 (± 6.8)	0.001
S. Creatinine (mg/dl)	0.97 (± 0.25)	0.95 (± 0.21)	0.818

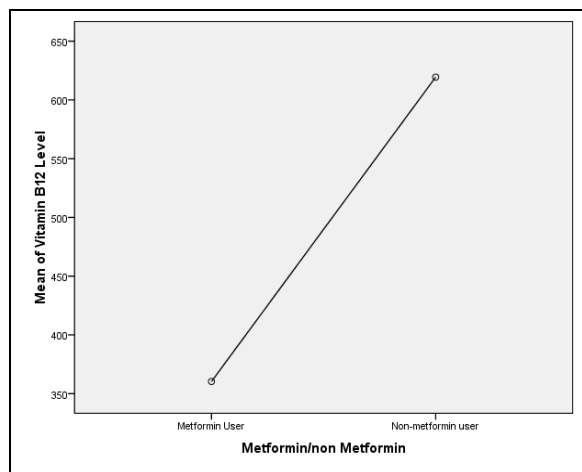


Figure-1: One Way ANOVA plot for mean Vitamin B12 levels among Metformin Vs Non-Metformin Groups showing reduced levels of Vitamin B12 among patients with Metformin usage.

DISCUSSION

One of the potential side effects of long-term metformin usage is vitamin B12 deficiency. Present study was conducted to assess the prevalence of vitamin B12 deficiency in patients of diabetes mellitus taking metformin as compared to patients not taking metformin. From our results, it can be seen that vitamin B12 deficiency was observed among 27.5% patients who were taking metformin. Similar results were seen in a study conducted by Iftikhar *et al* which revealed that 31% of patients taking metformin at least for 3 months had Vit B12 deficiency.⁶ Study conducted in Irish population showed similar results as 31% patients taking metformin for diabetes were having vitamin B12 deficiency while 9% patients who were not taking metformin also had vitamin B12 deficiency.⁷ Another study, conducted by Ahmad *et al*, found vitamin B12 deficiency in 38.1% of the patients taking metformin⁸. A similar study conducted by Nervo *et al* found 36.8 % patients had vitamin B12 level between 125–250 pg/ml (possibly low vitamin B12 levels).⁹

Some studies have different results for vitamin B12 deficiency in patients on metformin. For example, Filioussi *et al* detected megaloblastic anaemia secondary to B12 deficiency among 9% of the patients treated with biguanides for up to 11.8 years and all responded very well once cyanocobalamin was instituted.¹⁰ In another study conducted by de Groot-Kamphuis in Netherland, vitamin B12 deficiency was presented in 9.7% of patients on metformin compared to 4.4% of patients not taking metformin.¹¹ The reason for the difference in these results were due to different definition of cut-off value for vitamin B12 deficiency. In study conducted by de-Groot, vitamin B12 deficiency was defined as levels <150 pmol/l. On the other hand, vitamin B12 deficiency was defined as levels <220 pmol/L in our study.

Considering <220 pmol/l as low vitamin B12 level is important because it helps in prompt diagnosis followed by vitamin B12 replacement to avoid neurological complication associated with its deficiency. In our study, duration of diabetes had negative correlation with vitamin B12 deficiency ($p=0.395$). Similar results were obtained in other studies. For example, one study conducted Sun-Hye *et al* at Korea showed that diabetes duration did not affect vitamin B12 deficiency in metformin patients ($p=0.671$).⁵

This study showed that vitamin B12 deficiency was more common in elderly people as compared to younger diabetic patients ($p=0.042$). Other studies by Marwan *et al* and Kang *et al* also showed similar positive correlation between increasing age and vitamin B12 deficiency.^{8,12} The possible reason for this correlation might be due to lack of balanced diet in elderly patients as compared to younger age group. In this study, no significant correlation was found between vitamin B12 deficiency and HbA1C ($p=0.672$). In a study conducted by Khan *et al*, high HbA1C was not associated with vitamin B12 deficiency ($p=0.31$).¹³ Other studies by Sun-Hy *et al* and Liu *et al* also could not find any association between vitamin B12 deficiency and HbA1C.^{5,14}

CONCLUSION

It was concluded that long term use of metformin is significantly associated with vitamin B12 deficiency. So, treating physicians must do annual surveillance for all patients who are taking metformin for more than two years by laboratory testing of vitamin B12 and treat early if patient is found to be vitamin B12 deficient.

AUTHORS' CONTRIBUTION

Mujeeb Ur Rehman Abid Butt designed the study, supervised the write up of the study with substantial input in its improvement. Najam Ul Hasan and Izza Abid carried out data collection. Mujeeb Ullah Makki was involved in data analysis and drafting of manuscript.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes 2010. *Diabetes Care* 2010;33(Suppl 1):11–61.
2. IDF Diabetes Atlas Update Poster, 7th ed. International Diabetes Federation, Brussels, Belgium; 2015.
3. Shera AS, Jawad F, Maqsood A. Prevalence of diabetes in Pakistan. *Diabetes Res Clin Pract* 2007;76(2):219–22.
4. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism* 2016;65(2):20–9.
5. Ko SH, Ko SH, Ahn YB, Song KH, Han KD, Park YM, *et al*. Association of Vitamin B12 Deficiency and Metformin Use in Patients with Type 2 Diabetes. *J Korean Med Sci* 2014;29(7):965–72.
6. Iftikhar R, Kamran SM, Qadir A, Iqbal Z, Usman HB. Prevalence of Vitamin B12 deficiency in patients of type 2

- diabetes mellitus on metformin: a case control study from Pakistan. *Pan Afr Med J* 2013;16:67.
7. Marar O, Senturk S, Agha A, Thompson C, Smith D. Prevalence of Vitamin B12 deficiency in patients with type 2 diabetes mellitus on metformin. *Royal Coll Surg Ireland Stud Med J* 2011;4(1):16–20.
 8. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. *BMC Pharmacol Toxicol* 2016;17(1):44.
 9. Nervo M, Lubini A, Raimundo FV, Faulhaber GA, Leite C, Fischer LM, *et al.* Vitamin B12 in metformin treated diabetic patients, a cross-sectional study in Brazil. *Rev Assoc Med Bras (1992)* 2011;57(1):46–9.
 10. Filioussi K, Bonvoas S, Katsaros T. Should we screen diabetes patients using biguanides for megaloblastic anaemia. *Aust Fam Physician* 2003;32(5):383–4.
 11. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling ST, Bilo HJ, Kleefstra N. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. *Neth J Med* 2013;71(7):386–90.
 12. Kang D, Yun JS, Ko SH, Lim TS, Ahn YB, Park YM, *et al.* Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: a cross-sectional study. *PLoS One* 2014;9(10):e109878.
 13. Khan A, Shafiq I, Shah MH. Prevalence of Vitamin B12 Deficiency in Patients with Type II Diabetes Mellitus on Metformin: A Study from Khyber Pakhtunkhwa. *Cureus* 2017;9(8):e1577.
 14. Liu KW, Dai DLK, Lau E, Woo J. Metformin-associated vitamin B12 deficiency in the elderly. *Asian J Gerontol Geriatr* 2011;6(2):82–7.

Submitted: 19 November, 2017

Revised: 4 May, 2018

Accepted: 19 June, 2018

Address for Correspondence:

Mujeeb Ullah Makki, Medicine Department, Services Hospital Lahore-Pakistan

Email: mujeebmakki@hotmail.com