ROLE OF VITAMIN B12 SUPPLEMENTATION IN METFORMIN INDUCED DIABETIC NEUROPATHY IN INDIAN PATIENTS. CAN SUPPLEMENTATION HELP?

Dr. Fatema. S. Merchant¹, Dr. Arwa. S. Merchant²

¹Internal Medical Trainee at Northampton General Hospital, NHS Trust- United Kingdom.

²Intern at Mahatma Gandhi Mission Medical College, Hospital and Research Center, Aurangabad - India

Article Info: Received 10 October 2019; Accepted 24 November. 2019

DOI: <https://doi.org/10.32553/ijmbs.v3i11.743>

Corresponding author: Dr. Fatema. S. Merchant

Conflict of interest: No conflict of interest.

Abstract:

Metformin is one of the most commonly used oral hypoglycemic drug amongst type II diabetes mellitus patients, particularly overweight with normal kidney functions. Literature reports an average of 10-30% of patients taking metformin for longer duration (more than 4 years) have shown some signs of vitamin B12 deficiency.

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 was assessed for improvement in terms of VPT (Vibration perception threshold) score assessed by Biothesiometer which is a simple, portable, reliable, non-invasive method to screen the peripheral neuropathy

Unique about this study is, evaluating the effect of B12 supplementation on Indians patients. They being primarily vegetarian are at more risk to develop Vitamin B12 deficiency, so, metformin induced Cobalamin deficiency assumes greater risk in such patients in terms of development and progression of peripheral neuropathy.

Introduction:

Recent data from International Diabetes Federation shows that 463 million adults are currently living with diabetes. Diabetes is one of the fastest growing health challenges of the 21st century, with the number of adults living with diabetes having more than tripled over the past 20 years. 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 DM¹

Metformin, representing Biguanide class 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, proposes 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 globally²⁻⁴

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.

Malabsorption of vitamin B12 in diabetic patients treated with metformin was first noted in 1969. Subsequent studies revealed a prevalence of vitamin B12 deficiency in the range of 10 to 30% of diabetic patients using metformin. The mechanisms are thought to be related to slowing of the bowel transit time resulting in bacterial overgrowth and interference of the Biguanide with the absorption of vitamin B12⁵

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 metformin⁶⁻⁹

This low Vitamin B12 levels may lead to exhaustion of vitamin B12 stores. However, insidious or asymptomatic side effects resulting from long-term treatment, such as vitamin B12 deficiency, may not be easily detected without close attention.

Vitamin B12 is a neurotropic, water soluble vitamin and its deficiency is one of the major causes 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 further 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^{10, 11}. However, the relationship between metformin use and vitamin B12 deficiency in the Indian population has not been widely investigated and hence we planned to conduct this study amongst Indian population. Also being vegetarian Indians are also at risk to develop more chances of Vitamin B12 deficiency.

In 2009, the Regional Disciplinary Medical Board in Eindhoven stated that an overdose is not possible: "There can be no question of an overdose of hydroxocobalamin, as the excess is excreted in urine by the kidneys and therefore cannot accumulate in the body¹². Screening of serum vitamin B12 is a bit costly test; hence B12 supplementation appears to be a clinically feasible option for prevention of peripheral neuropathy especially in countries where cost of medicine can be a concern for the patients.

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 factors) it was planned to study the presence of peripheral neuropathy due to vitamin B12 deficiency in type 2 DM who are on long term Metformin therapy.

Pathology: 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 or may not necessarily improve. Avoidance of neurotoxins (alcohol) and smoking, supplementation with vitamins for possible deficiencies B12, folate and symptomatic treatment forms the basis 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. All the diabetic patients should undergo comprehensive foot exam once a year. The goal of this examination is to determine the risk factors that may result in foot ulcer and consequently amputation of the affected organ.¹³. 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, 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 biothesiometer¹⁴

Aims and Objectives: To study the effect of vitamin B12 supplementation along with the metformin therapy on peripheral neuropathy in type 2 diabetes mellitus patients as assessed by VPT score

Inclusion criteria: Type 2 diabetes mellitus patients aged between 40-70 years who are on metformin therapy for more than 4 years.

Exclusion criteria: Other potential causes of peripheral neuropathy such as

1. Leprosy [nerve hypertrophy].
2. HIV infections [HIV neuropathy and antiretroviral toxic neuropathy].
3. Diphtheria [lesions by diphtheria toxins].
4. Drugs –
 - a. Isoniazid

b. Phenytoin etc.

5. Hypothyroidism [fluid retention exerting pressure on peripheral nerves]

6. Pregnant women.

Patients with newly diagnosed type 2 diabetes (duration < 4 years)

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.

Materials and Methods: 180 patients were included in this study suffering from peripheral neuropathy (PN) as assessed by the biothesiometer. Their initial values of VPT (vibration perception threshold) were taken and they were given supplemental Vitamin B12 in the dose of 1.5 mg daily for 6 months. On follow up visits over 6 months, VPT scores were repeated with the help of Biothesiometer.

Statistical Analysis was done using SPSS data software v.23.0.

Table 1: VPT scoring system: 11-15 MILD 16-25 MODERATE >25 SEVERE

VPT SCORING	GRADE
0-10	NORMAL
11-15	MILD
16-25	MODERATE
>25	SEVERE

Results:

The table shows that more the dose and duration of metformin use, more are the VPT scores which might mean that there are more chances of development of

peripheral neuropathy in such patients and the results were in line with the data already available in the medical literature.

This graph shows that the effect of supplementing Vitamin B12 for a period of 6 months. It shows reduction on VPT scores in all 3 groups of patient and which was statistically significant.

Discussion:

We demonstrated that metformin dosage and treatment duration could be consistent risk factors for development of vitamin B12 deficiency in type 2 Diabetes patients.

Dose and duration are interdependent factors which may lead to development and progression of diabetic Peripheral neuropathy

Supplementation of B12 may lead to reduction in neuropathy scores and this may lead to halting or reversal of symptoms of peripheral neuropathy in patients of type 2 diabetes mellitus which further needs to be confirmed clinically.

A study done by Pierce et al¹³ concluded that Vitamin B(12) was not routinely monitored in patients on high-dose metformin, even in those at highest risk (≥10 years of therapy), or in those with potential manifestations of vitamin B(12) deficiency (neuropathy).

Cases of vitamin B(12) deficiency and resulting anemia or neuropathy may be undiagnosed and untreated because of lack of monitoring. Prospective studies examining the effect of increased vitamin B 12 monitoring on identification and treatment of vitamin B12 deficiency in patients on metformin are warranted.

G H Tomkin et al⁸ 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. 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.

CONCLUSION

Patients of DM on metformin may suffer from silent cobalamin deficiency which might add to their existing symptoms of neuropathy.

Considering high cost of laboratory investigation for B12 deficiency with increasing prevalence of diabetes, laboratory tests for B12 at times is not possible in all diabetic patients.

Thus we propose routine supplementation of Vitamin B12 in patients of DM on Metformin Therapy, unless contraindicated as symptoms of peripheral neuropathy can possibly get reversed or might be halted to some extent. Such practice would reduce pain and suffering of diabetic patient and can improve quality of life of the patients

Such supplementation seems to be a clinically prudent and a cost-effective approach to combat peripheral neuropathy without much fearing for its overdose as B12 is a water soluble vitamin.

Thus routine supplementation of vitamin B₁₂ in proper doses (as per RDA) to patients on long-term metformin therapy seems to be clinically prudent and a cost-effective approach to combat neuropathy which might be induced by vitamin B12 deficiency due to prolonged use of metformin.

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: S11-66.
3. Committee of Clinical Practice Guideline. Treatment guideline for diabetes. 4th ed. Seoul: Korean Diabetes Association, 2011.
4. Wulffele M, Kooy A, Leher 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. Joyce Zalaket, Vitamin B12 deficiency in diabetic subjects taking metformin: A cross-sectional study in a Lebanese cohort: Journal of Nutrition & Intermediary Metabolism 11 (2018); 9-13
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, Jayatilke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000; 23:1227-31.
10. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J. 2010; 103:265-267.
11. 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.
12. Regionaal Tucht college voor de Gezondheidszorg te Eindhoven. (Regional Disciplinary Medical Board Eindhoven verdict) Uitspraak van 15 april 2009 nr. 113b Juni 2011 <https://stichtingB12.tekort.nl/wetenschap/stichting-B12-tekort-artikelen/English/intrinsic-factor-and-pernicious-anaemia/> accessed on 21 Nov 2019
13. Bijan Iraz et al , Prevention of Diabetic foot ulcer, Int. Journal of Preventive Medicine, 2013 March; 4(3); 373-376
14. Harrison's principles of internal medicine. 18th ed. New York: McGraw Hill, health professions division; 2015