Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Review Article

# The role of methylcobalamin in managing neuropathic pain: Addressing challenges and exploring solutions for improved patient outcomes

**Yatri A Dave**[1]*, **Keshini S Dhande**[1], **Dimpal D Maurya**[1]

[1]*Dept. of Medical Services, Corona Remedies Pvt. Ltd, Ahmedabad, Gujarat, India*

ARTICLE INFO

*Article history:*
Received 06-05-2024
Accepted 21-05-2024
Available online 27-06-2024

*Keywords:*
Methylcobalamin
Neuropathic Pain
Diabetes
Subcutaneous
Pre Filled Syringe

ABSTRACT

The escalating global diabetes burden, particularly in India, where 77 million cases exist, is exacerbated by factors such as obesity and unhealthy habits, with an anticipated rise to 134 million by 2045. Diabetic neuropathy affects 29.2% of the Indian population, with majority experiencing vitamin B12 deficiency. Challenges in B12 absorption arise from acid-suppressing medications, metformin use and increased reverse osmosis (RO) water consumption. Methylcobalamin, a bioactive B12 form, shows promise for neuropathy management, with subcutaneous administration preferred for its efficacy and convenience over intramuscular injections. The methodology involved a thorough search of PubMed and Google Scholar using relevant keywords, with articles screened based on specific criteria. In our study, we surveyed physicians, diabetologists, orthopaedics and neurophysicians using a questionnaire. We focused on the usage of vitamin B12 injections in patients with diabetic neuropathic pain and gathered feedback on their efficacy. It focused on comparative studies of SC (Subcutaneous) and IM (Intramuscular) administration of vitamin B12 in diabetes-related neuropathic pain. Methodological quality assessment and data synthesis summarized key findings on bioequivalence, pharmacokinetics, clinical outcomes and practitioner preferences for SC versus IM administration. Intramuscular administration is often avoided due to discomfort and frequent clinic visits. About 50% of practitioners prefer subcutaneous vitamin B12 injections. Metformin therapy may cause vitamin B12 deficiency. Despite some reluctance, a regimen of five vitamin B12 injections alternated every other day is recommended. Compliance with injections is moderate. Two-thirds of practitioners are aware of the subcutaneous route for vitamin B12 administration, but few know about comparative trials. Patient compliance could improve with self-administered pre-filled syringes (PFS). The conventional IM method of administering methylcobalamin may lead to patient non-compliance due to injection site discomfort. However, subcutaneous PFS of methylcobalamin provide a solution to this issue. PFSs offer a practical option for diverse patient groups, including those on long-term metformin therapy, individuals with low adherence to vitamin B12 supplements and recently diagnosed cases of vitamin B12 deficiency. The convenience of at-home PFS administration reduces the necessity for frequent clinic visits.



## 1. Introduction

The global burden of diabetes is substantial and on the rise, particularly in developing nations such as India, largely driven by escalating rates of overweight/obesity and unhealthy behaviours. Estimations from 2019 indicated that India possessed 77 million cases of diabetes, a figure projected to surpass 134 million by 2045. Notably, approximately 57% of these cases remain undiagnosed.[1] Based on the prevailing circumstances within the Indian population, the incidence of diabetic neuropathy stands at 29.2%.[2] Among patients with diabetic neuropathy, majority

* *Corresponding author*.
*E-mail address*: yatrid@coronaremedies.com (Y. A. Dave).

https://doi.org/10.18231/j.ijn.2024.015

of them were having vitamin B12 deficiency.[3]

Cobalamin, a water-soluble vitamin, functions as a cofactor in numerous methylation processes. Its deficiency disrupts DNA synthesis, cell metabolism and red blood cell function. Adenosylcobalamin and methylcobalamin are the biologically active cofactor forms of vitamin B12. Cobalamin plays a vital role in the myelination of both central and peripheral nervous systems and its deficiency leads to demyelination in dorsal and lateral columns, as well as peripheral and optic nerves. Absorption occurs with intrinsic factor, synthesized by parietal cells in the stomach, primarily in the terminal ileum, and is eventually stored in the liver.[4] The primary cause for vitamin B12 deficiency prevalent today is food-bound cobalamin malabsorption, there is a hindered release of vitamin B12 from consumed food. For instance, achlorhydria, gastritis, gastrectomy and the usage of proton pump inhibitors (PPIs) or antacids all result in reduced secretion of hydrochloric acid, consequently diminishing the liberation of vitamin B12 from dietary proteins. A recent trial exhibited a dose- and time-dependent correlation between the use of PPIs or histamine H2-receptor antagonists and the eventual development of vitamin B12 insufficiency. Pervasive utilization of acid-suppressing agents may thus induce vitamin B12 deficiency, which could go unnoticed due to insufficient awareness. Similarly, the use of metformin also influences vitamin B12 levels. The alteration in cobalamin was concomitant with an elevation in serum homocysteine, noted to potentially amplify the risk of cardiovascular disease development in patients with type 2 diabetes mellitus.[5] Furthermore, there has been an increase in the utilization of RO water, a factor that may contribute to a further reduction in the vitamin B12 levels within the population.[6]

Methylcobalamin (MeCbl) represents one bioactive form of vitamin B12 capable of directly engaging in homocysteine metabolism. Increasing research demonstrates the advantageous impact of MeCbl on both clinical and experimental peripheral neuropathy. IM injection of vitamin B12 is preferred as it has well defined pharmacokinetics and infrequent maintenance dosing. Nevertheless, the intramuscular route may induce pain and irritation at the injection site leading to patient non-adherence to long-term therapy.[7] The SC administration of methylcobalamin is currently preferred due to its equivalent bioavailability compared to the IM route. SC administration offers faster absorption and the added benefit of self-administration, which surpasses the IM route.[8]

## 2. Materials and Methods

The methodology involved a comprehensive literature search across PubMed and Google Scholar databases using keywords related to vitamin B12, diabetes, neuropathic pain and administration routes. We incorporated a questionnaire-based survey targeting physicians, diabetologists, orthopaedics and neurophysicians. Within our study design, we incorporated inquiries pertaining to the utilization of vitamin B12 injections in patients afflicted with diabetic neuropathic pain, with a specific focus on eliciting feedback regarding their usage. Articles published were screened based on inclusion and exclusion criteria, focusing on comparative studies for SC and IM administration. Methodological quality assessment was performed using appropriate tools and data synthesis involved a narrative approach, summarizing key findings regarding bioequivalence, pharmacokinetics, clinical outcomes and practitioner preferences for SC versus IM administration of vitamin B12 in neuropathic pain management.

### *2.1. Questionnaire based survey analysis among patients with diabetic neuropathic pain*

To explore the therapeutic potential of subcutaneous methylcobalamin for diabetic neuropathic pain management, we conducted a survey using a questionnaire to assess awareness levels among physicians, diabetologists, orthopaedics and neurophysicians. The conventional IM administration method is often avoided due to patient-reported injection site discomfort, irritation, the need for frequent clinic visits for administration and patients' time constraints. Conversely, the SC route may offer greater convenience for this patient demographic. The practitioners reached a consensus to prescribe the SC route under the stipulation that its pharmacokinetic profile matches to that of the IM route in all respects. Approximately 50% of healthcare professionals elect to recommend the administration of subcutaneous injections containing vitamin B12 to individuals diagnosed with diabetic neuropathic pain. After thoroughly assessing patients' serum vitamin B12 levels, this targeted approach aims to address deficiencies and improve overall health outcomes, particularly in diabetic neuropathic pain management. Long- term metformin therapy can contribute in development of vitamin B12 deficiency, primarily attributed to its influence on absorption mechanisms. Specifically, metformin is believed to hinder the binding of the calcium-dependent intrinsic factor-vitamin B12 complex to the ileal cubilin receptor by antagonizing the calcium cation. Generally, healthcare providers opted to administer a regimen of five vitamin B12 injections to patients, alternately every other day, aiming to enhance therapeutic outcomes. Patients who received vitamin B12 injections demonstrated an average compliance rate. Numerous factors contribute to suboptimal adherence to vitamin B12 injections, including the necessity for frequent clinic visits, discomfort associated with intramuscular injection, constraints on time for multiple appointments and administrations. $2/3^{rd}$ of practitioners were aware

that vitamin B12 injection can be given via subcutaneous route. A minority of practitioner's demonstrated awareness regarding trials pertaining to the bioequivalence of vitamin B12 injections administered IM versus SC. The consensus among practitioners indicated that patient compliance rates can be enhanced through the self-administration of vitamin B12 injections using PFS via subcutaneous route.

## 3. Discussion

The article presented findings from a questionnaire-based study investigating healthcare practitioners' awareness of the bioequivalence between subcutaneous and intramuscular administration of vitamin B12 for neuropathic pain management. By assessing practitioners' understanding of this equivalence in pharmacokinetic profiles and clinical outcomes, the study aimed to shed light on the prevailing knowledge among healthcare professionals regarding optimal treatment approaches for managing vitamin B12 deficiency.

A study on treatment of vitamin B12 deficiency anemia suggested that cobalamin serves as a crucial cofactor for synthase and mutase enzymes, which play integral roles in maintaining methylation reactions within the brain. Insufficiency of cobalamin can lead to the impairment of myelin synthesis and enhancement of various neurotoxic processes. The classic manifestation of cobalamin deficiency is characterized by macrocytic megaloblastic anemia.[9–11]

A research investigation into the prevalence of vitamin B12 deficiency among the population of North India determined that 47.0% of individuals in this demographic exhibit insufficient levels of vitamin B12[12]. Furthermore, a study on vitamin B12 deficiency in metformin-treated type-2 diabetes patients, suggested that out of 121 patients, the prevalence of vitamin B12 deficiency was 29.1% among patients with diabetic neuropathy.[3] Ankar et al. presented that pernicious anemia (vitamin b12 deficiency) arises from an autoimmune response where antibodies target intrinsic factor, inhibiting its function in facilitating vitamin B12 absorption in the terminal ileum. Gastric bypass surgery poses a risk for B12 deficiency due to the altered route bypassing intrinsic factor production by parietal cells. Damage to the terminal ileum, as seen in Crohn's disease surgical resections, can also impair B12 absorption. Additionally, conditions like celiac disease, Diphyllobothrium latum infection and prolonged vegan diets can lead to B12 deficiency despite adequate liver stores.[13] Green et al. conducted a study investigating the implications of vitamin B12 deficiency, highlighting its potential impact across all age groups. Their findings suggest that individuals, particularly infants, children, adolescents and women of reproductive age have higher susceptibility to vitamin B12 deficiency, especially in regions where dietary access to B12-rich animal-derived foods is limited.[14]

A systematic review and meta-analysis on association between neuropathy and B- vitamins by Stein et al revealed that patients diagnosed with peripheral neuropathy demonstrated higher susceptibility for vitamin B12 deficiency.[15] In a study investigating vitamin B12 deficiency among individuals with type 2 diabetes mellitus (T2DM) receiving metformin treatment, it was observed that nearly one-third of patients with a prior diagnosis of T2DM and peripheral neuropathy exhibited signs of vitamin B12 deficiency.[3] Neuropathies frequently stem from evident vitamin B12 deficiency, characterized by low serum B12 levels concurrent with elevated concentrations of B12-dependent metabolites, namely methylmalonic acid (MMA) and/or homocysteine (HCys).[16]

Roy et al. suggested that metformin, the primary medication for managing Type 2 diabetes, is effective in controlling glucose levels. However, it can lead to deficiencies in vitamin B12 and folic acid, raising homocysteine levels and potentially causing peripheral neuropathy. Supplementing with vitamin B12 is advisable and monitoring B12 levels annually for long-term users is recommended.[17] A comprehensive study evaluating the respective therapeutic outcomes of vitamin B12 and nortriptyline in the context of alleviating symptomatic painful diabetic neuropathy underscored the superior efficacy of vitamin B12 as compared to nortriptyline. This finding suggests that vitamin B12 may represent a more favourable treatment option for individuals afflicted with painful diabetic neuropathy, highlighting its potential significance in clinical management strategies for this condition.[18]

Methylcobalamin, whether utilized independently or in conjunction with other agents, demonstrates notable analgesic potential in various patient cohorts and animal models, including those afflicted with nonspecific low back pain, neck pain, diabetic neuropathic pain, subacute herpetic neuralgia, glossopharyngeal neuralgia and trigeminal neuralgia. Recent investigations suggest several plausible mechanisms: firstly, MeCbl enhances nerve conduction velocity; secondly, it promotes the regeneration of injured nerves, thereby restoring neuromuscular function and mitigating peripheral hyperalgesia (increased pain from a stimulus that usually provokes pain) and allodynia (pain due to a stimulus that does not usually provoke pain); and thirdly, it suppresses ectopic spontaneous discharges originating from peripheral primary sensory neurons during states of neuropathic pain. Given its classification as a vitamin, MeCbl holds promise as a potentially safe therapeutic option for peripheral neuropathy management.[19]

A research investigation assessing the efficacy of various routes of vitamin B12 supplementation in treating individuals with vitamin B12 deficiency indicated

preference for administration routes. IM delivery emerged as the most favoured and conventional route, followed by sublingual (SL) administration and oral ingestion. Although conventional IM route can be associated with injection site pain. These findings underscore the comparative effectiveness and acceptability of IM, SL and oral routes for vitamin B12 supplementation in the management of vitamin B12 deficiency within clinical practice.[20]

A study on sciatic nerve injection injury suggested that nerve injury frequently arises as a consequence of intramuscular injection, with the sciatic nerve emerging as the most frequently affected, notably prevalent among paediatric, geriatric and underweight patients. The spectrum of neurological manifestations encompasses a broad range, extending from minor transient pain to severe sensory disturbances and motor loss, characterized by poor recovery.[21]

SC injections offer immediate advantages over both intravenous (IV) and IM injections. They necessitate the use of a smaller needle and injections of volumes up to 1 mL are generally not painful. For patients necessitating multiple doses, SC injections provide a wider array of alternative sites. Furthermore, drug absorption following SC administration is slower compared to IV injections, potentially avoiding the risks associated with bolus administration, such as infusion reactions. SC injections generally exhibit a superior safety profile when compared to IV or IM injections. If an infectious agent is introduced subcutaneously, its effects are usually confined to a local rather than systemic infection. Additionally, unlike the skilled healthcare personnel required for IV and IM injections, SC injections can be self-administered by the patient or a caregiver, thereby facilitating potential at-home administration in certain cases.[22]

A study published in the 2023 edition of the IP Indian Journal of Neurosciences compared the bioavailability of methylcobalamin administered via SC injection at a dose of 1500 mcg against IM injection. The research determined that commercially available oral vitamin B12 tablets suffer from restricted bioavailability. The SC injection method exhibited non-inferiority to the IM injection regarding bioavailability, displaying analogous pharmacokinetic characteristics. Safety assessments affirmed the well-tolerated and safe nature of both treatment modalities.[8]

## 4. Conclusion

The conventional IM administration route of methylcobalamin may pose challenges, as patients often exhibit non-compliance due to pain related discomfort at the injection site. Furthermore, intramuscular injections frequently damage the sciatic nerve. However, this issue can be mitigated by employing subcutaneous PFS of methylcobalamin. Prefilled syringes of methylcobalamin offer a viable option across various patient demographics, including those undergoing prolonged metformin therapy for diabetes, individuals with poor adherence to vitamin B12 supplementation and those recently diagnosed with diabetic neuropathic pain. The convenience of administering PFS at home eliminates the need for frequent clinic visits.

## 5. Author Contributions

Dr. Yatri Dave conceptualized, designed, conducted data research and drafted the article. Dr. Keshini Dhande and Dimpal Maurya participated in the review and revision process of the draft article for the journal.

## 6. Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## 7. Abbreviations

HCys: Homocysteine: IM: Intramuscular; MeCbl: Methylcobalamin; MMA: Methylmalonic acid; PFS: Prefilled Syringes; PPI: Proton Pump Inhibitors; RO: Reverse Osmosis; SC: Subcutaneous; SL: Sublingual; T2DM: Type 2 Diabetes Mellitus

## 8. Source of Funding

None to declare.

## 9. Conflict of Interest

None to declare.

## Acknowledgments

Acknowledgments are extended to Nimesh Modi, Manager, for his invaluable contributions in reviewing and providing feedback on the draft of this paper for publication in the journal.

## References

1. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol*. 2021;69(11):2932–8.
2. Bansal D, Gudala K, Muthyala H, Esam HP, Nayakallu R, Bhansali A, et al. Prevalence and risk factors of development of peripheral diabetic neuropathy in type 2 diabetes mellitus in a tertiary care setting. *J Diabetes Investig*. 2014;5(6):714–21.
3. Singla R, Garg A, Surana V, Aggarwal S, Gupta G, Singla S, et al. Vitamin B12 deficiency is endemic in Indian population: a perspective from North India. *Indian J Endocrinol Metab*. 2019;23(2):211–4.
4. Gwathmey KG, Grogan J. Nutritional neuropathies. *Muscle Nerve*. 2020;62(1):13–29.
5. Shipton MJ, Thachil J. Vitamin B12 deficiency - A 21st century perspective. *Clin Med (Lond)*. 2015;15(2):145–50.
6. Gupta ES, Sheth SP, Ganjiwale JD. Association of vitamin B12 deficiency and use of reverse osmosis processed water for drinking: a cross-sectional study from western India. *J Clin Diagn Res*. 2016;10(5):37–40.

7. Wentworth BJ, Copland AP. Revisiting vitamin B12 deficiency: A clinician's guide for the 21st century. *Pract Gastroenterol*. 2018;182:28–49.
8. Modi NP, Jaiswal AJ, Vasu P. Methylcobalamin injection 1500 mcg SC route versus IM route: A randomized parallel comparative bioavailability study. *IP Indian J Neurosci*. 2023;9(3):141–7.
9. Lane LA, Rojas-Fernandez C. Treatment of vitamin b(12)-deficiency anemia: oral versus parenteral therapy. *Ann Pharmacother*. 2002;36(7-8):1268–72.
10. Weir DG, Scott JM. Brain function in the elderly: role of vitamin B12 and folate. *Br Med Bull*. 1999;55(3):669–82.
11. Herman NE. Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy. *Drugs Aging*. 1998;12(4):277–92.
12. Stein J, Geisel J, Obeid R. Association between neuropathy and B-Vitamins: A systematic review and meta-analysis. *Eur J Neurol*. 2021;28(6):2054–64.
13. Ankar A, Kumar A. Vitamin B12 deficiency. InStatPearls [Internet]. StatPearls Publishing; 2022.
14. Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, et al. Vitamin B12 deficiency. *Nat Rev Dis Primers*. 2017;3(1):17040. doi:10.1038/nrdp.2017.40.
15. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. *BMC Pharmacol Toxicol*. 2016;17:44. doi:10.1186/s40360-016-0088-3.
16. Solomon LR. Functional vitamin B12 deficiency in advanced malignancy: implications for the management of neuropathy and neuropathic pain. *Support Care Cancer*. 2016;24(8):3489–94.
17. Roy RP, Ghosh K, Ghosh M, Acharyya A, Bhattacharya A, Pal M. Study of Vitamin B12 deficiency and peripheral neuropathy in metformin-treated early Type 2 diabetes mellitus. *Indian J Endocrinol Metab*. 2016;20(5):631–7.
18. Talaei A, Siavash M, Majidi H, Chehrei A. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. *Int J Food Sci Nutr*. 2009;60(Suppl 5):71–6.
19. Zhang M, Han W, Hu S, Xu H. Methylcobalamin: a potential vitamin of pain killer. *Neural Plast*. 2013;p. 424651. doi:10.1155/2013/424651.
20. Abdelwahab OA, Abdelaziz A, Diab S, Khazragy A, Elboraay T, Fayad T, et al. Efficacy of different routes of vitamin B12 supplementation for the treatment of patients with vitamin B12 deficiency: A systematic review and network meta-analysis. *Ir J Med Sci*. 2024;193(3):1621–9.
21. Jung KH, Park SH. Sciatic nerve injection injury. *J Int Med Res*. 2014;42(4):887–97.
22. Dychter SS, Gold DA, Haller MF. Subcutaneous drug delivery: a route to increased safety, patient satisfaction, and reduced costs. *J Infus Nurs*. 2012;35(3):154–60.


## Author biography


**Yatri A Dave,** Executive https://orcid.org/0009-0007-0206-2415

**Keshini S Dhande,** Executive https://orcid.org/0009-0000-2785-6085

**Dimpal D Maurya,** Executive https://orcid.org/0009-0005-8468-4255


**Cite this article:** Dave YA, Dhande KS, Maurya DD. The role of methylcobalamin in managing neuropathic pain: Addressing challenges and exploring solutions for improved patient outcomes. *IP Indian J Neurosci* 2024;10(2):64-68.