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EFFICACY OF STANDALONE ORAL METHYLCOBALAMIN IN THE MANAGEMENT OF DIABETIC DISTAL SYMMETRIC POLYNEUROPATHY IN INDIA: A SYSTEMATIC REVIEW

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Abstract

Background: Diabetic distal sensory Polyneuropathy (DSPN) is an annoying and disabling complication of long standing type 2 diabetes mellitus (T2DM). These patients are also deficient in vitamin B12. Methylcobalamin (MeCbl), an active form of vitamin B12, is widely used in India especially by primary care providers to manage DSPN, yet its efficacy as a standalone oral therapy remains uncertain.

Objectives: To systematically review Indian studies examining the efficacy of standalone oral Methylcobalamin in the management of DSPN among patients with T2DM.

Methods: We followed PRISMA 2020 guidelines for systematic review. A comprehensive search of PubMed, EMBASE, Scopus, IndMED, and Google Scholar was conducted up to early 2025. Inclusion criteria: Indian studies (RCTs or observational) on T2DM patients with symptomatic DSPN treated with oral Methylcobalamin mono-therapy. Excluded: studies involving injectable or combination therapies, non-T2DM patients, or those lacking outcome data. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane RoB 2.0 and Newcastle-Ottawa tools.

Results: Out of 300 records, 2 studies (n=342 patients) met eligibility. One RCT (Sharma et al., 2021) showed minimal improvement in pain and sensory function with MeCbl 1500 µg/day. One comparative study (Maladkar et al., 2009) showed epalrestat outperformed MeCbl 500 µg TID in relieving neuropathic symptoms. Both studies had moderate-to-high risk of bias. No included study reported quality-of-life outcomes or conducted placebo-controlled trials.

Conclusion: Limited and low-quality Indian evidence suggests that standalone oral methylcobalamin offers minimal benefit in the management of DSPN in T2DM. Larger, blinded, placebo-controlled trials are needed to clarify its role.

Keywords: Methylcobalamin; Diabetic Neuropathies; Distal Sensory Polyneuropathy; Type 2 Diabetes Mellitus; India; Vitamin B12; Monotherapy; Systematic Review.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common micro vascular complication of type 2 diabetes mellitus (T2DM), affecting an estimated 10–30% of Indian patients with T2DM[1]. Occurrence of Diabetic Neuropathy significantly correlates with duration of diabetes, Fasting Blood Sugar, and

Insulin Resistance. When adjusted for other risk factors, age was not significantly correlated to neuropathy[2]. In India, vitamin B_{12} (Methylcobalamin) deficiency is frequently observed, particularly among metformin-treated patients[3–5]. This deficiency may worsen existing neuropathic symptoms, delay nerve regeneration, and complicate clinical management[6] of neuropathy.

Methylcobalamin, the active neurologically functional form of vitamin B_{12}, has shown neurotrophic and neuro protective properties and is commonly prescribed in India for managing DPN[7]. However, international guidelines such as those by the American Diabetes Association and other expert panels do not recommend it as first-line treatment, primarily due to insufficient large-scale randomized evidence[8,9]. Moreover, its efficacy as a standalone oral therapy (monotherapy) for painful diabetic neuropathy remains inconclusive.

This systematic review aims to critically appraise and synthesize existing Indian studies evaluating the efficacy of standalone oral methylcobalamin in the management of distal symmetric polyneuropathy (DSPN) among T2DM patients, focusing on outcomes related to pain relief, sensory function, and quality of life.

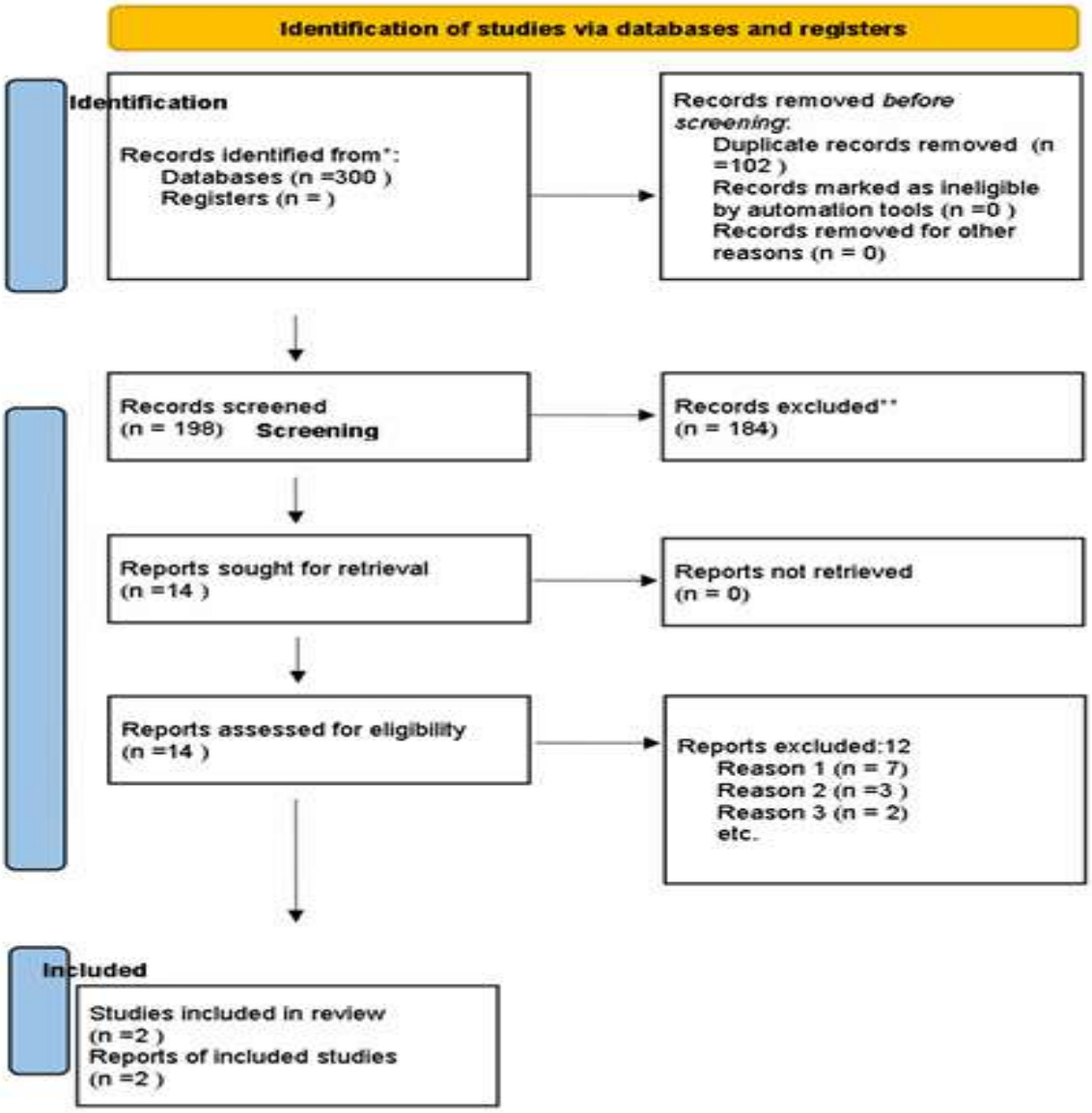
METHODS

We followed PRISMA 2020 standards for systematic reviews. We searched PubMed, EMBASE, Scopus, IndMED, and Google Scholar up to early 2025 for English-language studies conducted in India on type 2 diabetic patients with symptomatic DSPN treated with oral Methylcobalamin (monotherapy). Search terms included combinations of “methylcobalamin”, “mecobalamin”, “vitamin B12”, “diabetic neuropathy”, “India”, “type 2 diabetes”. Eligible studies were randomized controlled trials (RCTs) or observational trials. Excluded were studies from outside India, non-type 2 diabetes or mixed neuropathies, injectable or combination therapies, or lacking neuropathy outcome data.

Two reviewers independently screened titles and abstracts, followed by full texts review for inclusion. Discrepancies were resolved by consensus. We extracted study details (author, year, design, sample size, duration, MeCbl dose, outcomes) and assessed the risk of bias using Cochrane RoB 2.0 tool for RCTs (randomization, blinding, etc.) and Newcastle-Ottawa Scale for non-randomized studies (selection, comparability, outcome).

Study selection: Fig. 1 (PRISMA flow diagram) summarizes the selection process. In total,300 records were identified; after duplicates and screening, 2 studies (n=342 patients) met criteria.

Figure 1. PRISMA flow diagram of study selection



RESULTS

Study Characteristics

Two eligible clinical trials conducted in India met the inclusion criteria for this systematic review (Table 1):

1. **Sharma C et al.** (2021) conducted a prospective, randomized, open-label, parallel-group RCT in 100 patients with painful type 2 diabetic sensory motor Polyneuropathy (DSPN) in Punjab , India[10]. Patients were randomized into three groups:

Group A (n ≈ 33) received oral methylcobalamin (MeCbl) 1500 µg/day alone;

Group B received MeCbl + Pregabalin;

Group C received MeCbl + Duloxetine.
The follow-up duration was 12 weeks.

Primary outcomes included Visual Analog Scale (VAS) for pain and clinical sensory assessments (vibration, touch, and temperature).

2. **Maladkar et al**. (2009) conducted a prospective, open-label, comparative, multi-center trial in 242 patients with type 2 DSPN[7]. Participants received either oral epalrestat 50 mg three times daily or oral methylcobalamin 500 µg three times daily for 12 weeks. Outcomes measured included neuropathy symptom scores (burning, tingling, numbness), clinical sensory/motor function, and nerve conduction velocity.

No additional Indian randomized controlled trials (RCTs) or observational studies were found that evaluated standalone oral methylcobalamin. Studies using combination therapy with other B vitamins, lipoic acid, or antiepileptics were excluded from this review to isolate MeCbl's individual effect.

Table 1. Study Characteristics of Trials of Oral Methylcobalamin in Indian Type 2 Diabetic DSPN

Study (year)	Design	N (T2DM with DSPN)	Duration	MeCbl dose (oral)	Comparator	Outcomes	Key findings
Sharma *et al.* 2021	RCT (open-label)	100.00	12 wk	1500 µg/day	(methylcobalamin alone vs. combos)	-VAS pain; -128 hz tuning-fork, -10 gram monofilament, thermal tests	MeCbl alone gave minimal improvement (vibration sense ↑11.6%, VAS ↓0.58) vs. much larger gains in combo groups. Group C (MeCbl+duloxetine) had greatest benefit.
Maladkar *et*	Open-	242.00	12 wk	500 µ	Epalrestat	-Neuropathy	Both groups improved;

Study (year)	Design	N (T2DM with DSPN)	Duration	MeCbl dose (oral)	Comparator	Outcomes	Key findings
al. 2009	label comparative			g TID	50 mg TID	symptoms, -exam, electrophysiology	however, epalrestat produced significantly greater improvement in all neuropathy parameters than MeCbl. Authors concluded epalrestat > methylcobalamin in efficacy.

Abbreviations: TID – three times daily; VAS – visual analog pain score; MeCbl – methylcobalamin; DSPN – distal symmetric polyneuropathy.

Risk of Bias

The RCT study (Sharma 2021) used computer randomization for allocation of interventions, but was open-label (no blinding), raising high risk of performance and detection bias. Allocation concealment was not described. There was no significant loss to follow-up, and outcomes (sensory tests, VAS) were reported for all randomized patients. Using Cochrane RoB 2.0, we rated this trial as moderate-to-high risk of bias due to lack of blinding and potential selective reporting. The comparative trial (Maladkar 2009) was non-randomized and unblinded; no matching or adjustment for baseline differences was described. Using the Newcastle-Ottawa Scale, this study had serious selection and confounding bias (no random allocation, no blinded outcome assessment) and only routine outcome follow-up. Thus both studies provide low-quality evidence.

Table 2. Risk of Bias Summary

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Sharma et al., 2021	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Maladkar et al., 2009	Unclear Risk	Unclear Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear

Outcomes:-

Pain and Sensory Scores

Sharma et al. quantified pain using the Visual Analog Scale (VAS) and assessed sensory function through vibration, pressure, and thermal modalities. Methylcobalamin (MeCbl) monotherapy at 1500 µg/day produced only a 0.58-point reduction in VAS (from baseline ≈6–7) after 12 weeks of therapy, a change considered clinically negligible [10]. In contrast, MeCbl combined with duloxetine led to a 4.17-point VAS reduction, and restored vibration sense in 41.4% of patients, compared to only 11.6% in the MeCbl-only group [10]. These findings suggest that MeCbl alone has minimal efficacy in relieving pain or improving sensory deficits in diabetic neuropathy.

Comparative Symptom Relief

Maladkar et al. did not report numerical pain scores but described subjective symptom improvement in both treatment groups [7]. However, epalrestat was consistently rated superior by both investigators and patients. Specific neuropathic symptoms such as burning, paresthesia, and stabbing pain showed greater improvement with epalrestat, while MeCbl offered modest relief of numbness or cramps—substantially less than in the epalrestat group [7].

Nerve Conduction and Electrophysiology

Neither trial reported detailed nerve conduction velocity (NCV) data or quantitative electrophysiological measures specifically for the MeCbl monotherapy group. Maladkar et al. mentioned that electrophysiological parameters were assessed, but group-wise results were not tabulated separately in the publication abstract. The general conclusion was that epalrestat improved nerve conduction more than MeCbl [7]. Sharma et al. did not perform NCV studies, limiting their evaluation to clinical bedside sensory tests [10].

Quality of Life (QoL) and Functional Outcomes

Neither study employed validated QoL instruments or measured functional status. No data on sleep quality, mood, or general well-being were collected. Although Sharma et al. administered a disability index (likely the Michigan Neuropathy Screening Instrument – MNSI), the results were not reported separately for each treatment group [10]. Therefore, the QoL effects of methylcobalamin remain unknown.

Summary of Efficacy

Taken together, oral methylcobalamin monotherapy emerged as the least effective intervention across both studies. The Indian RCT showed no statistically or clinically significant improvements with MeCbl alone [10]. In the larger multicenter trial, although MeCbl modestly improved some symptoms, a standard neuropathy drug (epalrestat) yielded consistently better outcomes [7]. Notably, neither study used a placebo-only control, which raises the possibility that some improvements in the MeCbl arms reflect placebo effects or natural symptom fluctuation.

DISCUSSION

This systematic review found very limited Indian evidence on stand-alone oral methylcobalamin (MeCbl) for DSPN. Only two eligible trials (342 patients total) have been published, both with

significant methodological limitations. The available data suggest that high-dose oral MeCbl (1.5 mg/day) is at best minimally efficacious as a single agent for symptomatic DSPN in type 2 diabetes.

In Sharma et al. [10], the only RCT, MeCbl 1500 µg/day for 12 weeks did not produce meaningful pain relief or sensory recovery. By contrast, adding standard neuropathy drugs (pregabalin or duloxetine) yielded much larger improvements over the same period [10]. This aligns with global evidence suggesting that vitamin B12 alone is weaker than first-line agents for painful DSPN.

The large Clinical trial by Maladkar et al. [7] found symptom improvement in both treatment arms, but epalrestat (an aldose-reductase inhibitor) was markedly superior to MeCbl on every outcome. The authors explicitly concluded that epalrestat "has better efficacy and safety" than methylcobalamin [7]. This suggests that even in routine clinical settings, MeCbl was perceived as substantially less effective than an approved neuropathy therapy.

LIMITATIONS: Our review is constrained by the paucity of available data. The two included studies were heterogeneous in design (one RCT and one multicenter open-label trial), and neither was placebo-controlled or double-blind. Small sample size (especially for the MeCbl monotherapy arm in the RCT) and short follow-up duration (12 weeks) further limit our ability to draw firm conclusions. The open-label design of the RCT introduces bias due to lack of blinding. Furthermore, neither study provided detailed nerve conduction studies or validated quality-of-life metrics.

IMPLICATIONS

Clinicians should be cautious in expecting significant therapeutic benefit from oral MeCbl alone for DSPN. While vitamin B_{12} supplementation is critical in deficient patients—especially those on metformin, the high-dose MeCbl does not appear to control neuropathic pain or reverse neuropathy when used as monotherapy. Current Indian data suggest MeCbl may be better utilized as an adjunct to guideline-recommended therapies like duloxetine or pregabalin rather than a monotherapy.

Future research should include robust, well-powered, placebo-controlled RCTs of standalone MeCbl in Indian populations, ideally stratified by B_{12} status, to better define its potential role in DSPN management.

CONCLUSION

Current Indian evidence does not support strong efficacy of standalone oral methylcobalamin for type 2 diabetic DSPN. Only small trials are available, showing at most modest symptom relief and no demonstrated nerve recovery with MeCbl monotherapy. High-quality RCTs are needed, but until then, methylcobalamin alone should not replace standard neuropathic pain treatments.

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