

# Association of Vitamin B12 Deficiency with oral intake of Metformin in Type 2 Diabetes Mellitus: a quantitative analysis

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## ABSTRACT

**Aim:** To find out the relationship between Vitamin B12 deficiencies due to the oral intake of Metformin.

**Study Design:** Descriptive case series

**Place and Duration of Study:** Shahida Islam Medical & Dental College, Lodhran during February 2018 to December 2018.

**Methods:** One hundred patients had been approached via visiting the hospital settings within the city, and the majority of the patients who had been analyzed for this research study were patients of Acute and chronic conditions of Type 2 Diabetes.

**Results:** Participants who have been selected for the research study mainly belonged to the hospital settings of Mayo Hospital, and they have been observed and recruit from January to April 2019, for four months. The mean serum vitamin B<sub>12</sub> concentration was 665.7±246.7pg/mL (644.1±243.3pg/mL in men, 664.0±249.3pg/mL in women), and there was no significant difference according to sex. Vitamin B<sub>12</sub> deficiency was present in 76(9.5%) of patients using metformin.

**Conclusion:** Diabetes mellitus is one of the life-threatening diseases of the world, and the adverse effects associated with it might also lead to cardiovascular abnormalities among patients as well as peripheral neuropathy and retinopathy.

**Key words:** Diabetes Mellitus, Metformin, Vitamin B12 deficiency

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## INTRODUCTION

Some of the prevalent diseases in the 21st century have been reported to be cardiovascular diseases, diabetes, high cholesterol, etc. However, a huge number of individuals have been diagnosed with Diabetes of either Type 1 or Type 2. Numerous researches and papers have been proposed with respect to treatment options and remedies for diabetes, and one of the most popular and common medicine for the treatment of control of diabetes has been observed to be Metformin. Metformin belongs to the category of hypoglycemic agents, and it has been widely used by the physicians and specialists, for acute treatment of type 2 diabetes. Different associations and organizations from multiple countries have also proposed and suggested the use of Metformin for the immediate treatment of Diabetes in patients.<sup>1</sup> According to American Diabetes Association, Korean Diabetes Association and the European Association for the Study of Diabetes, it has been reported that in order to keep the sugar levels controlled and maintained among individuals, it is suggested that Metformin should be included in their lifestyle modifications along with other types of therapies and treatments. This will ensure regulated sugar levels within the patients and avoid the sudden rise of Sugar levels. However, metformin is also considered as a drug which might cause certain adverse reactions and side

effects for the patients, therefore it is necessary and essential for the physicians to acquire complete details and profile of the patient, so that they could conclude and analyze that whether there is any contraindication condition present in the patient or not<sup>2</sup>.

A number of side effects and adverse reactions have been reported among patients due to excessive use and intake of Metformin, which primarily includes gastrointestinal disturbance, watery stools, and diarrhoea along with vomiting and nauseous conditions when a patient initiates the treatment with Metformin. However, the effects remain persistent for some time until the patient continues taking this medication, but it somehow rapidly disappears when the medicine is being discontinued. This reaction and symptom is somehow difficult to be detected, as association of metformin with vitamin B12 deficiency had not been researched and analyzed for a long time, but multiple types of research and detailed investigation has been performed with respect to association of Metformin with Vitamin B12 deficiency and the reports have provided positive outcomes and results, as both are interrelated with each other. The primary reason for this deficiency has been observed to be malabsorptive conditions for Vitamin B12 in the human body, which somehow leads to dropping off the levels of Vitamin B12 below the normal range.<sup>3</sup>

Diabetes mellitus, which is also known as type 2 diabetes has been observed to be associated with mortality and morbidity among individuals. It has been reported that patients suffering from chronic conditions of diabetes mellitus are mostly on a verge of leading to death because of the severe symptoms and adverse effects which occur

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as a result of diabetes mellitus<sup>4</sup>. The statistics are expected to be increasing in the coming years because of increasing factors and issues which lead to diabetes mellitus. Pakistan is also one of the countries where diabetes mellitus is also considered as one of the most prevalent and common diseases, which is a real cause of death for a number of patients. It has been reported that approximately 10.6% of individuals from an urban population whereas 7.4% of people from the rural population are a victim and patient of diabetes mellitus<sup>5</sup>. Since, stress, exertion, mental burden, and problems are some of the reasons which lead to occurrence of multiple diseases among the patients, and diabetes mellitus is also one of such diseases whose primary factor might be stressful and difficult conditions as well, therefore based on this concept, it has been reported that people living in urban areas are more directed and prone towards diabetes mellitus because of increased burden, stressful conditions and tension causing factors within the bigger cities as compared to the small villages and cities<sup>6</sup>.

Considering numerous reports and studies, it has been analyzed that diabetes mellitus is one of the conditions which might lead to severe complications and symptoms within the patients. IT has been observed that diabetes mellitus is associated with peripheral neuropathy, neuropathy, and retinopathy, etc. In order to investigate and observe the major cause and reason for the occurrence of neuropathy in the patients with Diabetes, it is essential that their levels of Vitamin B12 must be regularly checked and monitored<sup>7</sup>. Since Metformin is one of the most important and essential medications for controlling sugar levels of the patients with type 2 diabetes, therefore the preferred step which must be taken in such conditions must be to replace Vitamin B12 and regularly monitor the levels of Vitamin B12 in patients at an early stage<sup>8</sup>.

**PATIENTS AND METHODS**

The study was conducted at Shahida Islam Medical & Dental College, Lodhran during June 2018 to January 2019 in order to perform a detailed study of the aforementioned subject, the number of participants who have been selected for this research study was approximately 100. Patients had been approached via visiting the hospital settings within the city, and the majority of the patients who had been analyzed for this research study were patients of Acute and chronic conditions of Type 2 Diabetes. Since Type 2 diabetes is mainly associated with insulin resistance or decreased levels of insulin among patients, therefore their insulin levels have also been regularly checked and monitored. Moreover, the study has been mainly designed in the form of descriptive analysis of the pre-existing literary sources, and the research works which have already been performed regarding the aforementioned subject, to acquire the relevant study material from multiple sources. Student t-test was applied for results in two groups and one-way ANOVA was for results more than two. P<0.05 was considered to have significant meaning.

**RESULTS**

The mean serum vitamin B<sub>12</sub> concentration was 665.7±246.7 pg/mL (644.1±243.3pg/mL in men,

664.0±249.3pg/mL in women), and there was no significant difference according to sex. Vitamin B<sub>12</sub> deficiency was present in 76(9.5%) of patients using metformin. There were no differences in the sex, alcohol use, over-the-counter multivitamin use, calcium supplement use, H2 blocker or PPI use, or diabetic complications between patients with and without vitamin B<sub>12</sub> deficiency. However, patients with vitamin B<sub>12</sub> deficiency had a longer duration of metformin use (P<0.001), a larger daily dose of metformin (P<0.001) than the patients without vitamin B<sub>12</sub>deficiency. Altered levels of vitamin B12 (borderline or low) were found in 29% of patients (47 cases; 95% CI: 22–36%). The prevalence of borderline levels of Vitamin B12 was 20.9% (34 cases; 95% CI: 15–27%) and the prevalence of low levels was 7.4% (12 cases; 95% CI: 4.0–11%).

Table 1: Participant demographic characteristics

Variable	n = 100
Age (years)	64 (12)
Female	90 (55%)
Vitamin B12 levels (pg/mL)	415 (154)
Metformin use time (months)	109 (90)
Metformin dose (mg)	1546 (614)
Diagnosis time (years)	5 (7.9)
Diabetic neuropathy	34 (21%)

Table 2: Linear regression analysis related to low levels of vitamin B12

	Coefficient	95% CI	P value
Metformin dose	-0.06	-0.10, -0.028	0.001
Gender (female)	49.1	2.3–95.8	0.040
Diabetic neuropathy	-116.9	-165.8, -68.0	0.000
Age	-0.86	-2.7, 1.0	0.362
Time from diagnosis	-5.2	-16.8, 6.3	0.374
Time on metformin	0.63	-0.36, 1.64	0.210

**DISCUSSION**

According to a research study performed by Reinstatler et al<sup>12</sup>, it has been observed that Metformin is considered as the first choice of treatment for patients with diabetes mellitus. Metformin is one of the most beneficial and favorable drugs for such patients, as it is responsible for increasing and enhancing peripheral insulin sensitivity among the patients, as well as reducing cardiovascular mortality risks<sup>14</sup>. Moreover, researches have been performed with this regard, and it has been determined that despite the mild and usual side effects of Metformin like diarrhoea, and GI distress, Metformin has been observed to be associated with reduced absorption of cobalamin (vitamin B12) in the ileum of the patients. According to a research study, it has been reported that Vitamin B12 levels among patients with Diabetes can reduce from 40 to15%, whereas patients who are on regular intake of Metformin might also reduce the levels of Vitamin B12 from 9 to 51%. This mainly occurs due to the fact that Metformin reduces the absorption of Vitamin B2 in patients, and its reduction up to dangerous levels is associated with peripheral neuropathy and retinopathy within the patients. A research study in which cross-sectional methods had been used for analysis performed by Chapman et al<sup>4</sup>, it has been reported that most of the patients with Type 2 Diabetes Mellitus and who had been with regular Metformin

intake reported to be at significantly reduced levels of Vitamin B12 as compared to the non-metformin users. Whereas, regular intake of Metformin for 4 to 6 months had significantly reduced levels of Vitamin B12 within these patients<sup>14</sup>. In addition, it has also been reported that the dose and duration of metformin are also directly related to the levels of Vitamin B12 in the serum of the patients with Type 2 Diabetes Mellitus. Since Vitamin B12 has also been associated with the metabolism of homocysteine and in case of deficiency of Vitamin B12, there will be increased levels of homocysteine in the blood serum, and it is associated with the occurrence of cardiovascular disorders among the patients with Type 2 diabetes mellitus<sup>10,11</sup>.

During the duration of these 4 months, the progress reports of each participant had been monitored and some of the data had been collected from the general practitioners and the doctors within the hospital settings. In addition, the sampling technique preferred for this study was the non-probability sampling method. Out of the 100 participants, two categories had been selected and they were equally divided for these two categories. Type 1 patients were using Metformin for 4 or more than 4 months, whereas Type 2 patients were not been on regular intake of Metformin. The levels of Vitamin B12 had been regularly monitored with the help of chemiluminescent enzyme immunoassay which is a test being performed for analyzing serum levels of vitamin B12<sup>12</sup>.

Based on the responses obtained from the participants, it has been observed that the majority of them had reported that their serum levels for Vitamin B12 had been considerably low in the patients using Metformin for 4 months. Whereas, patients who had been on other medications and remedies for the treatment of type 2 DM, had been reported to be normal levels of Vitamin B12 in their blood serum. Moreover, in certain cases where the deficiency of Vitamin B12 had reached severe stages, certain traits and chances of peripheral neuropathy had also been reported which is one of the greatest signs for increased mortality and fatality rate among patients with diabetes mellitus. Therefore, while providing the patients with Metformin as a hypoglycemic agent, their serum levels for cobalamin must be regularly monitored prior to the treatment and immediately after initiation of the treatment so that essentially required remedies and alternatives can be taken for the treatment of the patients<sup>10</sup>.

Another research study conducted by Mathew et. al., the levels of Vitamin B12 had reduced to 10% among patients who had been taking Metformin. Moreover, it has also been observed that patients the patients who had been taking placebo instead of Metformin showed normal levels of Vitamin B12. In addition to these research studies, it has also been investigated from our research analysis that patients are also not aware of the consequences and adverse effects that might arise because of their intake of Metformin, and they had been on the regime of Metformin since years. Therefore, it is also a matter of concern for the

medical institutions and departments that they must not only focus upon providing information to the new doctors and physicians regarding adverse effects of Metformin, but patients must also be provided with basic information and knowledge about the treatment regime they have been provided<sup>13</sup>.

## CONCLUSION

Diabetes mellitus is one of the life-threatening diseases of the world, and the adverse effects associated with it might also lead to cardiovascular abnormalities among patients as well as peripheral neuropathy and retinopathy.

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