

Role of Vitamin B₁₂ Supplementation in Type 2 Diabetes Cases on Prolonged Metformin Therapy

Preeti Bajaj*, Pratik Tawri**

*Professor & Head, Department of Pathology **Intern, Dr. Vasanttrao Pawar Medical College, Hospital & Research Centre, Nashik, Maharashtra 422003, India.

Abstract

Vitamin B₁₂ is a neurotropic, water soluble vitamin and is one of the major cause of development of Diabetic peripheral neuropathy. Metformin is known to cause depletion of vitamin B₁₂ stores resulting in its deficiency. Thus Looking at the increased incidence of type 2 Diabetes mellitus, and the increased prevalence of vitamin B₁₂ deficiency in the Indian population (vegetarian diet being one of the factor) and since the screening of serum vitamin B₁₂ is a bit costly test, according to the result of this study we may arrive to a conclusion regarding supplementation of vitamin B₁₂ for prevention of peripheral neuropathy in diabetes. Long term use of Vitamin B₁₂ supplements in patients will not cause any harm owing to the fact that it being a water soluble vitamin will be excreted in urine if in excess. Biothesiometer is a simple, portable, reliable, non-invasive method to screen the peripheral neuropathy.

Keywords: Vitamin B₁₂; Diabetes mellitus; Metformin Therapy; Biothesiometer.

Introduction

In recent years, the global community has been preoccupied with the threat of a resurgence of infectious disease. However, Diabetes is a growing public health problem throughout the world. The worldwide prevalence of Diabetes Mellitus has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 382 million in 2013 of these more than 90% are type 2 DM [1]. Metformin, represents Biguanides class of agents is the drug of choice for hyperglycemia. Most of the current global clinical practice recommendations, including those of the American Diabetes Association, the European Association for the Study of Diabetes, and the Korean Diabetes Association, propose that metformin, if there are no contraindications, should be initiated with concurrent lifestyle modifications at initial diabetes diagnosis and is thus most widely used

oral hypoglycemic globally [2-4]. Despite good benefits it may have fewer mild or short term gastrointestinal side effects such as diarrhea, anorexia, nausea, metallic taste. The major toxicity of metformin - lactic acidosis, is very rare and can be prevented by careful patient selection. However Vitamin B₁₂ levels are 10-30% lower during metformin treatment as it interferes with the absorption in the intestine and may lead to exhaustion of vitamin B₁₂ stores usually after four to five years and it might go unnoticed as mostly they are asymptomatic [5].

The prevalence of biochemical B₁₂ deficiency was present in 5.8% of those with diabetics using metformin compared with 2.4% of those not using metformin [6-9].

Vitamin B₁₂ is an essential micronutrient required for optimal hemopoetic, neuro-cognitive and cardiovascular function. Biochemical and clinical vitamin B₁₂ deficiency has been demonstrated to be highly prevalent among patients with type 1 and type 2 diabetes mellitus. It presents with diverse clinical manifestations ranging from peripheral neuropathy, sub acute combined degeneration of the spinal cord, impaired memory, dementia, delirium, megaloblastic anemia and pancytopenia [10,11]. Vitamin B₁₂ is a

Corresponding Author: Preeti Bajaj, Professor & Head, Department of Pathology, Dr. Vasanttrao Pawar Medical College, Hospital & Research Centre, Nashik, Maharashtra 422003, India.

E-mail: dr.prbajaj@gmail.com

(Received on 21.06.2017, Accepted on 28.06.2017)

neurotropic, water soluble vitamin and its deficiency is one of the major cause of development of Diabetic peripheral neuropathy. However, a common, potentially damaging, and well-documented complication of metformin – vitamin B₁₂ malabsorption – is poorly recognized and not screened for or treated prophylactically by the majority of physicians who prescribe metformin. Therefore, peripheral neuropathy due to vitamin B₁₂ deficiency may be confused with diabetic peripheral neuropathy or may contribute to the aggravation of diabetic peripheral neuropathy. This is unfortunate since a correctable cause of irreversible damage to the central and peripheral nervous system may be overlooked [12,13]. However, the relationship between metformin use and vitamin B₁₂ deficiency in the Indian population has not been widely investigated.

Screening of serum vitamin B₁₂ is a bit costly test, according to the result of this study we may arrive to a conclusion regarding supplementation of vitamin B₁₂ for prevention of peripheral neuropathy in diabetes by testing their VPT score using biothesiometer. Long term use of Vitamin B₁₂ supplements in patients will not cause any harm owing to the fact that it being a water soluble vitamin will be excreted in urine if in excess [14]. Thus looking at the increased incidence of type 2 Diabetes mellitus, and the increased prevalence of vitamin B₁₂ deficiency in the Indian population (vegetarian diet being one of the factor) it is necessary to derive the prevalence of peripheral neuropathy due to vitamin B₁₂ deficiency in type 2 DM who are on long term Metformin therapy.

Aims & Objectives

1. To determine the prevalence of peripheral neuropathy due to vitamin B₁₂ deficiency in type 2 DM who are on long term Metformin therapy.
2. To study the effect of Vitamin B₁₂ supplementation along with metformin therapy on peripheral neuropathy in type 2 DM patients.

Materials and Methods

Sample size = 135.

Out of which 100 samples were taken as they were appropriately fitting for the criteria or some refused to conduct the biothesiometer testing on them or were found to be newly diagnosed or not willing or were having other potential causes of peripheral neuropathy.

So the final sample size taken was 100.

It is a hospital based study. Will be carried out in the Medicine - Diabetic OPD of a tertiary care institute for over 2 months period to find out the prevalence of peripheral neuropathy due to vitamin B₁₂ deficiency in type 2 DM who are on long term Metformin therapy.

During this study, Biothesiometer (duly calibrated) of a standard company will be used to assess peripheral neuropathy, and the patients who are having significant neuropathy on their VPT score will be supplemented with therapeutic dose of vitamin B₁₂ of 1.5mg/day for 2 months.

Follow-up data - to be assessed again with Biothesiometer to check their VPT score after 60days of their regular medication of Metformin along with the supplementation of 1.5mg methylcobalamin.

VPT Scoring System

VPT Scoring	Grade
0-10	Normal
11-15	Mild
16-25	Moderate
>25	Severe

Inclusion Criteria

- Established Type 2 DM patients aged 30-80 years, who are on Metformin for > 4 years.

Exclusion Criteria

- Patients with newly diagnosed type 2 diabetes (duration < 4 years)
- Pregnant women.
- Patients with decreased renal function (serum creatinine levels >1.7 mg/dL for men and >1.5 mg/dL for women), prior vitamin B₁₂ injections, gastrectomy, colectomy, inflammatory bowel disease, and pernicious anemia.
- Patients with any severe medical illness, such as sepsis, severe infection, malignancy, liver cirrhosis, heart failure.
- Patients with potential causes for peripheral neuropathy other than diabetes and Vitamin B₁₂ deficiency will also be excluded.

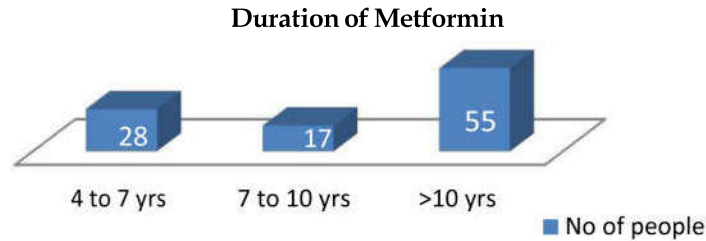
Statistical Analysis will be done using SPSS data software v.23.0.

Observation & Result

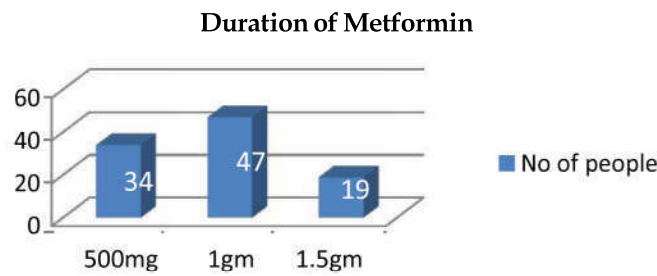
out of which 100 samples were taken as they were appropriately fitting for the criteria or some refused to

conduct the biothesiometer testing on them or were found to be newly diagnosed or not willing or were having other potential causes of peripheral neuropathy.

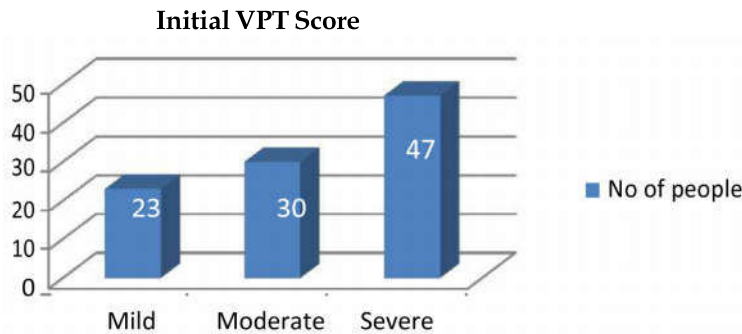
So the final sample size taken was 100, were further analyzed using SPSS software v.23.0 for showing their co-relation and proving whether they are statistically significant or not.



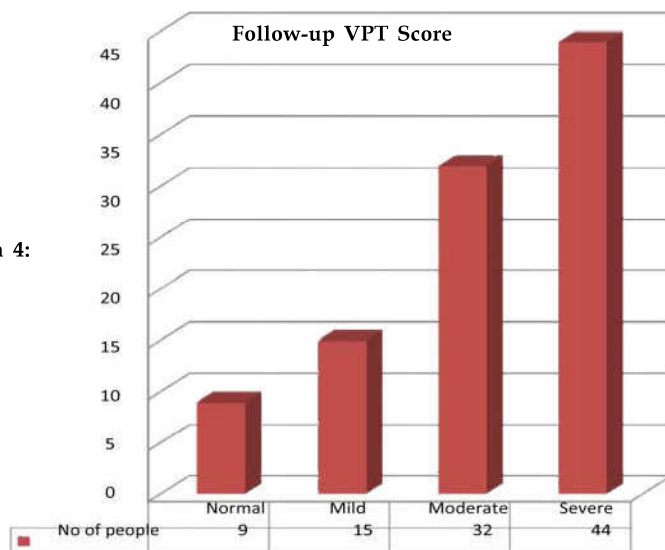
Graph 1: Duration of years patient is taking Metformin tablet.



Graph 2: Dose of metformin tablet the DM type 2 patient is taking.



Graph 3:

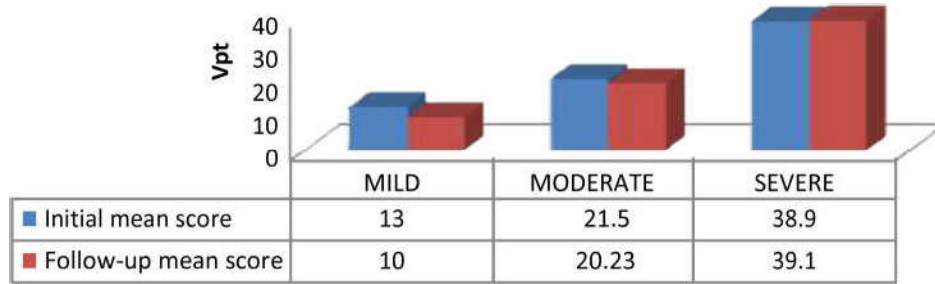


Graph 4:

Table 3, states that 23 patients were initially in mild category of the VPT score which is unit of peripheral neuropathy on biothesiometer. 30 patients were in moderate category and 47 patients were in severe category peripheral neuropathy.

This Table 4, shows us the effect of supplementing Vitamin B₁₂ and these are the score of peripheral neuropathy after the 2 months of follow-up of patients. It shows that 9 DM type 2 patients who are on metformin when supplemented Vit B₁₂ among them 9 patients were returned back to the normal category, proving clinical significance.

Comparing Means of Initial and Follow-Up VPT Score to Find out the Clinical Significance

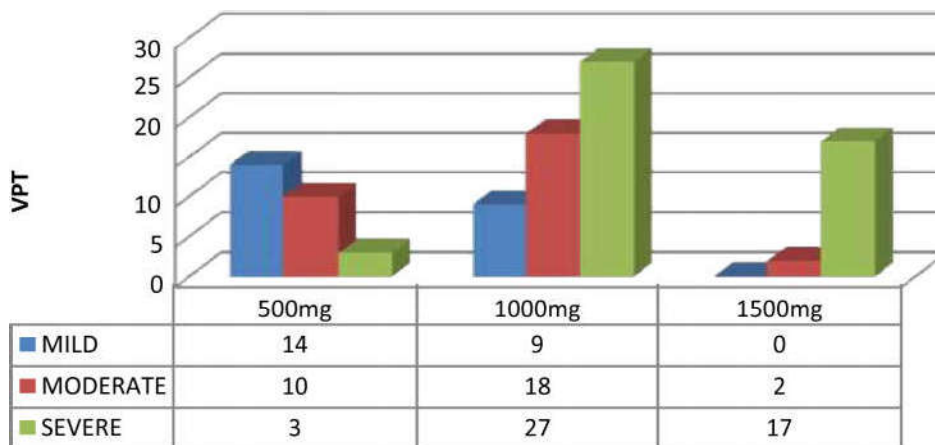


Graph 5: Compares the Initial VPT mean score and the 2months follow-up VPT mean score.

Table 5:

Mild	13	10	3
Moderate	21.5	20.23	1.27
Severe	38.9	39.1	-0.2

Co-relation between Dose and VPT score



Graph 6:

Table 6 shows the co-relation between Dose of metformin and the initial VPT score, It shows that patients taking 500mg of metformin were more prone to develop mild category of peripheral neuropathy while those were on higher dose 1500mg of metformin were prone to develop severe peripheral neuropathy.

Discussion

According to this study

- 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 which was found to be statistically significant .

- We demonstrated that metformin dosage and treatment duration were consistent risk factors for vitamin B₁₂ deficiency leading to Peripheral neuropathy and supplementation of B₁₂ lead to reduction in neuropathy scores.
- To the best of our knowledge, this study is one of its kind that was specifically designed to investigate the occurrence of peripheral neuropathy in metformin users amongst Indian patients

On comparing our study with Sun-Hye ko et al [17] a Korean study which states that patients with vitamin B₁₂ 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 B₁₂ deficiency, so this is highly

A study done by Pierce et al [13] came out with the

findings Subjects (N = 235) had a mean metformin dose of 2050 mg/day and mean duration of treatment of 5.2 years. Sixty percent did not have vitamin B₁₂ measured. Of subjects receiving metformin for 10 years or more, nearly half (46%) never had vitamin B₁₂ measured. New documentation of vitamin B₁₂ deficiency or cyanocobalamin supplementation was found in 5.5% of the population, and anemia was found in 12%. Of the 14% with new neuropathy, 42% did not have vitamin B₁₂ measured.

G H Tomkin et al [8] concluded that malabsorption of B₁₂ in patients on long-term metformin therapy is a frequent finding and of clinical importance as 21 of the patients examined had B₁₂ malabsorption and four of these were found within six years of beginning therapy to be B₁₂ deficient. This drug was introduced to general use only about 10 years ago and it is to be expected that further patients with B₁₂ deficiency will be encountered as more patients continue to take the drug for longer periods.

G H Tomkin also suggested that it is important that all patients on long-term metformin therapy should have annual serum B₁₂ estimations, as there is a risk that the initial symptoms of subacute combined degeneration of the cord may be mistaken for diabetic neuropathy in these patients.

Berchtold et al [18] found pathologically low levels of B₁₂ absorption in patients who had been treated with metformin for up to three months.

A European study by Miriam E Tucker [4] concluded that Per "gram-year" of metformin, there was an overall non-significant increase in neuropathy score of 0.032 ($P=0.34$). This reflects metformin's competing protective effect. However, with the 0.039- $\mu\text{mol/L}$ increase in MMA factored in, the net effect came to a 0.25-point increase in the Valk neuropathy score. However our study has got a relationship with the increasing dose of metformin and its increase in the effect of peripheral neuropathy.

This European study also does not agree that the supplementation of Vit B₁₂ along with the Metformin therapy, but we have a statistically significant data that proves that on supplementation of Vit B₁₂ along with the Metformin is very effective in reducing the peripheral neuropathy in Diabetes mellitus and can also reverse the neuropathy in mild stage or may reduce in the higher stages of neuropathy.

We also suggest that Diabetic Neuropathy should not be overlooked as most of times it may not cause any signs or symptoms and ignoring may worsen the complication, and if its metformin induced peripheral neuropathy it can be reversed to some extent. Hence Supplementation of Methycobalamin along with

Metformin therapy should be done - it should go like METHylcobalamin for METformin (MET for MET).

Pathology of Diabetic Nephropathy: Diabetic neuropathy occurs in about 50% of individuals with long standing type 2 DM. it manifests as polyneuropathy or mononeuropathy however the most common form of DN is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss and pain, but upto 50% of patients do not have symptoms of neuropathy. Hyperesthesia, paresthesia and dysesthesia also may occur. Any combination of these symptoms may develop as neuropathy progresses.

Symptoms may include a sensation of numbness, tingling, sharpness or burning that begins in the feet and spread proximally. Physical examination reveals sensory loss, loss of ankle deep-tendon reflexes and abnormal position sense. Treatment of DN is less than satisfactory. Improved glycemic control should be aggressively pursued and will improve nerve conduction velocity, but symptoms of DN may not necessarily improve. Avoidance of neurotoxins (alcohol) and smoking, supplementation with vitamins for possible deficiencies B₁₂, folate and symptomatic treatment are the mainstays of therapy. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae, consequently, prevention of such problems is of paramount importance. Patient with symptoms or signs of neuropathy should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulceration as they may further complicate resulting in Diabetic Foot [15].

Nerve damage is due to formation of sorbitol from sugar. Sorbitol causes demyelination of large fibers. New arterio-venous communications open beneath skin, diverting nutrient flow away from it. This ischemic tissue is vulnerable for infection causing nerve ischemia. Loss of vibration sense and deep tendon reflexes occurs early. Later, joint position, touch, pain and temperature sensations are lost. As a result of this, trophic ulcer develops. It progresses and can penetrate deeper and deeper. Very often the patient is unaware of this.

Therefore ADA recommends annual screening for distal symmetric neuropathy beginning with initial diagnosis of diabetes. Approaching patient, an annual foot examination should assess blood flow, sensation (vibratory sensation - 128MHz tuning fork at the base of the great toe), the ability to sense touch with a monofilament - 5.07, 10-g monofilament, pinprick sensation, testing for ankle reflex, and vibration perception threshold using a biothesiometer [16].

Conclusion

- Patients of DM on metformin may be suffering from silent cobalamin deficiency which may add to their existing symptoms of neuropathy.
- Thus we propose that supplementation of Vit B₁₂ should be given in patients of diabetes on Metformin therapy as it seems clinically prudent that users may be helpful in retarding Peripheral Neuropathy.
- Considering cost of laboratory investigation to rule out B₁₂ deficiency and increasing prevalence of diabetes, it is uncertain that such monitoring will be possible in all diabetic patients.
- Thus routine supplementation of vitamin B₁₂ to patients on long-term metformin therapy seems to be clinically prudent and a cost-effective approach to combat neuropathy.

Peripheral neuropathy can take away smile of your diabetic patient; Timely recognition and appropriate management can get him back the smile.

Acknowledgement

We sincerely acknowledge Dr Mrinalini Kelkar, Dr Jeetendra Singh, Dr Reshma Tejale, Dr Aditya Atal, Dr Rishika Atal, Dr Akash Geet, Dept of Community medicine, CRL as well as Dr Mrunal Patil, Dean of MVP's Dr Vasanttrao Pawar Medical College, Hospital and Research centre, Nashik for their help and support.

References

1. K.Park; Park's Textbook of preventive and social medicine; Banarsidas bhanot publishers; Epidemiology of non-communicable diseases; Diabetes mellitus; 23rd edition 2015; pg no.393.
2. American Diabetes Association. Standards of medical care in diabetes: 2013. *Diabetes Care* 2013;36:511-66.
3. Committee of Clinical Practice Guideline. Treatment guideline for diabetes. 4th ed. Seoul: Korean Diabetes Association, 2011.
4. Wulffele M, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med*. 2003;254:455-63.
5. Tripathy KD. *Essentials of Medical Pharmacology*. 6th ed. New Delhi: Jaypee brothers medical publishers (p) Ltd; 2014.
6. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B; Professional Practice Committee, American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2006;49:1711- 21.
7. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193-203.
8. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. *Br Med J*. 1971;2:685-7.
9. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care*. 2000;23:1227-31.
10. De Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010; 340:c2181.
11. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. *Arch Intern Med*. 2006;166:1975-9.
12. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. *South Med J*. 2010;103:265-267. [PubMed].
13. Pierce SA, Chung AH, Black KK. Evaluation of vitamin B12 monitoring in a veteran population on long-term, high-dose metformin therapy. *Ann Pharmacother*. 2012;46:1470-1476. [PubMed].
14. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. *Diabetes Res Clin Pract* 2012;97:359-67.
15. J.Singh. Vitamin B12 deficiency among patients with type II diabetes mellitus: is routine screening and supplementation necessary? An Indian prospective. *Journal of association of physicians of Maharashtra oct 2015;1:58-61*.
16. Harrison's principles of internal medicine. 18th ed. New York: McGraw Hill, health professions division; 2015.
17. Butler C, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Fam Pract*. 2006;10:279-85.
18. Berchtold, P., Bolli, P., Arbenz, U., and Keiser, G. (1969). *Diabetologia*, 5.