

Association of Vitamin B-12 Deficiency with use of metformin in diabetic patients.

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Abstract

Objective: To find out the frequency of vitamin B12 deficiency in patients with type II diabetes mellitus using metformin. **Methodology:** Ninety two patients were involved after getting informed consent. This cross – sectional study was done at department of Medicine, Nishtar Hospital, Multan. HbA1c, body mass index and blood pressure and deficiency for vitamin B12 was assessed by using electro-chem-iluminescence immunoassay method. B12 levels were categorized as normal ($>220\text{pg/ml}$), possibly deficient (150 to 220 pg/ml) and definitely deficient ($<150\text{pg/ml}$). Neuropathy was assessed and was classified by using Toronto clinical scoring system by the researcher himself. All the data was subjected to statistical analysis using computer software SPSS version 23. Continuous variables were analyzed by their mean and standard deviation while quantitative variables were analyzed by frequency and percentages. Chi square test was applied and P value less than or equal to 0.05 was taken as significant. **Results:** Mean Serum B-12 levels were $378.42\pm 161.27\text{ pg/ml}$ and $488.90\pm 147.02\text{ pg/ml}$ in metformin and non-metformin groups, respectively. The difference was statistically significant ($p=0.001$). The patients who were possibly deficient and definitely deficient were 15 (28.30%) and 5 (9.43%) in metformin group and were significantly more ($p=0.006$) than non-metformin group i.e. 4 (10.26%) and 0. The mean Toronto Neuropathy Score was statistically different ($p<0.001$) between metformin group (6.03 ± 1.73) and non-metformin group (4.13 ± 1.75). The patients who had mild neuropathy and moderate neuropathy were 23 (43.39%) and 5 (9.43%) in metformin group, while 6 (15.38%) and 2 (5.13%) in non-metformin group. Statistically, both the groups were significantly different ($p=0.005$). **Conclusion:** At the end of this study conclusion can be made that metformin use for type II diabetes mellitus is strongly associated with vitamin B12 deficiency and worsening of already susceptible neuropathy.

Keywords: vitamin B12, Type II diabetes mellitus, neuropathy.

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Introduction:

For almost forty years it has been known that metformin use has a hand in lowering vitamin B12 levels. Vitamin B12 deficiency is a common phenomenon among the elderly ¹. Clinically it may present as hematological disease or neuropsychiatric illness and at times it is difficult to detect in certain scenarios ². Usually vitamin B12 deficiency is basically caused by malabsorption leading to classical condition of pernicious anemia. Two case reports have been found which showed evidence of vitamin B12 deficiency causing peripheral neuropathy ³ and in the light of these reports annual supplementation of vitamin B12 has been recommended for the patient receiving metformin for type II diabetes mellitus. In some parts of the world it is now considered as an empirical therapy for peripheral neuropathy.

Metformin is one of the first line drugs in the treatment of patients with type II diabetes mellitus⁴ and is associated least no. of side effects. It is strictly anti-hyperglycemic and also reduces the overall morbidity and mortality in diabetic patients. But it has one major setback which is deficiency of vitamin B12, a preventable and very much recoverable condition if diagnosed at optimum time. This deficiency can lead in deterioration of already present peripheral neuropathy in diabetic patients. In order to differentiate vitamin B12 deficiency caused peripheral neuropathy and usual peripheral neuropathy caused by the diabetes itself a systemized and well performed study is required. So that a perfect estimate of the level of deficiency can be developed which leads to the development of B12-deficiency induced neuropathy. Vitamin B12 concentrations in blood are not very good predictors of B12 deficiency⁵, as it is usually normal even in clinically diagnosed B12 deficiency patients. On the other hand mild decrease in concentration of B12 in serum does not establish its deficiency. For this purpose two specific tests have been developed which are more sensitive to B12 deficiency as compared to B12 concentration itself. Holotranscobalamin (holoTC)⁶ is a biological fraction of vitamin B12 and methylmalonic acid (MMA), are two markers for the diagnosis of status of vitamin B12⁷.

Correlation between vitamin B12 deficiency and metformin use has been studied worldwide but there are very little evidence present about the level to which it is decreased and its clinical impact as changes in neurological status and peripheral neuropathy. Moreover this correlation has not been studied in our population that is why we are not only going to assess the correlation between long term metformin use but also going to assess whether this deficiency has any impact over neuropathy among patients being treated with metformin for type II diabetes mellitus.

Materials and Methods:

An observational, cross-sectional study was conducted in Department of Medicine Nishtar Hospital, Multan. Study was conducted on consecutive patients with type 2 diabetes mellitus on drug treatment seen at outpatient department of Nishtar Hospital Multan. Ethical approval for this study was obtained from Hospital Ethics Committee. Ninety two patients were involved after getting informed consent. Sampling technique of Non probability consecutive sampling was used to collect the sample size. Sample was calculated using the reference study by AK Singh et al⁸. Patients were excluded if they gave history of alcoholism, ongoing pregnancy, liver disease, renal disease, thyroid disorders or history suggestive of malabsorption disorders. Type 1 diabetes mellitus patients were also excluded from analysis. Patients were selected by adhering strictly to these inclusion and exclusion criteria.

Most of the patients taking part in this study were on hypoglycemic drugs for their diabetes mellitus type II. Detailed drug history was obtained and diet history was recorded as well. Patients were divided into two groups; those on treatment with metformin were segregated as one group and others as the second group. Cumulative dosage of metformin and duration of the use of the drug was recorded.

After detailed history and examination following parameters were measured and recorded in the form of a performed performance; HbA_{1c}, body mass index and blood pressure. Deficiency for vitamin B12 was assessed by using electro-chem-luminescence immunoassay method. Samples for serum levels were kept for no more than 8 hours and at a temperature range of 15 to 30° C. B12 levels were categorized as normal (>220pg/ml), possibly deficient (150 to 220 pg/ml) and definitely deficient (<150pg/ml).

Standard neurological examination was performed on all the patients who took part in study including, deep tendon reflexes, tone and power of the muscles and sensory function. At the end of all the procedures of history, general physical examination and standard neurological examination, the resultant outcome of neuropathy was assessed and was classified by using Toronto clinical scoring system by the researcher himself. Gradation of the patients was carried out on the basis of score and grades were described as 0 to 5= No neuropathy, 6 to 9 mild neuropathy, 10 to 12 moderate neuropathy and greater than 12 as severe neuropathy. All the data was subjected to statistical analysis using computer software SPSS version 23. Continuous variables were analyzed by their mean and standard deviation while quantitative variables were analyzed by frequency and percentages. Chi square test was applied and P value less than or equal to 0.05 was taken as significant.

Results:

Mean age, weight, HbA_{1c}, Mean blood pressure, hemoglobin and Mean Corpuscular Volume were 42.87±10.07years, 58.32±13.84kg, 7.90±0.60, 124.96±7.30mmHg, 12.07±2.91mg/dl and 91.85±11.31 fl in metformin group; and 46.82±9.18years, 62.31±14.31kg, 8.04±.65, 126.10±6.22mmHg, 12.15±2.89mg/dl and 92.15±11.23 fl in Non-metformin group. Both the groups were comparable. The patients who were simultaneously

using insulin were 13 (24.5%) in metformin group and 19 (48.7%) in non-metformin group. The difference was statistically significant ($p=0.016$). (Table-I)

Mean Serum B-12 levels were 378.42 ± 161.27 pg/ml and 488.90 ± 147.02 pg/ml in metformin and non-metformin groups, respectively. The difference was statistically significant ($p=0.001$). The patients who were possibly deficient and definitely deficient were 15 (28.30%) and 5 (9.43%) in metformin group and were significantly more ($p=0.006$) than non-metformin group i.e. 4 (10.26%) and 0. (Table-II)

The mean Toronto Neuropathy Score was statistically different ($p<0.001$) between metformin group (6.03 ± 1.73) and non-metformin group (4.13 ± 1.75). The patients who had mild neuropathy and moderate neuropathy were 23 (43.39%) and 5 (9.43%) in metformin group, while 6 (15.38%) and 2 (5.13%) in non-metformin group. Statistically, both the groups were significantly different ($p=0.005$). (Table-II)

Table-I
Baseline Variables

Variable	Metformin N=53	Non-metformin N=39	p-value
Age (Years)	42.87±10.07	46.82±9.18	.057
Male n (%)	44 (83)	33 (84.6)	.838
Weight (Kg)	58.32±13.84	62.31±14.31	.182
HbA1c	7.90±0.60	8.04±.65	.280
Mean blood pressure (mmHg)	124.96±7.30	126.10±6.22	.433
Hemoglobin (mg/dl)	12.07±2.91	12.15±2.89	.898
Mean Corpuscular Volume (fl)	91.85±11.31	92.15±11.23	.898
Parallel Therapy			
Insulin n (%)	13 (24.5)	19 (48.7)	.016
Sulfonylureas n (%)	39 (73.6)	33 (84.6)	.205
Pioglitazone n (%)	21 (39.6)	14 (35.9)	.716

Variables are mentioned as mean ± S.D or number (percentage); Independent t test and chi-square test was applied.

Table-II
Vitamin B-12 level and Toronto Clinical Neuropathy Score

Variable	Metformin	Non-Metformin	p-value
Serum B-12 (pg/ml)	378.42±161.27	488.90±147.02	0.001
Possible deficiency N (%)	15 (28.30)	4 (10.26)	0.006
Definite Deficiency N (%)	5 (9.43)	0 (0)	
Toronto Neuropathy Score	6.03±1.73	4.13±1.75	<0.001
No Neuropathy N (%)	25 (47.17)	31 (79.49)	0.005
Mild Neuropathy N (%)	23 (43.39)	6 (15.38)	
Moderate Neuropathy N (%)	5 (9.43)	2 (5.13)	

Variables are mentioned as mean ± S.D or number (percentage); Independent t test and Fischer exact test was applied.

Discussion:

In this study results are in favor of the notion that metformin use in the treatment of type II diabetes mellitus does result in lowering the serum vitamin B12 levels. Peripheral neuropathy was also evidently more in the metformin users and was associated with lower levels of vitamin B12 in serum.

Previously numerous studies have gave the evidence of lowering of vitamin B12 in people who use metformin for longer of duration of time ^{9,10,11,12,13} and a few case reports ^{14, 15} have also gave the evidence of association of increased incidence of neuropathy with low levels of B12 in serum and metformin use chronically. In a study 18% of patients in metformin group had the evidence of low B12 levels as compared to the placebo group ¹⁰. Another retrospective study gave almost similar results in which 13 % patients with chronic use of metformin had the evidence of deficiency of vitamin B12 and 5.6% of the patients were definitely deficient in their serum levels of

vitamin B12 (<150 pg/ml) ⁹. A cross sectional study in the region of Canada ¹² and Hong Kong ¹¹ showed similar results to our study as they also observed deficiency of vitamin B12 in metformin user diabetic of type two diabetes mellitus as 31% and 37% respectively.

Mechanism by which B12 deficiency occurs has been shown to involve calcium dependent ileal membrane antagonism, which results in low levels of serum B12 and malabsorption of B12 from lumen by chronic use of metformin. This effect can be reversed by the use of calcium as has been reported in recent studies ¹⁶. A Chinese case control study reported that not only long term use of metformin can cause vitamin B12 deficiency but its higher doses can have the similar effects irrespective of the presence of other clinical variables ¹⁷. A diabetes prevention program outcome study has given similar results to our study stating that metformin use not only lowers serum B12 level but also can cause its complications, like anemia (pernicious anemia) ¹⁸. A meta-analysis performed recently has demonstrated a close relation between chronic metformin use and low levels of vitamin B12 in serum of patients with type two diabetes mellitus ¹⁹. All of these studies have suggested that early detection of serum B12 deficiency is required in long term users of metformin as vitamin B12 deficiency can lead to serious complications like anemia and also can precipitate neuropathic effect of diabetes mellitus.

Conclusion:

At the end of this study conclusion can be made that metformin use for type II diabetes mellitus is strongly associated with vitamin B12 deficiency and worsening of already susceptible neuropathy. Suggestions can be made that vitamin B12 levels should be assessed in patients with long term metformin use so that hazardous increase of risk among these patients can be prevented.

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