

## Association of Metformin use with Vitamin B12 Deficiency and Peripheral Neuropathy in Indian Type 2 Diabetes Mellitus Patients: Can Supplementation Help

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### Abstract:

**Background:** Type 2 diabetes mellitus is one of the most common endocrine disorders in the world. Metformin is being used as monotherapy or in combination with other medications. In addition, lifestyle counselling, weight loss and exercise are usually recommended to every diabetic person particularly overweight and having normal renal functions. Literature is full of reports suggesting association between long-term metformin use and vitamin B12 deficiency.

**Objectives:** To study the effect of vitamin B<sub>12</sub> supplementation along with themetformin therapy on peripheral neuropathy in type 2 diabetes mellitus patients.

**Materials and Methods:** This was a Cross sectional study conducted at a Tertiary care hospital of the city in 180 patients of Type 2 diabetes mellitus aged between 40-70 years who were on metformin therapy for more than 4 years to see the association.

**Results:** The mean age of the patients were 54.6 +- 10.2 years, with 62% being men and 38% being women. Patients of type 2 diabetes mellitus on metformin for more than 4 years having VPT score more than 10 when given with vitamin B<sub>12</sub> supplementation for 6 months, showed an improvement in their VPT scores though was found to be not statistically significant.

**Conclusions:** Patients of DM on metformin may be suffering from silent cobalamin deficiency which might add to their existing symptoms of neuropathy and may impair their quality of life. Considering cost of laboratory investigation to rule out B<sub>12</sub> deficiency and increasing prevalence of diabetes, it is not feasible that such monitoring will be possible in all diabetic patients of our country. The study proposes that supplementation of Vitamin B<sub>12</sub> can be given in patients of diabetes on Metformin therapy. This might reduce the occurrence of peripheral neuropathy, reduce pain and suffering of diabetic patients and can improve their quality of life. It is a cost-effective approach to take care of peripheral neuropathy as chances of

hypervitaminosis is less since Vitamin B12 is a water-soluble vitamin. However, such therapeutic approach should be done under expert medical supervision. Also, Larger studies needs to be planned to understand the exact mechanism of B12 malabsorption while on metformin, also to ascertain the association and the probable interventions to attenuate the peripheral neuropathy caused by metformin in the lager interest of our patients.

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## Introduction

Type 2 diabetes mellitus is one of the most common endocrine disorders in the world. Metformin is being used as monotherapy or in combination with other medications. In addition, lifestyle counselling, weight loss and exercise are usually recommended to every diabetic person [1] particularly overweight and having normal renal functions [2]

Various guidelines propose that in the absence of contraindications for metformin, it should be preferred for type-2 DM while initiating the therapy with concurrent lifestyle modifications [3]

In 1969, Berchtold et al [4] reported evidence of vitamin B12 malabsorption in patients who had been treated with metformin for as little as 3 months. In 1971, Tomkin et al [5] recommended that all patients on long-term metformin therapy have annual serum B12 testing, based on a cross-sectional evaluation.

Since then, cross-sectional, retrospective, and longitudinal observational studies [6,7], as well as case reports [8,9], have suggested a clinical association between long-term metformin use and vitamin B12 deficiency [10]

Various studies have reported that an average of 10-30 % of patients taking metformin for longer duration and at higher dosage have shown vitamin B12 deficiency. [5,11-13]

Thus, the present study was planned to assess the development of peripheral neuropathy in metformin users due to vitamin B12 deficiency and effect of its supplementation for any clinical

improvement.

Unique feature about this study is that we have evaluated the effect of B<sub>12</sub> supplementation on Indian diabetic patients.

Indians being primarily vegetarian are also at risk of Vit. B<sub>12</sub> deficiency, so, metformin induced cobalamin deficiency assumes greater risk in such patients in terms of development and the progression of peripheral neuropathy.

## Objectives

To study the effect of vitamin B<sub>12</sub> supplementation along with themetformin therapy on peripheral neuropathy in type 2 diabetes mellitus patients.

To study the association between development of peripheral neuropathy with dose and duration of metformin therapy in patients of type 2 diabetes mellitus

## Materials and Methods

It was a Cross sectional study conducted at a Tertiary care hospital of the city in 180 patients of Type 2 diabetes mellitus aged between 40-70 years who are on metformin therapy for more than 4 years.

**Inclusion criteria:** Type 2 diabetes mellitus patients aged between 40-70 years who are on metformin therapy for more than 4 years suffering from diabetic peripheral neuropathy as assessed by the biothesiometer.

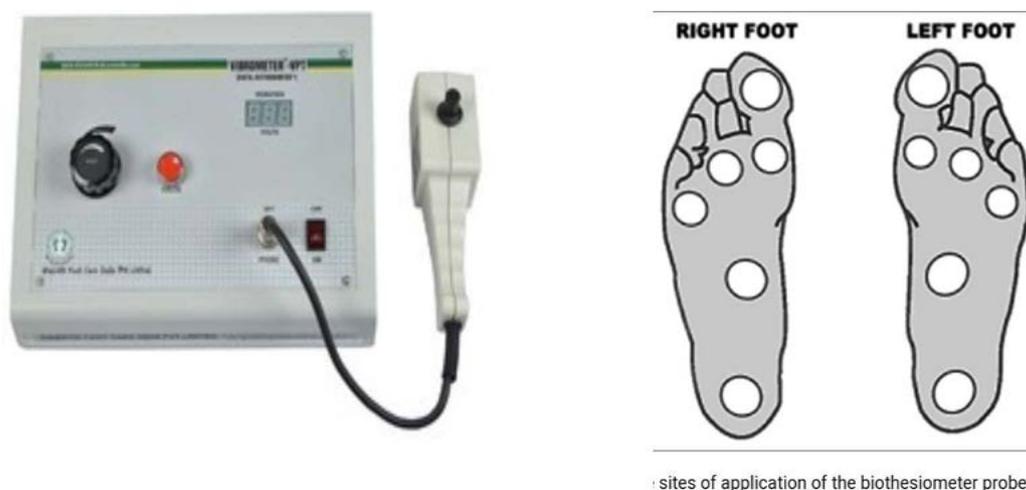
**Exclusion criteria:** Other potential causes of peripheral neuropathy such as leprosy, HIV, hypothyroidism, drug-induced, alcoholism and pregnant women were

excluded.

### Research Instrument: Biothesiometer

Vibration perception threshold (VPT) was measured with a biothesiometer – Vibrometer VPT® (Diabetic Foot Care, Madras Engineering Service, India) in a standardized fashion by a single observer. The biothesiometer probe, which vibrates at amplitude proportional to the square of the applied voltage, was applied perpendicular to the test site with a constant and firm

pressure. Subjects were initially familiarized with the sensation by holding the probe against the distal palmar surface of hand. The first probe was applied to patients hand to explain the feel of vibration early. Then patient is asked to concentrate on feet and to tell as soon as he starts feeling the vibration, and the value is noted. During recording, the voltage was increased from 0 to 50 V. The mean of three records was taken and neuropathy was diagnosed.



**Figure 1:**

### Study design:

Permission to conduct the research was obtained from appropriate authorities.

A total of 240 patients were identified during the study period, out of which 180 eligible patients with T2DM were recruited in this study suffering from peripheral neuropathy (PN), assessed by the biothesiometer.

Their initial values of VPT (vibration perception threshold) were taken and they were given supplemental Vit B12 in the dose of 1.5 mg daily for 6 months.

Grades of peripheral neuropathy based on VPT scores:

Mild: 10-15 Volts

Moderate: 16-25 Volts

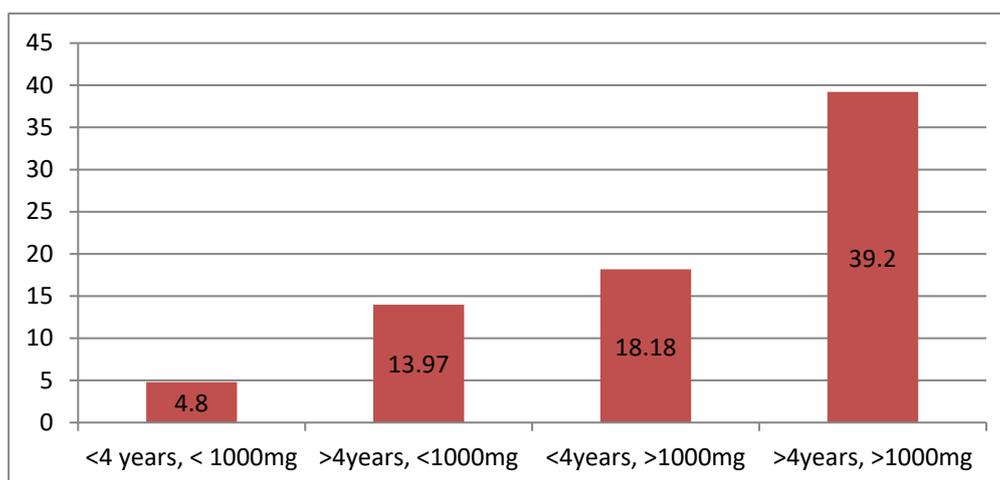
Severe: >25 Volts

On follow up visits over 6 months, VPT scores were repeated with the help of the biothesiometer.

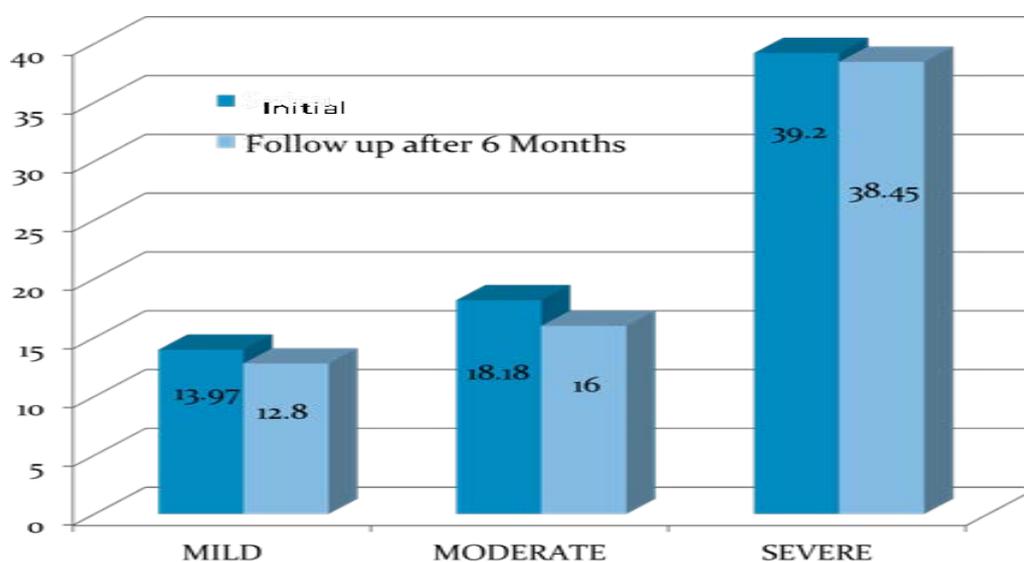
### Results

The mean age of the patients were 54.6 ± 10.2 years, with 62% being men and 38% being women.

Patients of type 2 diabetes mellitus on metformin for more than 4 years having VPT score more than 10 when given with vitamin B12 supplementation for 6 months, showed an improvement in their VPT scores though was found to be not statistically significant



**Graph 1: VPT scores of peripheral neuropathy due to duration and dose of metformin**



**Graph 2: VPT scores in patients before and after giving B12 supplementation**

## Discussion

Although several studies have shown that the use of metformin has an important effect on VitB12 levels in patients with T2DM, there is no published recommendations which states the requirement of regular screening tests for VitB12 deficiency in these patients. The mechanism by which metformin reduces serum vitamin B12 levels has not been elucidated, but the most likely hypothesis is that metformin interferes with calcium-dependent membrane action which is responsible for vitamin B12 intrinsic factor absorption in the terminal ileum. [14] In its most recent report (2019), the American Diabetes Association recommended regular

screening for VitB12 level in metformin-treated patients with T2DM who had anemia or peripheral neuropathies. [14]

This study was planned specially in Indian subjects as owing to their vegetarian status there might be higher chances of B12 deficiency.

Mean VPT score before giving vitamin B12 in mild, moderate and severe cases were 13.9, 18.18 and 39.2 respectively which was decreased to 12.8, 13 and 38.4 after giving vitamin B12 for 6 months in this study.

It appears that vitamin B12 deficiency occurs commonly among patients with type-2 diabetes taking metformin therapy

for longer duration and at higher dosage. This highlights the role of routine screening of vitamin B12 level among type-2 DM, especially those consuming metformin for more than four to five years with average dose of more than 1g/day, even in the absence of hematological and neurological abnormalities. The fact that the symptoms of diabetic neuropathy resemble metformin-induced neuropathy will add to the confusion. [15]

However, considering increasing prevalence of diabetes and cost of laboratory investigation for B12 estimation, it is uncertain that such monitoring will be possible in all diabetic patients due to economic concerns. The amount of B12 available in general multivitamins preparations seen in the market may not be enough to correct metformin induced vitamin B12 deficiency among those with diabetes. Hence vitamin B12 supplementation might be given in doses of >100 µg/ day in alimentary causes and doses of 500–2000 µg/day in disorders resulting from malabsorption for the treatment and prophylaxis of vitamin B12 deficiency under medical supervision. Thus, routine supplementation of vitamin B12 given to patients under medical supervision on long-term high dose metformin therapy seems to be a cost-effective approach. [3] We also need to monitor for signs and symptoms of hypervitaminosis though chances are less if given with in recommended doses under medical supervision being a water-soluble vitamin. However large clinical studies are required to determine the precise amount of supplementation of B 12 in cases of diabetes patients on metformin suffering from signs and symptoms of peripheral neuropathy. [16]

### Conclusions

Patients of DM on metformin may be suffering from silent cobalamin deficiency which might add to their existing symptoms of neuropathy and may impair their quality of life.

Considering cost of laboratory investigation to rule out B12 deficiency and increasing prevalence of diabetes, it is not feasible that such monitoring will be possible in all diabetic patients of our country

Thus, this study proposes that supplementation of Vitamin B12 can be given in patients of diabetes on Metformin therapy. This might reduce the occurrence of peripheral neuropathy, reduce pain and suffering of diabetic patients and can improve their quality of life. It is a cost-effective approach to take care of peripheral neuropathy as chances of hypervitaminosis is less since Vitamin B12 is a water-soluble vitamin. However, such therapeutic approach should be done under expert medical supervision. Also, Larger studies needs to be planned to understand the exact mechanism of B12 malabsorption while on metformin, also to ascertain the association and the probable interventions to attenuate the peripheral neuropathy caused by metformin in the lager interest of our patients.

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