

Metformin Use and Vitamin B₁₂ Deficiency in Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Aim: To determine any the association between metformin use and vitamin B12 deficiency.

Study Design: A cross sectional study.

Methods: Sixty patients of diabetes mellitus were enrolled. Patients were divided in two groups, Group-I was on metformin for diabetes mellitus while group-II was not on metformin. Vit B12 levels were checked in all the patients and value of <150pmol/L was taken as vitamin B12 Deficiency. Data was analyzed using SPSS 21.

Results: Out of sixty (60) patients, thirty two (53.3%) patients were taking metformin while 28 patients (47.7%) were not taking metformin. Patients mean age was 58±8 years (57 for metformin and 59 for non-metformin group). Serum vitamin B12 level mean was 424±158 pg/ml in metformin group while it was 619±177pg/ml in non-metformin group P value 0.0001 (significant). On further analysis, it was seen that patient age, duration of disease, MCV level, HbA1c level was not significantly associated with vitamin B 12 deficiency. **Conclusion:** We concluded from our study that metformin is associated with vitamin B12 deficiency in type-II diabetic patients.

Keywords: Type 2 Diabetes mellitus, metformin, vit. B12 deficiency, metformin

INTRODUCTION

Diabetes Mellitus (DM) is one of the leading cause of morbidity and mortality worldwide. According to American Diabetes Association (ADF), it is sixth leading cause of death worldwide¹. According to International Diabetes Federation (IDF) and World Health Organization (WHO), 422 million people were diagnosed with diabetes mellitus in 2014 as compared to 108 million people in 1980. Diabetes mellitus is very prevalent in Pakistan as well and according to one study conducted by Shera et al., it has been estimated that 10.6% of urban population and 7.7% of rural population of Pakistan is suffering from diabetes mellitus². Type-II diabetes is due to either insulin resistance or relative deficiency of insulin. There are various treatment options for type-II DM. Metformin is a preferred hypoglycemic drug used for treatment on DM type-II along-with life style modifications³⁻⁴. There are various side effects of metformin like lactic acidosis, abdominal distress and diarrhea. In addition to that, use of metformin has also been associated with serum vitamin B12 deficiency in various studies. According to one study conducted by Pflipson et al., serum vitamin B12 deficiency was found to be 22% in type-II diabetic patients who were on metformin⁵.

Diabetes mellitus causes many microvascular and microvascular complications including peripheral neuropathy, nephropathy, retinopathy

etc. Serum vitamin B-12 deficiency also causes peripheral neuropathy. Neuropathy resulting as complication of diabetes may be worsened and masked by vitamin B12 deficiency induced neuropathy. So it is important to investigate the serum vitamin B12 levels in patients of diabetes type-II who are using metformin. As a result, if vitamin B 12 deficiency found in patients on metformin, replacement of vitamin B12 or withdrawal of metformin will result in improvement of patients.

Purpose of this study was to investigate vitamin B 12 levels in diabetes type-II patients. So early diagnosis of vitamin B12 deficiency will lead to the prompt treatment in the form of B12 replacement in such patients. Furthermore, if significant vitamin B 12 deficiency is found with metformin, then guidelines may be formulated for proper follow up of patients and early B 12 replacement to avoid those complications

The objective of study was to determine the association between metformin use and vitamin B12 deficiency.

METHODOLOGY

This is an observational cross sectional study. Patients of diabetes mellitus, whether taking metformin or not, who presenting to Medical Outdoor were included. Sampling technique was non-probability convenient sampling.

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Sixty (60) patients of diabetes type-II between ages of 30-70 years were included in the study. Only those patients were included. History of any type of anemia, alcohol intake, renal insufficiency, prior gastric surgery, patients on current parenteral or enteral nutritional support prior transfusion and thyroid illness as assessed on History or previous record. Patients with malabsorption syndrome, use of B12 supplements (oral or parenteral), vegetarians, on proton pump inhibitors, with unstable cardiopulmonary, neurological, or psychiatric disease, hepatocellular carcinoma or other malignancies were excluded. All Patients were divided in two groups, Group-I was taking metformin for more than 2 years while group-II was not taking metformin. Detailed history and examination was done. Vitamin B12 levels were sent along-with other laboratory investigations. All the information were written on preformed questionnaire. Patients contact number was noted. Patients were requested to follow after vitamin B12 levels. Serum B 12 levels were noted on same questioners along with other labs. Data was then entered in SPSS. Data was analyzed using student's t-test and X2 analysis was applied to see

the significance between two groups keeping p value > 0.05 as significant.

RESULTS

Out of sixty (60) patients, thirty two (53.3%) patients were taking metformin while 28 patients (47.7%) were not taking metformin. Patients mean age was 58±8 years (57 for metformin and 59 for non-metformin group). Serum vitamin B12 level mean was 424±158 pg/ml in metformin group while it was 619±177pg/ml in non-metformin group with a P value of 0.0001 i.e. significant. Regarding duration of disease, mean duration of disease for patient taking metformin vs not taking metformin was 7 years. On further analysis, it was seen that MCV levels for patients on metformin was 74±13 and while mean MCV level for patients who were not taking metformin was 77±8. P value was 0.294 i.e. non-significant. While looking for serum creatinine levels, it was not significantly different in two population groups 1±0.2 vs 1±0.1. Our further analysis showed that mean HbA1C level for patients on metformin was 9.0±1.4 whereas mean HbA1C level for patients not on metformin was 8.4±1 and p value was 0.0645.

	Taking Metformin (32)		Not taking Metormin (28)		T Test Value	P Value
	Mean	St. Deviation	Mean	St. Deviation		
Age	57	8	59	8	0.966	0.338
Vitamin B12 Level	424	158	619	177	4.509	0.0001
Duration of Disease	7	3	7	5	0.00	1.0
MCV	74	13	77	8	1.058	0.294
Creatinine	1.0	.2	1.0	.1	0.00	1.0
HbA1C Level	9.0	1.4	8.4	1.0	-1.885	0.0645

DISCUSSION

Diabetes mellitus is important health problem worldwide. It leads to peripheral neuropathy, nephropathy and many other complications. Biguanides which include metformin are main stay of treatment of type-II DM. Serum vitamin B12 deficiency is one of the complications of metformin usage. Our study showed that serum vitamin B12 levels were significantly low in patients who were taking metformin as compared to other patients who were not taking metformin and p-value was 0.0001. According to one study conducted by Mathew et al., it was seen that serum vitamin B12 levels were significantly lower in patients who were taking metformin as compared to the patients who were not taking metformin i.e., p-value was ±0.01⁶. In another study conducted by Aroda and his colleagues showed that mean B12 levels were 10% lower in

patients taking metformin as compared to placebo i.e. 4.3 vs 2.4% with a p-value of 0.02⁷. Similarly in another study conducted by Kos' et al. showed that vitamin B₁₂ levels in patients of DM type-II were significantly lower in patients who were using metformin as compared to those who were not using i.e. P value was <0.0001⁸. Another study conducted at japan by Sato et al., showed that Metformin use was independently associated with vitamin B12 deficiency in DM type-II patients (P=0.02, r = -0.25)⁹.

According to the results of our study mean serum vitamin B12 level was 424±158 pg/ml in metformin group while it was 619±177pg/ml in non-metformin group. Similar results were also obtained in other studies. In one study conducted at USA by Reinstatler and his colleagues showed that mean serum vitamin B₁₂ levels were 430.2±13.0 pg/mL in patients who were using metformin compared to mean serum B 12 levels of 524.0±10.6 pg/mL in non-

metformin users¹⁰. Another study at UK showed that mean vitamin B₁₂ were reduced to statistically significant value after 1.5-3 months use of metformin. i.e. from -35 to -79pmol/L at CI of 95% CI¹¹. Similar results were also obtained by de Jager et al., who showed that metformin was associated with decreased serum B₁₂ levels as compared to patients who were not on metformin¹².

CONCLUSION

We conclude from our study that metformin was associated with serum vitamin B₁₂ deficiency.

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