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Occurrence of Cobalamin (B-12) Deficiency in Metformin using Type II Diabetes Mellitus Patients

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Abstract:
Objective: To observe the occurrence of cobalamin (B12) deficiency and neuropathy in type II diabetic patients using metformin.
Study Design: Prospective, cross-sectional study.
Site and Duration of Study: Department of General Medicine and Diabetic Clinic, Nishtar Hospital Multan, from June 10, 2017 to February 25, 2018.
Methodology: Ninety two patients underwent proper detailed clinical history and examination, after which weight, mean blood pressure, $HbA1_c$, hemoglobin, mean corpuscular volume, serum cobalamin levels, Toronto Neuropathy Score were entered on a preformed performa. Electro-chemi-luminescence was used measurement of cobalamin. Toronto Neuropathy Score was calculated from history, clinical and neurological examination. Independent t-test was applied on continuous data and chi-square test was applied on nominal data using SPSS v.23. Confidence interval was taken as 95%.
Results: Mean serum cobalamin (B12) levels were 373.13±166.78 pg/ml and 538.48±172.29 pg/ml in M-Group and N-Group, respectively, difference being statistically significant ($p<0.001$). In M-Group, cobalamin (B12) deficient patients were statistically more in number ($p=0.006$) and Toronto Neuropathy Score was statistically higher ($p<0.001$). Number of patients developing neuropathy was also statistically higher ($p=0.002$) in M-Group.
Conclusion: After performing this study, we concluded that there is a strong association of metformin use with cobalamin (B12) deficiency in type-II diabetes mellitus patients. This can also lead to de novo development of peripheral neuropathy or can profoundly worsen the pre-existing diabetic neuropathy.
Keywords: Cobalamin, Type II diabetes mellitus, neuropathy, metformin.

Introduction:

The role of metformin in causing the deficiency of cobalamin (vitamin B12) has been recognized for more than forty years. In elderly population, deficiency of cobalamin is a more common problem when compared with younger population [1]. In many cases, clinical assessment of cobalamin deficiency is challenging but in others, it may present as some kind of neurological and psychiatric ailment or hematological illness [2]. Generally, pernicious anemia is the clinical picture in which there is malabsorption of cobalamin and thus its deficiency occurs. The evidence that cobalamin deficiency results in peripheral neuropathy was observed in two study reports [3]. According to those reports, it was recommended that the patients who are suffering from type II diabetes mellitus and are using metformin, should be given cobalamin supplements on annual basis. In many countries, cobalamin supplementation is considered a part of empirical therapy for the treatment of peripheral neuropathy.

Metformin is a euglycemic agent and is included in first line agents to be used for the treatment of type-II diabetes mellitus patients [4]. Metformin is firmly anti hyperglycemic drug and is known to decrease the morbidity and mortality rates in the type-II diabetes mellitus patients. It causes the minimum number of adverse effects, one of the being the deficiency of cobalamin. If diagnosed early, it can be prevented and very well recovered. The deficiency of cobalamin can lead to peripheral neuropathy or can exaggerate the already present peripheral neuropathy in the diabetic patients. A very well executed and systematic study is required to differentiate between the neuropathy caused by cobalamin deficiency and the neuropathy caused by diabetes mellitus itself. This can help to define a cutoff value for the deficiency of cobalamin which leads to development of neuropathy in the absence of diabetes-induced neuropathy.

Cobalamin deficiency cannot be well predicted by measuring the serum level of cobalamin [5] as it can be normal in the clinically diagnosed B12 deficient patient. On the contrary, slight fall in serum levels of cobalamin does not really determine its deficiency. Two more specific tests have been devised which are much more sensitive to cobalamin deficiency than cobalamin concentrations itself. These include the testing of Holotranscobalamin (holoTC) [6], a biological fraction of cobalamin and methylmalonic acid (MMA), both representing the status of cobalamin [7].

Studies have been performed to analyze the association of cobalamin deficiency with metformin use but the level of cobalamin, which leads to development of clinical manifestations in the form of peripheral neuropathy and the

change in neurological status, has not been very well studied. Moreover, regional data is lacking regarding this issue. Therefore, current study is aimed at assessing the association between long term use of metformin and cobalamin (B12) deficiency as well as its effect on neuropathy among type-II diabetes mellitus patients being treated with metformin.

Materials and Methods:

A prospective, cross-sectional study was performed in the department of General Medicine and Diabetic Clinic at Nishtar Hospital Multan, from June 10, 2017 to February 25, 2018. We performed the study after obtaining the ethical approval from the hospital ethics committee. Sample size was calculated using the study by Singh AK et al. [8] as reference and a total of ninety two patients were selected for study, using the non-probability consecutive sampling technique. Informed consent was acquired from every patient in written form. Type II diabetes mellitus patients who were between the age of eighteen and sixty five years were included in our study. Patients who were alcoholic; pregnant; suffering from chronic liver disease, chronic renal disease, thyroid dysfunction or malabsorption syndromes; and the patients who were diagnosed of type I diabetes mellitus were excluded from our study. Inclusion as well as exclusion criteria were strictly followed for the selection of the patients. Majority of the patients were being treated for type II diabetes mellitus with oral hypoglycemic drugs. Thorough drug history was recorded along with dietary history. Use of metformin was the criterion applied to divide the patients into two separate groups. The patients who were taking metformin were included in M-Group and the rest of the patients were put in N-Group (non-metformin group). Aggregate dose and the duration of the use of metformin was logged.

All the patients underwent proper hospital procedure of detailed clinical history and examination. After that following parameters were noted down on a preformed performa: age, weight, mean blood pressure, $HbA1_c$, hemoglobin and mean corpuscular volume. Electro-chemi-luminescence was the method of choice for the measurement of cobalamin (B12). Blood samples for the serum levels were collected and were stored at a temperature between 15^{o}C to 30^{o}C for no more than 6 hours. Patients having cobalamin levels above 220pg/ml were considered to be normal, levels between 150 to 220 pg/ml were considered to be possibly deficient and the levels below 150 pg/ml were considered to be definitely deficient. All the patents who were included in the study underwent standardized neurological examination which included tone and power of the muscles, deep tendon reflexes and examination of the sensory system. Total neuropathy outcome was assessed from detailed history, clinical examination and standardized neurological examination by the researcher himself, and the results were categorized on the basis of Toronto Neuropathy Scoring System. The grading of the patients was done on the basis of their neuropathy score i.e. score of 0-5 was graded as “No neuropathy”, score of 6-9 was graded as “Mild neuropathy”, score of 10-12 was graded as “moderate neuropathy” and the score above 12 was graded as “severe neuropathy”.

Independent t-test was applied on continuous data while Pearson Chi-square test was applied on the nominal data using SPSS v.23 computer software. Confidence interval was taken as 95%.

Results:

In M-Group and N-Group, mean age was 43.58±10.18 and 45.59±9.48 years (p=0.331); mean weight was 57.71±14.11 and 62.52±13.81 kg (p=0.102); mean $HbA1_c$ was 7.91±0.63% and 8.01±.62% (p=0.420); mean blood pressure was 125.88±7.06 and 124.98±6.67 mmHg (p=0.533); mean hemoglobin was 12.13±2.83 and 12.09±2.97 mg/dl (p=0.955); and mean corpuscular volume was 91.00±11.55 and 93.05±10.86 fl (p=0.385), respectively. Both the groups were comparable in terms of sulfonylureas (p=0.837) and pioglitazones (p=0.470). Insulin was being used by 13 (27.1%) of the patients in M-Group and 22 (50%) of the patients in N-Group, and the difference was found to be statistically significant (p=0.024). (Table-I)

Mean serum cobalamin (B12) levels were 373.13±166.78 pg/ml and 538.48±172.29 pg/ml in M-Group and N-Group, respectively, difference being statistically significant (p<0.001). The patients who were found to be possibly deficient and definitely deficient in cobalamin (B12) were 14 (29.2%) and 6 (12.5%) in M-Group and were significantly more (p=0.006) than N-Group i.e. 6 (13.6%) and 0. (Table-II)

Toronto Neuropathy Score was statistically higher (p<0.001) in M-Group (6.03±1.73) than in N-Group (4.13±1.75). In M-Group, 20 (41.7%) patients had mild neuropathy and 8 (16.6%) patients had moderate neuropathy; and in N-Group, 7 (15.9%) patients had mild neuropathy and 3(6.8%) patients had moderate neuropathy. Statistically, the difference was significant (p=0.002). (Table-II)

Table-I

Baseline Data

Variable	M-Group (n=48)	N-Group (n=44)	p-value
Age (Years)	43.58±10.18	45.59±9.48	0.331
Male n (%)	42 (87.5)	31 (70.5)	0.044
Weight (Kg)	57.71±14.11	62.52±13.81	0.102
$HbA1_c$	7.91±0.63	8.01±.62	0.420
Mean blood pressure (mmHg)	125.88±7.06	124.98±6.67	0.533
Hemoglobin (mg/dl)	12.13±2.83	12.09±2.97	0.955
Mean Corpuscular Volume (fl)	91.00±11.55	93.05±10.86	0.385
Parallel Therapy			
Insulin n (%)	13 (27.1)	22 (50)	0.024
Sulfonylureas n (%)	39 (81.3)	35 (79.5)	0.837
Pioglitazone n (%)	21 (43.8)	16 (36.4)	0.470

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

Table-II

Serum Cobalamin (B12) Level and Toronto Clinical Neuropathy Score

Variable	M-Group (n=48)	N-Group (n=44)	p-value
Serum Cobalamin (pg/ml)	373.13±166.78	538.48±172.29	<0.001
Possible deficiency N (%)	14 (29.2)	6 (13.6)	0.005
Definite Deficiency N (%)	6 (12.5)	0 (0)	
Toronto Neuropathy Score	5.87±1.70	4.53±2.03	0.001
No Neuropathy N (%)	20 (41.7)	34 (77.3)	0.002
Mild Neuropathy N (%)	20 (41.7)	7 (15.9)	
Moderate Neuropathy N (%)	8 (16.6)	3 (6.8)	

Data is mentioned as mean ± S.D or number (percentage); Independent t-test and Chi-square test was applied.

Discussion:

We observed in our study that the use of metformin for the treatment of type II diabetes mellitus results in a significant fall in serum cobalamin levels. About 30% patients who were prescribed metformin were possibly deficient in serum cobalamin and 12.5% were definitely deficient. Of the patients who were using metformin, 58.3% patients showed the signs of neuropathy which was a significantly higher percentage as compared to the patients who were not using metformin (22.7%).

Many studies have been conducted worldwide and have provided evidence about the role of prolonged use of metformin in decreased serum cobalamin (B12) levels [9-13]. A few case reports [14, 15] have been published showing the association of decreased serum cobalamin with the increased rate of development of peripheral neuropathy. According to a retrospective study conducted by Reinstatler L et al. [9], 13% of the patients with type II diabetes mellitus being treated with metformin for a long period were found to be almost deficient in serum cobalamin whereas 5.6% of the patients were found to be definitely deficient in their serum cobalamin (less than 150 pg/ml). In another similar study, when compared with the placebo group, 18% of the metformin using patients showed the clinical evidence of low serum cobalamin (B12) [10]. Results, similar to those of our study, were shown in cross sectional studies, one conducted in Hong Kong [11] while the other one conducted in Canada [12]. The deficiency of cobalamin was observed 37% and 31% of type II diabetes mellitus patients being treated with metformin in above mentioned studies, respectively. As opposed to our conclusion, Chen S et al. [13] stated that there were no effect of metformin on peripheral neuropathy in spite of a decrease in serum vitamin B12 levels.

Calcium dependent membrane channels antagonism in the ileum is thought to be involved in the mechanism of development of cobalamin deficiency. There is decrease in serum cobalamin levels and malabsorption of cobalamin in the lumen of the ileum occurs following the long term use of metformin. As shown in a recent study by Bauman WA et al. [16], the above mentioned effect can be effectively reversed if calcium supplementation is provided. In a case control study performed on Chinese population, it was seen that there was a rise in risk of developing vitamin B12 deficiency if the patients had received higher doses of metformin or a prolonged treatment with metformin [17]. These effects were observed independent of all other clinical factors.

Results similar to our study were observed in a diabetes prevention program outcome study showing that metformin use not only causes a decrease in the serum cobalamin levels but also results in other clinical manifestations such as pernicious anemia [18]. A close correlation between prolonged metformin use and decreased serum vitamin B12 level in the patients suffering from type-II diabetes mellitus was revealed in a recently performed meta-analysis [19]. Most of the studies discussed above suggest that there is need to monitor serum cobalamin level in type-II diabetes mellitus patients who are using metformin so that serious neuropathic complications can be prevented and prompt measures can be undertaken if necessary.

Conclusion:

After performing this study, we concluded that there is a strong association of metformin use with cobalamin (B12) deficiency in type-II diabetes mellitus patients. This can also lead to de novo development of peripheral neuropathy or can profoundly worsen the pre-existing diabetic neuropathy. There is need to monitor cobalamin status in the diabetic patients who are using metformin for a long time, so that adverse outcome can be prevented in time.

Conflict of Interest:

No conflict of interest was found concerning the current study.

Funding Source:

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