International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 28-12-2018; Accepted: 31-01-2019
www.medicalsciencejournal.com
Volume 5; Issue 2; February 2019; Page No. 101-105

Assessment of Vitamin B12 deficiency and peripheral neuropathy in patients with diabetes

Dr. Prabhat Kumar Sinha
Associate Professor, Department of Medicine, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar, India

Abstract
The extended use of metformin, accompanied by vitamin B12 deficiency, may lead to increasing the considerable problem of peripheral neuropathy in non-insulin-dependent diabetes mellitus (NIDDM) patients. Neuropathy, being an impending health abnormality occurring due to vitamin B12 deficiency affects around 30% diabetics who are over 40 years of age and state about having a diminished sensory perception in their feet. Based on the above findings the present study was planned to evaluate the association between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes.
The current study was planned in the Department of Medicine in Darbhanga Medical College. Total 25 patients of the diabetes with peripheral neuropathy and 25 control patients with diabetes only were enrolled in the present study. The serum vitamin B12 concentration was evaluated in all the patients. Patients were defined as type 2 diabetes if they met the American Diabetic Association criteria with an age at diagnosis above 30 years. Serum vitamin B12 levels of the patients were determined using high performance liquid chromatography (HPLC).
The present study concludes that metformin use in Type 2 diabetes patients is associated with B12 deficiency and worsening clinical neuropathy, which is a dose-dependent effect. Hence we suggest for screening of B12 levels in long-term metformin users and treating them if they are deficient. The metformin use was associated with a significantly lower serum Vitamin B12 levels when adjusted for duration of diabetes. Serum Vitamin B12 deficient patients did not have a higher prevalence of anemia or neuropathy. Further study of the impact of duration of diabetes on serum Vitamin B12 levels and of functional markers of Vitamin B12 deficiency on haematological and neurological parameters will be interesting.

Keywords: vitamin B12, B12, peripheral neuropathy, neuropathy, diabetes

Introduction
Diabetic neuropathies are nerve damaging disorders associated with diabetes mellitus. These conditions are thought to result from a diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum) in addition to macrovascular conditions that can accumulate in diabetic neuropathy. Relatively common conditions which may be associated with diabetic neuropathy include third, fourth, or sixth cranial nerve palsy [1]. mononeuropathy; mononeuropathy multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy.
Diabetic neuropathy affects all peripheral nerves including sensory neurons, motor neurons, but rarely affects the autonomic nervous system. Therefore, diabetic neuropathy can affect all organs and systems, as all are innervated. There are several distinct syndromes based on the organ systems and members affected, but these are by no means exclusive. A patient can have sensorimotor and autonomic neuropathy or any other combination. Signs and symptoms vary depending on the nerve(s) affected and may include symptoms other than those listed. Symptoms usually develop gradually over years.
Vascular and neural diseases are closely related and intertwined. Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow. The first pathological change in the small blood vessels is narrowing of the blood vessels. As the disease progresses, neuronal dysfunction correlates closely with the development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy. Blood vessel opening agents (e.g., ACE inhibitors, α1-antagonists) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Thus, small blood vessel dysfunction occurs early in diabetes, parallels the progression of neural dysfunction, and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy. Elevated levels of glucose within cells cause a non-enzymatic covalent bonding with proteins, which alters their structure and inhibits their function. Some of these glycated proteins have been implicated in the pathology of diabetic neuropathy and other long-term complications of diabetes. Also called the sorbitol/aldose reductase pathway, the polyol pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney, and nerves [2].
Diabetic peripheral neuropathy is the most likely diagnosis for someone with diabetes who has pain in a leg or foot, although it may also be caused by vitamin B12 deficiency or osteoarthritis. A 2010 review in the Journal of the American Medical Association's "Rational Clinical Examination Series" evaluated the usefulness of the clinical examination in diagnosing diabetic peripheral neuropathy. While the physician typically assesses the appearance of the feet, presence of ulceration, and ankle reflexes, the most useful physical examination findings for large fiber neuropathy are an abnormally decreased vibration perception to a 128-Hz tuning fork (likelihood ratio (LR) range, 16–35) or pressure

sensation with a 5.07 Semmes-Weinstein monofilament (LR range, 11–16). Normal results on vibration testing (LR range, 0.33–0.51) or monofilament (LR range, 0.09–0.54) make large fiber peripheral neuropathy from diabetes less likely. Combinations of signs do not perform better than these 2 individual findings. Nerve conduction tests may show reduced functioning of the peripheral nerves, but seldom correlate with the severity of diabetic peripheral neuropathy and are not appropriate as routine tests for the condition [3].

Except for tight glucose control, treatments are for reducing pain and other symptoms. Medication options for pain control include antiepileptic drugs (AEDs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and capsaicin cream. About 10% of people who use capsaicin cream have a large benefit [10]. A systematic review concluded that "tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants." A further analysis of previous studies showed that the agents carbamazepine, venlafaxine, duloxetine, and amitriptyline were more effective than placebo, but that comparative effectiveness between each agent is unclear. The only three medications approved by the United States' Food and Drug Administration for diabetic peripheral neuropathy (DPN) are the antidepressant duloxetine, the anticonvulsant pregabalin, and the long-acting opioid tapentadol ER [4]. Before trying a systemic medication, some doctors recommend treating localized diabetic peripheral neuropathy with lidocaine patches [3].

Basic laboratory evaluation of polyneuropathy includes: complete blood count, erythrocyte sedimentation rate, vitamin B12, folate, comprehensive metabolic panel (including fasting blood glucose and both renal and liver function tests), thyroid function tests, and serum protein immunofixation electrophoresis. An important cause of vitamin B12 deficiency is iatrogenic, linked to cumulative doses of metformin. Depending on the results of these studies and the patient's history, other studies may include: methylmalonic acid with or without homocysteine, drug and toxin screens, urinalysis, and urine protein electrophoresis with immunofixation. Whether these routine studies need to be performed in known diabetics or prediabetics is unclear. Prediabetics can be identified with a fasting glucose, HbA1c, or glucose tolerance test [5].

The extended use of metformin, accompanied by vitamin B12 deficiency, may lead to increasing the considerable problem of peripheral neuropathy in non-insulin-dependent diabetes mellitus (NIDDM) patients. Neuropathy, being an impending health abnormality occurring due to vitamin B12 deficiency affects around 30% diabetics who are over 40 years of age and state about having a diminished sensory perception in their feet [6]. Regrettably, symptoms and signs of both diabetic neuropathy and paresthesia are somewhat similar, reduced vibration sense and diminished proprioception (vibration sense) linked to vitamin B12 deficiency [7]. Several studies conducted lately vexed to explain the possible relationship among prolonged metformin usage and its vitamin B12 deficiency associated peripheral neuropathy with contradictory results.

Reports have shown that there is an association between metformin use and vitamin B12 deficiency [8, 9]. However, the mechanism through which metformin induces vitamin B12 deficiency (VBD) in patients with T2DM is presently unclear. Some of the suggested mechanisms include alteration in small bowel motility, which stimulates bacterial overgrowth and consequential vitamin B12 deficiency. Others include competitive inhibition or inactivation of vitamin B12 absorption, alteration in intrinsic factor levels and interaction with the cubulin endocytic receptor. Also, inhibition of the calcium dependent absorption of vitamin B12-intrinsic factor (IF) complex at the terminal ileum has been suggested as one of the mechanisms.

Based on the above findings the present study was planned to evaluate the association between vitamin B12 deficiency and peripheral neuropathy in patients with diabetes.

Methodology

The current study was planned in the Department of Medicine in Darbhanga Medical College. Total 25 patients of the diabetes with peripheral neuropathy and 25 control patients with diabetes only were enrolled in the present study. The serum vitamin B12 concentration was evaluated in all the patients. Patients were defined as type 2 diabetes if they met the American Diabetic Association criteria with an age at diagnosis above 30 years. Serum vitamin B12 levels of the patients were determined using high performance liquid chromatography (HPLC). Vitamin B12 deficiency was defined as serum concentration of <200 pg/dl and borderline deficiency as 200-300 pg/dl. [10] Concentrations >300 pg/dl were considered as normal.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Patients of the diabetes with peripheral neuropathy

Exclusion criteria: Patients with gastrectomy, small bowel resection, liver disease, chronic kidney disease and thyroid disease were excluded from this study. Also, patients with recent intake of oral or intramuscular vitamin B12 supplement

Results & Discussion

The data from the all the enrolled patients were collected and presented as below. The data were discussed with the already reported literature findings.

Vitamin B12 concentrations were not found to be associated with neuropathy in the general population with diabetes. Neither the mean vitamin B12 concentration nor incidence of vitamin B12 deficiency was significantly different between the Diabetes and Diabetes with peripheral neuropathy groups at any level presented. Similarly, two studies in patients with type 2 diabetes found no difference in neuropathy while investigating the impact of metformin use on vitamin B12 deficiency

Table 1: Incidence of Vitamin B12 Deficiency and Peripheral Neuropathy

Group	Diabetes only	Diabetes with peripheral neuropathy
No. of Patients	25	25
Age		
30 – 40 years	1	0
41 – 50 years	3	2
51 – 60 years	8	3
61 – 70 years	13	20
Sex		
Males	13	16
Females	12	9
Weight	54 – 83 kg	59 – 85 kg
HbA1C	7.2 – 8.3	7.6 – 9.2
Hemoglobin	9.1 – 15.3	10.3 – 14.7

Table 2: Average Vitamin B12 Concentration (pg/ml)

Group	Diabetes only	Diabetes with peripheral neuropathy
No. of Patients	25	25
All Patients	672 ± 25	696 ± 31
Patients on Metformin	560 ± 19	583 ± 23
Patients on Proton pump inhibitors	704 ± 36	761 ± 28
Patients on Histamine-2 antagonists	782 ± 32	823 ± 39

Metformin improves peripheral insulin sensitivity and cardiovascular mortality risk [11, 12]. Moreover, metformin has beneficial effects on carbohydrate metabolism, weight loss, and vascular protection [13]. Most of the side effects associated with metformin are mild, such as abdominal distress and diarrhea [14]. However, metformin is reported to diminish cobalamin (vitamin B12) uptake in the terminal ileum [15]. Several studies have shown that long-term use of metformin leads to malabsorption of vitamin B12, with a decrease in the concentration of serum vitamin B12 from 30% to 14% [16]. Additionally, randomized control trials and cross-sectional studies have reported a decrease in serum vitamin B12 level between 9% and 52% with metformin use [15, 17]. A systematic review by Chapman et al. (2016) of individuals with T2DM found 10 out of 17 observational studies reported that metformin users had significantly lower levels of vitamin B12 than non-metformin users. Furthermore, a meta-analysis within this review of four clinical trials demonstrated that metformin significantly reduced overall vitamin B12 levels after three to six months of use [18].

De jager et al. [19]. showed that the negative impact of metformin use on vitamin B12 level becomes profound with increasing years of metformin use. This observation has been attributed to either or a combination of alteration in small bowel motility (which stimulates bacterial overgrowth with consequential vitamin B12 deficiency), alteration in intrinsic factor levels, interaction with the cubulin endocytic receptor and inhibition of the calcium dependent absorption of vitamin B12-intrinsic factor complex at the terminal ileum [20].

An association between obesity and poor glycaemic control has been reported [21]. Nagrebetsky et al. [22]. showed that there is a significant association between lower BMI and lower glycated haemoglobin (HbA1c) concentration, an index of glycaemic control.

Ting et al. (2006) [21]. reported that the dose and duration of metformin use were directly correlated with reduction in levels of serum vitamin B12 [23]. Furthermore, because vitamin B12 participates in an essential pathway of homocysteine metabolism, a reduction in vitamin B12 would increase the plasma level of homocysteine, which is strongly linked to cardiovascular prognosis in T2DM [24].

Metformin use is associated with vitamin B12 deficiency and can result in neuropathy, ranging from paresthesia and decreased peripheral sensation to changes in mental status [11]. Unfortunately, the symptoms of diabetic neuropathy overlap with impaired vibration sensation and proprioception, as well as paresthesia, which has also been found to be associated with vitamin B12 deficiency [7].

Metformin-induced Vitamin B12 deficiency has been ascribed to the binding of the hydrophobic tail of biguanide to the hydrocarbon core of membranes. The biguanide group being positively charged (protonated) gives a positive charge to the membrane and can displace divalent cations such as calcium. The uptake of Vitamin B12 into the ileal cells is calcium dependent and can thus be impaired by metformin.[25] Indian diets have also been reported to be low in calcium.[26] This could be another factor causing higher prevalence of Vitamin B12 deficiency. However, in a cross-sectional study of two different ethnic groups with type 2 diabetes mellitus in India and the United Kingdom, the prevalence of Vitamin B12 deficiency of 12% was found in the Indian population compared to 27% in a European population [27].

Vitamin B12 forms a complex with cubulin (endocytic) receptor at ileum for absorption This B-12 endocytic receptor complex is normally taken by ileal cell surface by calcium dependent process. Metformin with its protonated biguanide group binds to the B12-cubulin complex and imparts positive charge to it, alters membrane potential and competitively repels the divalent calcium ions thus preventing calcium dependent uptake, leading to malabsorption of B12 Owing to this mechanism, some of the patients with metformin-induced B12 deficiency have been treated by calcium supplementation as well [28, 29]. It has also been proposed to act by increasing bacterial overgrowth, altering bowel motility, and by direct inhibition of B12 absorption.

The findings in this study suggest that a cumulative dose of metformin is associated with a fall in B12 levels and worsening neuropathy. However, metformin is corner stone

of therapy in type 2 diabetes mellitus and has also been seen to have multiple beneficial effects on diabetes patients by altering Advanced Glycosylation end products (age) [31]. and neurodegenerative process. [32]. Hence, we suggest that serum B12 levels should be regularly monitored on Type 2 diabetes patients already at higher risk of neuropathy like vegans and those on long-term metformin therapy. The issue of routine prophylaxis of vitamin B12 in patients on metformin is a complicated one, since in a recently published study using data from the NHANES survey, even people on metformin taking even B12 supplements were three-fold more likely to be B12 deficient. [33]. We suggest that this issue should be addressed in a prospective controlled clinical trial. In view of our findings and on the basis of current evidence, we suggest that B12 levels should be monitored in patients on long-term metformin, and in cases with neuropathic symptoms and B12 deficiency should be treated by intramuscular injections as is routinely done. The frequency of screening should also be explored in a prospective study.

Conclusion

The present study concludes that metformin use in Type 2 diabetes patients is associated with B12 deficiency and worsening clinical neuropathy, which is a dose-dependent effect. Hence we suggest for screening of B12 levels in long-term metformin users and treating them if they are deficient.

The metformin use was associated with a significantly lower serum Vitamin B12 levels when adjusted for duration of diabetes. Serum Vitamin B12 deficient patients did not have a higher prevalence of anemia or neuropathy. Further study of the impact of duration of diabetes on serum Vitamin B12 levels and of functional markers of Vitamin B12 deficiency on haematological and neurological parameters will be interesting.

References

1. "What Is Microvascular Cranial Nerve Palsy?". aao.org. 1 September 2017. Archived from the original on 22 December 2017.
2. Behl T, Kaur I, Kotwani A. "Implication of oxidative stress in progression of diabetic retinopathy". Surv Ophthalmol. 2015; 61(2):187–196.
3. King SA. "Diabetic Peripheral Neuropathic Pain: Effective Management". Consultant. 2008; 48(11).
4. "Prescribing Information" (PDF). Archived (PDF) from the original on 2016-02-08. Retrieved 2013-01-26.
5. D England, GS Gronseth, G Franklin, et al. Evaluation of distal symmetrical polyneuropathy: the role of laboratory and genetic testing. Muscle Nerve. 2009; 39:116-125.
6. Centers for Disease Control and Prevention: National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. [Aug; 2017];Centers for Disease Control and Prevention.
7. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. Lindenbaum J, Healton EB, Savage DG, et al. http://www.nejm.org/doi/full/10.1056/NEJM198806303182604. N Engl J Med. 1988; 318:1720–1728.
8. Liu KW, Dai LK, Jean W. Metformin related vitamin B12 deficiency. Age and Ageing. 2006; 35(2):200–201. [PubMed] [Google Scholar]
9. Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. Nutrition. 2009; 25:1150.
10. Qureshi S, Ainsworth A, Winocour P. Metformin therapy and assessment for vitamin B12 deficiency: is it necessary? Practical Diabetes. 2011; 28:3024.
11. Zinman B, Gerich J, Buse J, Lewin A, Schwartz S, Raskin P, et al. American Diabetes Association. Standards of medical care in diabetes-2010 (vol 33, pg S11, 2010). Diabetes care. 2010; 33(3):692. [Google Scholar]
12. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes research and clinical practice. 2012; 97(3):359–67. 10.1016/j.diabres.2012.06.001 [PubMed] [CrossRef] [Google Scholar]
13. Group UPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998; 352(9131):854–65. [PubMed] [Google Scholar]
14. Nathan D, Buse JB, Davidson M, Heine R, Holman R, Sherwin R, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetologia. 2006; 49(8):1711–21. 10.1007/s00125-006-0316-2 [PubMed] [CrossRef] [Google Scholar]
15. 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(9):1227–31. [PubMed] [Google Scholar]
16. Ting RZ-W, Szeto CC, Chan MH-M, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Archives of internal medicine. 2006; 166(18):1975–9. 10.1001/archinte.166.18.1975
17. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes care. 2010; 33(1):156–61. 10.2337/dc09-0606 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes & Metabolism. 42(5):316–27.
19. Viikari J, Rönnemaa T, Koskinen P. Glucagon-C-peptide test as a measure of insulin requirement in type 2 diabetes: evaluation of stopping insulin therapy in eleven patients. Ann Clin Res. 1987; 19(3):178–82. [PubMed] [Google Scholar]
20. Nagrebetsky A, Griffin S, Kinmonth AL, et al. Predictors of suboptimal glycaemic control in type 2 diabetes patients: the role of medication adherence and body mass index in the relationship between glycaemia and age. Diabetes Res Clin Pract. 2012; 96(2):119–28.
21. Ting RZ-W, Szeto CC, Chan MH-M, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Archives of internal medicine. 2006; 166(18):1975–9.
22. Hoogeveen EK, Kostense PJ, Beks PJ, Mackaay AJ, Jakobs C, Bouter LM, et al. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non–insulin-dependent diabetes mellitus. Arteriosclerosis, Thrombosis, and Vascular

Biology. 1998; 18(1):133–8.
23. 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.
24. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, et al. High prevalence of low dietary calcium, high phytate consumption, and Vitamin D deficiency in healthy South Indians. Am J Clin Nutr. 2007; 85:1062-7.
25. Adaikalakoteswari A, Jayashri R, Sukumar N, Venkataraman H, Pradeepa R, Gokulakrishnan K, et al. Vitamin B12 deficiency is associated with adverse lipid profile in Europeans and Indians with type 2 diabetes. Cardiovasc Diabetol. 2014; 13:129.
26. Gilligan MA. Metformin and vitamin B12 deficiency. Arch Intern Med. 2002; 162:484-5.
27. Andres E, Goichot B, Schlienger JL. Food cobalamin malabsorption: A usual cause of vitamin B12 deficiency. Arch Intern Med. 2000; 160:2061-2.
28. Tanaka Y, Uchino H, Shimizu T, Yoshii H, Niwa M, Ohmura C, et al. Effect of metformin on advanced glycation endproduct formation and peripheral nervefunction in streptozotocin-induced diabetic rats. Eur J Pharmacol. 1999; 376:17-22.
29. Tanaka Y, Uchino H, Shimizu T, Yoshii H, Niwa M, Ohmura C, et al. Effect of metformin on advanced glycation endproduct formation and peripheral nervefunction in streptozotocin-induced diabetic rats. Eur J Pharmacol. 1999; 376:17-22.
30. El-Mir MY, Detaille D, R-Villanueva G, Delgado-Esteban M, Guigas B, Attia S, et al. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Mol Neurosci. 2008; 34:77-87.
31. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: The national health and nutrition examination survey, 1999-2006. Diabetes Care. 2012; 35:327-33.