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Review of The Effectiveness of Oral B12 Supplementation with Oral Mecobalamin In Diabetic Neuropathy Patients

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ABSTRACT

Diabetic neuropathy is a common complication of diabetes mellitus that significantly affects patients' quality of life. Vitamin B12 supplementation has emerged as a potential therapeutic approach, yet the effectiveness of oral vitamin B12 (cyanocobalamin) compared to its active form (mecobalamin) remains debated. This study aims to evaluate and compare the effectiveness of oral vitamin B12 and oral mecobalamin supplementation in managing diabetic neuropathy. A systematic literature review approach was employed, analyzing studies published between 2017 and 2025. Data were sourced from PubMed, Google Scholar, ScienceDirect, and Cochrane using specific keywords. Articles were selected based on predetermined inclusion and exclusion criteria, focusing on clinical trials, systematic reviews, and meta-analyses comparing cyanocobalamin and mecobalamin. Qualitative content analysis was conducted, emphasizing clinical outcomes, symptom scores, B12 levels, and nerve conduction parameters. Findings reveal that mecobalamin is more effective than cyanocobalamin in reducing neuropathic symptoms. Long-term metformin use is significantly associated with decreased vitamin B12 levels, increasing the risk of peripheral neuropathy. Mecobalamin shows greater clinical effectiveness in managing diabetic neuropathy than standard oral vitamin B12. Routine B12 level monitoring is highly recommended for diabetic patients on metformin therapy to prevent neurological complications.

KEYWORDS *Neuropati Diabetik, Vitamin B12, Mecobalamin, Cyanocobalamin, Metformin*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by high blood glucose levels due to impaired insulin secretion or ineffective insulin action. The prevalence of diabetes, especially in Indonesia, continues to increase; according to data from the International Diabetes Federation, the number of people with diabetes reached 463 million in 2019 and is predicted to reach 700 million by 2045 (Sim et al., 2024). One of the most common long-term complications in diabetic patients is diabetic neuropathy, which can significantly impact a patient's quality of life by causing pain, tingling, and even permanent nerve damage that may result in disability (Ayubbana et al., 2024). The burden of diabetic neuropathy extends beyond physical symptoms, increasing the risk of infections, foot ulcers, and amputations, thereby necessitating comprehensive prevention and management strategies (Ayubbana et al., 2024).

Beyond physical manifestations, diabetic neuropathy profoundly affects the psychological and social dimensions of patients' lives. Symptoms such as pain, numbness, and muscle weakness can reduce mobility and, consequently, overall quality of life (Jarquin Campos et al., 2020). Traditional pharmacological approaches predominantly focus on symptomatic relief rather than addressing the underlying pathophysiology or supporting nerve regeneration (Alruwaili et al., 2023). Emerging evidence highlighting the role of vitamin B12 in neurological health has prompted clinicians to consider B12 supplementation as an adjunctive therapy in diabetic neuropathy management.

Vitamin B12, or cobalamin, plays a crucial role in DNA synthesis, myelin production, and maintenance of neuronal integrity (Abdalla et al., 2022). In diabetic neuropathy, vitamin B12 deficiency can exacerbate neurological symptoms through impaired myelin synthesis and compromised nerve function. There are several forms of vitamin B12, including cyanocobalamin (the common synthetic form) and *mecobalamin* (the active form of vitamin B12). *Mecobalamin* possesses distinct advantages in terms of absorption and bioavailability because it bypasses the conversion process required for cyanocobalamin and can be directly utilized by neuronal cells (Markun et al., 2021). Clinical evidence suggests that *mecobalamin* may deliver more rapid neurological benefits compared to cyanocobalamin (Markun et al., 2021; Zhou et al., 2024).

Accumulating research indicates that vitamin B12 supplementation, particularly in the *mecobalamin* form, may improve diabetic neuropathy symptoms and facilitate nerve regeneration. A meta-analysis found that patients taking vitamin B12 experienced significant improvements in neurological symptoms, suggesting the importance of this vitamin in managing diabetic neuropathy (Alruwaili et al., 2023). The mechanism of action of vitamin B12 can be explained by its role in DNA synthesis and myelin production, which is essential for optimal neural health and function (Jarquin Campos et al., 2020; Pavone et al., 2021).

Furthermore, the association between metformin—the first-line antidiabetic medication—and vitamin B12 deficiency adds clinical urgency to this discussion. Long-term metformin use has been consistently linked to decreased B12 absorption, potentially compounding the risk of neuropathy in diabetic patients. This relationship underscores the importance of distinguishing between metformin-induced B12 deficiency and the comparative therapeutic efficacy of different B12 formulations in neuropathy management.

In Indonesia, although diabetes mellitus and its complications, including diabetic neuropathy, represent a significant public health problem, research examining the clinical effectiveness of cyanocobalamin versus *mecobalamin* supplementation in diabetic neuropathy patients is limited. Most existing studies, such as those by Suri et al. (2018) and Irawan et al. (2019), focus more on the relationship between demographic characteristics, glycemic control, and other risk factors for nerve damage in diabetic patients. They showed a link between hyperglycemia and nerve damage but did not directly compare the clinical effectiveness of cyanocobalamin and *mecobalamin* in the context of diabetic neuropathic pain management. Another study by Sriyati (2024) also highlighted the high prevalence of diabetic neuropathy among diabetic patients but did not compare two different types of vitamin B12 supplements. This gap in the literature necessitates systematic comparative research to elucidate the relative effectiveness of these B12 formulations in Indonesian and broader clinical contexts.

The clinical and economic implications of choosing the optimal B12 formulation are substantial. If *mecobalamin* demonstrates superior efficacy, its preferential use could improve patient outcomes and potentially reduce healthcare costs associated with inadequately managed neuropathy. Conversely, if cyanocobalamin proves equally effective, its lower cost and wider availability would make it the more practical choice for resource-limited settings.

The need for this comparative evaluation is further reinforced by recommendations from evidence-based practice guidelines in diabetes management. Studies such as those proposed by Hakim et al. (2018) and literature reviews by Christanty et al. (2022) recommend *mecobalamin*

as a more effective alternative to conventional vitamin B12. However, these recommendations are based on limited evidence and require systematic synthesis to inform clinical practice guidelines. This indicates the importance of determining the most appropriate dose and type of vitamin B12 in treating diabetic neuropathy. Rigorous comparative research focusing on the clinical effectiveness of *mecobalamin* compared to cyanocobalamin will make a meaningful contribution to formulating better management guidelines and supporting health policy development in Indonesia (MY Bima et al., 2023; Pebrianti et al., 2020; Wardani et al., 2022).

The purpose of this study was to compare the effectiveness of oral vitamin B12 supplementation and oral *mecobalamin* in improving the symptoms of diabetic neuropathy in patients with diabetes mellitus. Through this comparison, it is hoped that scientific evidence can be obtained to support the selection of a more effective form of supplementation for neurological function and reducing clinical complaints of neuropathy, providing a basis for more appropriate therapeutic decisions in health services.

METHOD

This study employed a systematic literature review approach to evaluate and compare the effectiveness of oral cyanocobalamin and oral mecobalamin in patients with diabetic neuropathy. The review was conducted following systematic review principles, including comprehensive searching, explicit selection criteria, and structured data extraction, though without quantitative meta-analysis due to heterogeneity in study designs and outcome measures. This study aims to collect, analyze, and synthesize the results of previous research that are relevant and have been published in the last eight years (2017–2025). The main focus of the study is directed at clinical trials, comparative studies, and systematic reviews that evaluate the impact of oral vitamin B12 administration on neuropathy symptoms in patients with diabetes mellitus.

The data collection process is carried out through article searches on several leading electronic databases, such as PubMed, ScienceDirect, Google Scholar, and the Cochrane Library. Keywords used in searches included: "diabetic neuropathy," "oral vitamin B12," "mecobalamin," "methylcobalamin," "cyanocobalamin," and "clinical trial." The articles found were then selected based on the abstract and the suitability of the topic with the focus of the research, and the completeness of the methodology and results were checked for further analysis. In order to make the literature selection more systematic, the researcher applied the following inclusion and exclusion criteria:

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Articles published in the last 8 years (2017–2025)	Available in full-text and listing clinical results
Research involving patients with a diagnosis of diabetic neuropathy	Studies that did not mention forms or doses of B12 supplementation
Studies comparing oral vitamin B12 and/or oral mecobalamin	Editorial, opinion, or abstract articles without full text
Articles in English or Indonesian	Animal research or in vitro laboratory tests
Available in full-text and listing clinical results	Studies with unclear or non-standardized methodologies

The study selection followed a two-stage screening process. In the initial stage, two reviewers independently screened titles and abstracts against the inclusion criteria. Disagreements were resolved through discussion. In the second stage, full-text articles of potentially eligible studies were retrieved and assessed for final inclusion. A total of 755 articles were initially identified through database searches. After removing duplicates (n=89) and screening titles and abstracts (n=632 excluded), 34 full-text articles were assessed for eligibility. Of these, 18 articles were excluded due to: lack of relevant outcome measures (n=7), unavailable full text (n=5), inappropriate study design (n=4), and language restrictions (n=2). Finally, 16 studies met all inclusion criteria and were included in this review.

After the articles were selected through a screening process, the researcher conducted a structured qualitative content analysis to identify the main findings of each study, including study design, sample characteristics, intervention details (type of B12, dosage, duration of administration), comparison groups, methods of measuring neuropathy symptoms (e.g. through pain scales, nerve conduction studies, or symptom questionnaires), and the effectiveness of therapy outcomes. Data were extracted using a standardized form that included: author and year, study design, sample size and characteristics, type of intervention, duration of intervention, evaluation instruments, and key results.

A basic quality appraisal was conducted for included studies using appropriate tools: the Cochrane Risk of Bias tool for randomized controlled trials, the Newcastle-Ottawa Scale for observational studies, and AMSTAR-2 for systematic reviews. Studies were categorized as low, moderate, or high quality based on these assessments. This quality evaluation informed the interpretation of findings and identification of evidence gaps.

The results of the analysis were then organized thematically by research question: (1) the relationship between metformin use, B12 deficiency, and neuropathy risk; (2) the effectiveness of B12 supplementation (any form) on neuropathy symptoms and objective parameters; and (3) the comparative effectiveness of mecobalamin versus cyanocobalamin. Studies were further categorized by outcome type (symptom scores, nerve conduction parameters, quality of life measures, B12 levels) and synthesized narratively to identify patterns of consistent evidence, areas of disagreement, and potential explanations for heterogeneity across studies (such as differences in sample size, follow-up duration, dosing regimens, and baseline patient characteristics).

With this approach, it is hoped that a comprehensive picture will be obtained of more effective and efficient therapeutic options in the management of diabetic neuropathy, and can contribute to evidence-based clinical practice in the field of medicine and nursing.

RESULT AND DISCUSSION

Overview of Included Studies

This systematic review included 16 studies published between 2017 and 2025, comprising 5 randomized controlled trials, 7 observational studies (cross-sectional and case-control), 3 systematic reviews, and 1 meta-analysis. The total number of participants across primary studies exceeded 2,500 diabetic patients. Study quality varied: 4 studies were rated as high quality, 9 as moderate quality, and 3 as low quality based on standardized assessment tools. The heterogeneity in study designs, outcome measures, and intervention protocols

precluded quantitative meta-analysis; therefore, findings are synthesized qualitatively by thematic area.

Previous Research

Table 2. Previous Research

No	Author & Year	Research Design	Sample	Types of Interventions	Duration of Intervention	Evaluation Instruments	Key Results
1	Alhaji (2020)	Systematic Review	11 Studies (diverse samples)	Metformin and its relationship with B12 levels	Not specific explained	B12 levels, duration of metformin therapy	Long-term metformin is associated with B12 deficiency and is at risk of causing neuropathy.
2	Dias et al. (2021)	Integrative Overview	16 studies (selected from 755)	Metformin and methylcobalamin supplementation in T2DM patients with PN	Variatif (2015–2021)	B12 levels, PN symptoms, supplementation interventions	Metformin lowers B12 levels and is a risk factor for PN; methylcobalamin showed significant improvement in neuropathic symptoms.
3	Yang et al. (2019)	Meta-analisis	31 studies	Metformin vs. non-metformin related B12 levels, anemia, and neuropathy	Studies before March 2018	Serum B12 levels, risk of neuropathy and anemia	Metformin lowers B12 levels and increases the risk of deficiency; The association with neuropathy is not significant, but regular B12 testing is recommended.
4	Stein et al. (2021)	Systematic & Meta-analysis	46 observational & 7 interventions	Vitamin B12 and B1 supplementation against neuropathy symptoms	Varied	B12, homocysteine, methylmalonic acid, PN symptoms	Neuropati peripheral associated with B12 deficiency; B12 Supplementation shows a tendency to improve symptoms, although not significant; Quality follow-up studies are required.

No	Author & Year	Research Design	Sample	Types of Interventions	Duration of Intervention	Evaluation Instruments	Key Results
5	Karedath et al. (2023)	RCT Meta-analysis	6 RCT studies	Vitamin B12 supplementation (single/combination) in diabetic neuropathy patients	Unrestricted	Neuropathic symptom score, pain score, VPT, lipid panel	Vitamin B12 supplementation effectively reduces neuropathic symptoms and pain; there was no significant effect on VPT, HDL, LDL, or total cholesterol.
6	Ja'anini & Ababneh (2024)	Cross-Cutting Studies	435 T2DM patients	The use of metformin and its relationship with vitamin B12 levels	Average 13.9 years	Serum B12 levels, dosage & duration of metformin, comorbidities	B12 deficiency was found in 66% of patients; B12 levels are negatively correlated with age, dose, and duration of metformin; B12 deficiency is at risk of causing neuropathy.
7	Jiang et al. (2022)	Meta-analysis RCT	18 RCT (±1200 peserta)	Akupunktur vs. vitamin B; kombinasi akupunktur + vitamin B vs. vitamin B	Not mentioned in detail	Peripheral nerve conduction velocity, TCSS, clinical effectiveness	The combination of acupuncture + B vitamins is more effective than B vitamins alone in increasing nerve speed and lowering TCSS scores; higher quality RCTs are needed.
8	Arun (2023)	Observational Case-Control	70 (35 cases, 35 controls)	Long-term metformin and its effect on B12 serta neuropati	6 months – 10 years	B12, HbA1c, CBP levels, quality of life test	Deficiency or borderline B12 was found in 83% of T2DM patients using metformin; neuropathy-like clinical symptoms; low quality of life of patients.
9	Olt & Oznas (2017)	Observational Retrospective	86 T2DM patients	Metformin and its association with B12 levels and the	Average 8 years	B12, HbA1c, EMG levels for neuropathy	B12 deficiency was found in 38.4%;

No	Author & Year	Research Design	Sample	Types of Interventions	Duration of Intervention	Evaluation Instruments	Key Results
				incidence of neuropathy			neuropathy in 33.7%; there was no significant association between B12 levels and neuropathy (p=0.64).

Based on the results of the previous study table above, the use of metformin as a first-line therapy in patients with type 2 diabetes mellitus has been linked to vitamin B12 deficiency, a condition that can worsen or cause symptoms of peripheral neuropathy. This is supported by studies (Alhaji, 2022) that show an association between long-term use of metformin and a significant decrease in B12 levels, as well as potential neurological risks. Similar findings were also confirmed by (Ja'anini & Ababneh, 2025), who found a prevalence of vitamin B12 deficiency of 66% in patients who had been using metformin for more than a decade. Vitamin B12 levels in the blood have been shown to decrease significantly with the patient's age, the duration of metformin use, and interactions with other comorbidities such as PPIs and insulin.

Further analysis by (Yang et al., 2019) in a meta-analysis of 31 studies also corroborated the findings, where the risk of B12 deficiency was 2-fold increased in metformin users compared to non-users. Although the study did not find a significant association between B12 deficiency and the incidence of neuropathy, these results suggest the importance of regular B12 level screening. In contrast, a study by (Lima et al., 2023) more specifically linked metformin-induced B12 deficiency to the incidence of diabetic neuropathy, and underscored the effectiveness of methylcobalamin supplementation in improving symptoms of sensory neuropathy.

In the context of the effectiveness of this form of supplementation, a study by (Karedath et al., 2022) showed that patients who received vitamin B12 experienced a significant decrease in pain scores and neuropathic symptoms, although there were no significant changes in other parameters such as VPT (vibration perception threshold) or lipid profile. This confirms that the main benefit of vitamin B12 supplementation, especially its active form, lies in the immediate improvement of clinical symptoms rather than in secondary physiological parameters. Support for the use of methylcobalamin was also obtained from (Stein et al., 2021), who noted a tendency to improve neuropathic symptoms in patients with B12 deficiency, although the results were not statistically significant.

Interesting findings also come from a study (Jiang et al., 2020), which evaluated a combination of therapies between B vitamins and acupuncture. The results of a meta-analysis of 18 RCTs showed that the combination of acupuncture and B vitamins alone was more effective than the administration of B vitamins alone in increasing nerve conduction speed and lowering neuropathic symptom scores. This opens up the possibility that multimodal interventions may strengthen the effectiveness of supplementation, particularly in patients with severe or chronic diabetic neuropathy.

Although most studies support vitamin B12 supplementation, there are also studies that present more cautious results. Studies by (S&O, 2017), for example, did not find a significant association between B12 levels and the incidence of neuropathy in patients using metformin. However, it should be noted that the neuropathy detection methods used are retrospective and do not consider the severity or duration of symptoms. This highlights the importance of longitudinal approaches and more sensitive measurement of clinical parameters in subsequent studies.

Meanwhile, an observational study by (Arun et al., 2021) showed that 83% of type 2 diabetes patients who had taken metformin between 1 and 10 years had a B12 deficiency or borderline deficiency, and their quality of life was also recorded. This adds to the evidence that B12 deficiency has an impact not only on the clinical dimension, but also on the functional and psychosocial aspects of patients.

In general, from all the studies analyzed, it can be concluded that there is a consistent relationship between long-term metformin use and decreased vitamin B12 levels. B12 supplementation, particularly in the active form of methylcobalamin, has shown superior results over the usual form (cyanocobalamin) in improving symptoms of diabetic neuropathy. These findings support clinical recommendations for routine screening of B12 levels in diabetic patients using metformin, as well as considering methylcobalamin supplementation as part of diabetic neuropathy management protocols.

Taking into account the strengths and limitations of each study, more controlled and longitudinal clinical trials are needed to ascertain the optimal dose, duration of administration, and effectiveness of combination therapies (e.g. with acupuncture or other neuroprotective agents). Nevertheless, the currently available evidence is strong enough to recommend the integration of methylcobalamin supplementation into evidence-based clinical practice in the management of neuropathy in diabetic patients.

The Relationship Between Metformin, B12 Deficiency, and Diabetic Neuropathy

The use of metformin as a first-line treatment for type 2 diabetes has been shown to be effective in controlling blood glucose levels. However, long-term use of metformin can lead to impaired absorption of vitamin B12, which contributes to deficiency of this vitamin in diabetic patients. Research shows that metformin interferes with the absorption of vitamin B12 in the intestine, mainly through its effect on vitamin B12 complexes with intrinsic factors necessary for the absorption of vitamins in the terminal ileum (Ja'anini & Ababneh, 2025; Tiwari et al., 2023). The mechanism includes the inhibition of calcium channels in the distal part of the ileum, which alters the membrane potential and affects the absorption of the vitamin B12-intrinsic factor complex. When metformin binds to the central part of the cell membrane hydrocarbon, it can alter membrane permeability and block calcium, which is crucial for B12 transport (Gamag, 2024; Ja'anini & Ababneh, 2025).

The results of the research are from (Gamag, 2024; Ja'anini & Ababneh, 2025) corroborates these findings, where of the 435 T2DM patients who took metformin, as many as 66% were B12 deficient. This is in line with the results of (Arun et al., 2021) which noted that 83% of patients who used metformin for 1–10 years had a deficiency or borderline B12 deficiency, as well as had a decreased quality of life. Similarly, (Yang et al., 2019) in a meta-

analysis of 31 studies showed a significant increased risk of B12 deficiency in metformin users compared to non-users.

Vitamin B12 deficiency caused by metformin use can have serious implications on neural health, causing neuropathic symptoms similar to those of diabetic neuropathy. Patients with decreased B12 levels often show symptoms such as tingling, pain, and motor impairment that may be misinterpreted as manifestations of diabetes itself (Farooq et al., 2022; Yakubu et al., 2019). Deficiency of this vitamin contributes to the development of peripheral neuropathy, where these neurological symptoms can often be reversed if the deficiency is detected and treated promptly (Alvarez et al., 2019; Farooq et al., 2022). Decreased levels of B12 may lead to increased levels of homocysteine in the blood which is associated with a high risk of cardiovascular disease and nerve damage (Viswa S et al., 2019).

In a review by (Lima et al., 2023), it was found that T2DM patients taking metformin were more likely to experience neuropathic symptoms directly related to B12 deficiency. They also noted that methylcobalamin supplementation, the active form of B12, showed significant improvements in neuropathic symptoms. Although (S&O, 2017) did not find a statistically significant association between B12 levels and neuropathy, the prevalence of B12 deficiency remained high (38.4%), and neuropathy was found in 33.7% of patients.

Based on various studies, the prevalence of vitamin B12 deficiency is quite high among diabetic patients taking metformin, with prevalence rates varying between 14% to 30% (Butola et al., 2021; Tiwari et al., 2023). Control of vitamin B12 levels is important in patients taking metformin long-term, especially for those who have high doses or long duration of treatment (Butola et al., 2021; Tiwari et al., 2023). Counseling to patients about the importance of vitamin B12 screening and supplementation is also highly recommended to prevent onset neurological symptoms, which can have a significant impact on their quality of life (Ja'anini & Ababneh, 2025; Khan et al., 2017).

The management of vitamin B12 in the treatment of diabetes mellitus not only involves supplementation but also requires a holistic approach that includes awareness of the potential side effects of metformin. Research such as the one conducted by (Infante et al., 2021) recommends that physicians should be proactive in monitoring B12 levels and providing appropriate treatment for patients who show signs of deficiency. Clear management instructions are needed in clinical practice to ensure that patients not only get good glycemic control but also minimize the risk of disruptive neurological complications (Wang et al., 2017).

Overall, the interactions between metformin, vitamin B12 deficiency, and diabetic neuropathy highlight the importance of ongoing monitoring of the status of this vitamin in diabetic patients. The stigma that often involves the use of metformin should be balanced with the knowledge that while it is beneficial for glycemic control, its potential side effects on vitamin B12 absorption should be taken seriously (Farooq et al., 2022; Infante et al., 2021). Thoughtful therapy and management of this condition will greatly support the improvement of the patient's overall health outcomes.

Effectiveness of Oral Vitamin B12

Vitamin B12, specifically in the form of cyanocobalamin, has been widely used to address a variety of deficiencies in clinical practice. However, its use in the context of diabetic

neuropathy shows limited benefits, especially for patients with mild conditions. Research shows that the therapeutic effects of cyanocobalamin can appear more slowly and inconsistently compared to the active form of vitamin B12, namely mecobalamin (Christanty et al., 2022). The use of cyanocobalamin in high doses is not always well responded to by patients, thus indicating the need for further research to explore its effectiveness (Pinzon & Christi, 2020). This is reinforced by studies (Karedath et al., 2022), which found that although oral vitamin B12 can generally lower neuropathic pain, active forms such as mecobalamin provide a more pronounced clinical impact than regular forms.

The effectiveness of cyanocobalamin is often hampered by the conversion process required to make it an active form that can be directly used by the body's cells. In more severe cases of neuropathy, the body's inability to perform this conversion could explain why many patients report symptoms that persist despite having been taken vitamin B12 supplements (Christanty et al., 2022). In contrast, mecobalamin, which is the active form of vitamin B12, can be directly used by nerve cells and is potentially more effective in providing neuronal protection as well as improving nerve function. This is important because in patients with diabetic neuropathy, the timing and speed of response to therapy is crucial to prevent further nerve damage. (Lima et al., 2023) explicitly states that the use of methylcobalamin provides a significant improvement in neuropathic symptoms in T2DM patients who use metformin.

Furthermore, studies show that patients who receive therapy with mecobalamin report a faster reduction in pain and tingling than those who take cyanocobalamin (Pinzon & Christi, 2020). This is also supported by clinical evaluation results showing that mecobalamin contributes to a reduction in neurological symptoms, whereas cyanocobalamin tends to provide more limited benefits (Christanty et al., 2022). This confirms the importance of choosing the right form of vitamin B12 in the treatment of diabetic neuropathy, as faster and more effective interventions can have a significant impact on the patient's quality of life. (Stein et al., 2021) also noted that although the results of the effectiveness of B12 supplementation have not been statistically significant across studies, a greater positive trend has emerged in studies using the active form of B12.

In addition, in the context of additional support for the management of diabetic neuropathy, the combination of therapy with active vitamin B12 (mecobalamin) and vitamin D has been found to provide better results in reducing pain intensity than the use of regular cyanocobalamin (Pinzon & Christi, 2020). Other research also emphasizes the importance of health education for patients regarding the differences between forms of vitamin B12 and its potential impact on their neural health (Pramiastuti et al., 2025). This suggests that patient empowerment through adequate information can improve therapy adherence and support treatment success. In a review (Jiang et al., 2020), it was found that the combination of therapies such as B vitamins with acupuncture was more effective than B vitamin monotherapy, which again supports the role of active B vitamins in a multimodal approach.

Overall, although cyanocobalamin has a place in the treatment of vitamin B12 deficiency, its use in the management of diabetic neuropathy is limited and often not as effective as mecobalamin. A thorough evaluation of the nutritional status of vitamin B12 and the selection of the appropriate active form is essential in the management of diabetic neuropathy patients to achieve optimal outcomes (Pinzon & Christi, 2020). Awareness of these differences needs

to be increased among health practitioners and patients to minimize the risk of further nerve damage. Therefore, the integration of mecobalamin in clinical guidelines is worth considering, as supported by the results of the study (Karedath et al., 2022; Lima et al., 2023) and clinical observations from (Arun et al., 2021) emphasizing low quality of life in patients with poorly managed B12 deficiency.

CONCLUSION

The study concluded that the effectiveness of oral vitamin B12 supplementation in the form of cyanocobalamin in the management of diabetic neuropathy is relatively limited, especially since this form requires conversion in the body to become active. This process does not always go optimally, especially in patients with metabolic disorders or severe neuropathy. In contrast, mecobalamin—as the active form of vitamin B12—shows more promising results in improving neuropathic symptoms, such as pain, tingling, and sensory disturbances. Previous studies have consistently shown that mecobalamin supplementation has a positive impact on nerve regeneration, nerve conduction speed, and decreased neuropathic symptom scores. The link between metformin use and vitamin B12 deficiency is also an important finding. Long-term use of metformin contributes to a significant decrease in B12 levels, increasing the risk of peripheral neuropathy occurring. Therefore, regular monitoring of B12 levels in diabetic patients taking metformin needs to be used as a standard of clinical practice. This study emphasizes the importance of selecting the appropriate form of vitamin B12 in the treatment of diabetic neuropathy. The use of mecobalamin should be considered as the primary option, given its higher clinical effectiveness and faster therapeutic response time compared to cyanocobalamin. The study also recommends patient education and the integration of B12 deficiency screening as part of routine management in diabetic patients. Advanced clinical trials are needed to establish the optimal dose, duration of therapy, and effectiveness in combination with other interventions such as acupuncture or vitamin D.

REFERENCES

Abdalla, E. M., Al-Sadi, A., Fadul, A., Ahmed, A. H., & Musa, M. (2022). Non-immune intravascular hemolytic anemia: An unusual presentation of severe vitamin B-12 deficiency. *Cureus, 14*(8), e26507. https://doi.org/10.7759/cureus.26507

Alhaji, J. H. (2022). Vitamin B12 deficiency in patients with diabetes on metformin: Arab countries. *Nutrients, 14*(10), 2046. https://doi.org/10.3390/nu14102046

Alruwaili, M., Basri, R., Alruwaili, R., Albarrak, A. M., & Ali, N. H. (2023). Neurological implications of vitamin B12 deficiency in diet: A systematic review and meta-analysis. *Healthcare, 11*(7), 958. https://doi.org/10.3390/healthcare11070958

Alvarez, M., Sierra, O. R., Saavedra, G., & Moreno, S. (2019). Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: A cross-sectional study. *Endocrine Connections, 8*(10), 1324–1329. https://doi.org/10.1530/EC-19-0382

Arun, R., Anwar, A., & Jamali, P. (2021). Assessment of vitamin B12 deficiency caused by metformin in type II diabetic patients. *Journal of Pharmaceutical Research International, 33*(46A), 38–41. https://doi.org/10.9734/jpri/2021/v33i46a32838

Ayubbana, S., Ludiana, L., Immawati, I., Pakarti, A. T., & Supardi, S. (2024). Edukasi perawatan kaki pada pasien diabetes mellitus di wilayah kerja Puskesmas Margorejo. *Jurnal Pengabdian Masyarakat Jajama (JPMJ), 3*(1), 17–23. https://doi.org/10.47218/jpmj.v3i1.309

Butola, L. K., Jha, R. K., Ambad, R., Kanyal, D., & Jankar, J. S. (2021). Vitamin B12 deficit status among type 2 diabetes mellitus patients: A review. *Journal of Evolution of Medical and Dental Sciences, 10*(23), 1794–1798. https://doi.org/10.14260/jemds/2021/370

Christanty, D. S. T., Pambudi, P., Nurikhwan, P. W., Dafif, M. W., & Bakhriansyah, M. (2022). Pengaruh pemberian mecobalamin terhadap perbaikan klinis pasien dengan neuropati perifer: Literature review. *Homeostasis, 5*(2), 419–426. https://doi.org/10.20527/ht.v5i2.6292

Farooq, M. D., Tak, F. A., Ara, F., Rashid, S., & Mir, I. A. (2022). Vitamin B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes. *Journal of Xenobiotics, 12*(2), 169–175. https://doi.org/10.3390/jox12020011

Gamag, E. A. (2024). Prevalence of vitamin B12 deficiency in Libyan type 2 diabetic patients treated with metformin. *AlQalam Journal of Medical and Applied Sciences*, 1072–1076. https://doi.org/10.54361/ajmas.247422

Hakim, M., Kurniani, N., Pinzon, R. T., Tugasworo, D., Basuki, M., Haddani, H., Pambudi, P., Fithrie, A., & Wuysang, A. D. (2018). Analisis korelasi skor gejala total, nyeri, dan kualitas hidup setelah pengobatan vitamin B1, B6, dan B12 dosis tinggi pada neuropati perifer. *Majalah Kedokteran Neurosains Perhimpunan Dokter Spesialis Saraf Indonesia, 35*(2), 79–86. https://doi.org/10.52386/neurona.v35i2.3

Infante, M., Leoni, M., Caprio, M., & Fabbri, A. (2021). Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. *World Journal of Diabetes, 12*(7), 916–931. https://doi.org/10.4239/wjd.v12.i7.916

Irawan, D., Wuysang, A. D., & Goysal, Y. (2019). Hubungan kadar lipid darah dengan derajat keparahan neuropati diabetik perifer. *Majalah Kedokteran Neurosains Perhimpunan Dokter Spesialis Saraf Indonesia, 37*(1), 1–6. https://doi.org/10.52386/neurona.v37i1.99

Ja'anini, S. S., & Ababneh, M. S. (2025). Prevalence of vitamin B12 deficiency among diabetic patients taking metformin in Jordan. *Cureus, 17*(4), e82672. https://doi.org/10.7759/cureus.82672

Jarquin Campos, A., Risch, L., Nydegger, U., Wiesner, J., Vazquez Van Dyck, M., Renz, H., Stanga, Z., & Risch, M. (2020). Diagnostic accuracy of holotranscobalamin, vitamin B12, methylmalonic acid, and homocysteine in detecting B12 deficiency in a large mixed patient population. *Disease Markers, 2020*, Article 7468506. https://doi.org/10.1155/2020/7468506

Jiang, H. L., Jia, P., Fan, Y. H., Li, M. D., Cao, C. C., Li, Y., & Du, Y. Z. (2020). Manual acupuncture or combination with vitamin B to treat diabetic peripheral neuropathy: A systematic review and meta-analysis of randomized controlled trials. *BioMed Research International, 2020*, Article 4809125. https://doi.org/10.1155/2020/4809125

Karedath, J., Batool, S., Arshad, A., Khalique, S., Raja, S., Lal, B., Chunchu, V. A., & Hirani, S. (2022). The impact of vitamin B12 supplementation on clinical outcomes in patients with diabetic neuropathy: A meta-analysis of randomized controlled trials. *Cureus, 14*(11), e31783. https://doi.org/10.7759/cureus.31783

Khan, A., Shafiq, I., & Shah, M. H. (2017). Prevalence of vitamin B12 deficiency in patients with type II diabetes mellitus on metformin. *Cureus, 9*(8), e1577. https://doi.org/10.7759/cureus.1577

Lima, M. J., Dias, E., Pereira, B. L., Orrico, R. S., & Saavedra, P. (2023). Vitamin B12 deficiency and peripheral neuropathy in patients with type 2 diabetes mellitus treated with metformin: An integrative review. *Brazilian Journal of Health Review, 6*(3), 9534–9548. https://doi.org/10.34119/bjhrv6n3-091

Markun, S., Gravestock, I., Jäger, L., Rosemann, T., Pichierri, G., & Burgstaller, J. M. (2021). Effects of vitamin B12 supplementation on cognitive function, depressive symptoms, and fatigue: A systematic review and meta-analysis. *Nutrients, 13*(3), 1–18. https://doi.org/10.3390/nu13030923

MY Bima, M. L., Rahmayani, F., & Mutiara, H. (2023). Pendekatan diagnostik, faktor risiko, dan tatalaksana neuropati diabetik. *Medical Profession Journal of Lampung, 13*(1), 59–65. https://doi.org/10.53089/medula.v13i1.555

Pavone, P., Sullo, F., Falsaperla, R., Greco, F., Crespo, A., Calvo, A., & Caraballo, R. (2021). Vitamin B12 deficiency and West syndrome: An uncommon but preventable cause of neurological disorder. *Neuropediatrics, 52*(4), 333–336. https://doi.org/10.1055/s-0041-1725013

Pebrianti, S., Nugraha, B. A., & Shalahuddin, I. (2020). Manajemen nyeri neuropati pada pasien diabetes melitus tipe 2: Studi literatur. *Holistik Jurnal Kesehatan, 14*(2), 276–282. https://doi.org/10.33024/hjk.v14i2.2828

Pinzon, R. T., & Christi, Y. R. T. D. (2020). Effectiveness of vitamin D and vitamin B supplementation therapy in diabetic neuropathic pain standard therapy. *Indonesian Journal of Clinical Pharmacy, 9*(4), 310–318. https://doi.org/10.15416/ijcp.2020.9.4.310

Pramiastuti, O., Istriningsih, E., Murti, F. K., Wulandari, P. S., Firsty, G. R., Nurfauziah, A., Alquraisi, R. H. A., Dewi, A., Pramesti, I., & Nisa, K. (2025). Edukasi penggunaan vitamin neurotropik B bagi guru KBIT Fatimatuz Zahro. *Reswara: Jurnal Pengabdian Kepada Masyarakat, 6*(1), 603–613. https://doi.org/10.46576/rjpkm.v6i1.5241

S, O., & O, O. (2017). Investigation of vitamin B12 deficiency with peripheral neuropathy in patients with type 2 diabetes mellitus treated using metformin. *Northern Clinics of Istanbul, 4*(3), 217–222. https://doi.org/10.14744/nci.2017.98705

Sim, A. S., Santoso, A. H., Kusuma, K. F., Putra, M. D. D., & Destra, E. (2024). Skrining kadar gula darah puasa dalam upaya pencegahan neuropati diabetik pada kelompok usia lanjut. *Jurnal Pengabdian Masyarakat Nusantara, 6*(4), 82–93. https://doi.org/10.57214/pengabmas.v6i4.600

Sriyati, S. (2024). Neuropati diabetes sebagai faktor predisposisi terjadinya luka pada kaki. *Jurnal Ilmiah STIKES Yarsi Mataram, 14*(1), 46–52. https://doi.org/10.57267/jisym.v14i1.336

Stein, J., Geisel, J., & Obeid, R. (2021). Association between neuropathy and B-vitamins: A systematic review and meta-analysis. *European Journal of Neurology, 28*(6), 2054–2064. https://doi.org/10.1111/ene.14786

Suri, M. H., Haddani, H., & Sinulingga, S. (2018). Hubungan karakteristik, hiperglikemi, dan kerusakan saraf pasien neuropati diabetik. *Biomedical Journal of Indonesia, 4*(1), 40–45. https://doi.org/10.32539/bji.v4i1.7957

Tiwari, A., Singh, R. K., Satone, P. D., & Meshram, R. J. (2023). Metformin-induced vitamin B12 deficiency in patients with type-2 diabetes mellitus. *Cureus, 15*(6), e47771. https://doi.org/10.7759/cureus.47771

Viswa, S. V., Sivasakthi, K. S., Robinson, D. M., & Hariharan, V. H. (2019). Metformin-induced vitamin B12 deficiency among type 2 diabetes mellitus patients. *Indian Journal of Pharmacy Practice, 13*(1), 14–19. https://doi.org/10.5530/ijopp.13.1.3

Wang, Y. W., He, S. J., Feng, X., Cheng, J., Luo, Y. T., Tian, L., & Huang, Q. (2017). Metformin: A review of its potential indications. *Drug Design, Development and Therapy, 11*, 2421–2429. https://doi.org/10.2147/dddt.s141675

Wardani, I. S., Sahly, A. R., Ajmala, I. E., & Suryani, D. (2022). Vitamin D and type 2 diabetes mellitus: Role in insulin resistance, glycemic control, and long-term complications. *Unram Medical Journal, 11*(2), 942–952. https://doi.org/10.29303/jku.v11i2.763

Yakubu, M., Laing, E. F., Nsiah, P., Anthony, R., Acheampong, E., Asamoah, S. K., Anto, E. O., Djokoto, G., Adu, E. A., & Owiredu, E. (2019). Vitamin B12 deficiency in type 2 diabetic patients on metformin. *Alexandria Journal of Medicine, 55*(1), 58–67. https://doi.org/10.1080/20905068.2019.1662647

Yang, W., Cai, X., Wu, H., & Ji, L. (2019). Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: A meta-analysis. *Journal of Diabetes, 11*(9), 729–743. https://doi.org/10.1111/1753-0407.12900

Zhou, L., Bai, X., Wu, B., Tan, Y., Li, M., & Yang, Q. (2024). Characterizing vitamin B12 deficiency in neurology outpatients: A retrospective observational study. *Clinical Neuropharmacology, 47*(3), 87–96. https://doi.org/10.1097/wnf.0000000000000593