INPLASY

Dapagliflozin Combined with Methylcobalamin in the Treatment of Type 2 Diabetes Mellitus with Peripheral Neuropathy: A Protocol of Systematic Review and Meta-analysis

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Corresponding author:
Han-wei Huang

han-weihuang@outlook.com

Author Affiliation:
ZhongShan's Chenxinhai Integrated Chinese and Western Medicine Hospital.

Deng, XL; Wu, R; Lin, XX; Liang, JJ; Huang, HW.

ADMINISTRATIVE INFORMATION

Support - Not applicable.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202530084

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2025 and was last updated on 20 March 2025.

INTRODUCTION

Review question / Objective The objective of this study is to evaluate the efficacy and safety of combining dapagliflozin with methylcobalamin in the management of peripheral neuropathy in patients with T2DM. By comparing the clinical outcomes of the combination therapy to other modalities, we aim to determine whether the combined treatment is more effective in alleviating neuropathic symptoms, improving nerve conduction, and enhancing blood glucose levels.

Rationale Type 2 diabetes mellitus (T2DM) is a global health concern, with its prevalence rapidly increasing due to lifestyle changes and aging populations. Diabetic peripheral neuropathy (DPN) is one of the most common and debilitating complications of T2DM, affecting up to 50% of patients during their lifetime. DPN significantly impacts quality of life, leading to symptoms such as numbness, tingling, and pain, and in severe cases, can result in ulcers, infections, and amputations. Current treatments for DPN primarily focus on glycemic control and symptomatic relief, but these approaches often fail to address the underlying nerve damage, resulting in limited long-term efficacy.

Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, has shown promise not only in improving glycemic control but also in offering additional benefits such as weight reduction, blood pressure control, and cardiovascular protection. Emerging evidence suggests that SGLT-2 inhibitors may also have neuroprotective properties, potentially through anti-inflammatory and metabolic regulatory pathways. Methylcobalamin, the active form of vitamin B12, is known to support nerve repair and regeneration, making it a valuable component in the management of DPN. However, its effectiveness as a monotherapy is often insufficient for comprehensive symptom relief.

Given the complementary mechanisms of dapagliflozin and methylcobalamin, their combined use may offer a synergistic approach to managing DPN by addressing both the metabolic and

structural components of the disease. While current clinical guidelines do not explicitly recommend this combination, there is growing evidence supporting their individual benefits in managing DPN. This systematic review aims to evaluate the efficacy and safety of combining dapagliflozin with methylcobalamin in the treatment of DPN in T2DM patients, providing critical insights that could inform clinical practice and improve patient outcomes.

Condition being studied Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to insulin resistance and impaired insulin secretion. It is a major global health concern, with its prevalence rising rapidly due to lifestyle changes and population aging. T2DM is associated with numerous complications, including diabetic peripheral neuropathy (DPN), one of the most common and debilitating consequences of the disease.

DPN is a progressive condition resulting from prolonged hyperglycemia, which leads to nerve damage through mechanisms such as oxidative stress, inflammation, and vascular dysfunction. It primarily affects the peripheral nerves, causing symptoms such as numbness, tingling, burning pain, and sensory loss, particularly in the extremities. In severe cases, DPN can result in foot ulcers, infections, and even amputations, significantly impacting patients' quality of life. Up to 50% of individuals with T2DM are estimated to develop DPN during their lifetime, highlighting its substantial burden on healthcare systems and patients alike.

Current management strategies for DPN include glycemic control, symptomatic pain relief, and neurotrophic support. However, these approaches often provide limited relief and do not fully address the underlying nerve damage. This underscores the need for more effective therapies to prevent, manage, and potentially reverse the progression of DPN in patients with T2DM.

METHODS

Search strategy A thorough literature search was conducted across several databases, including PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure (CNKI), covering studies from the inception of each database to the September 30, 2024. Search terms included 'dapagliflozin,' 'methylcobalamin,' 'type 2 diabetes mellitus,' and 'peripheral neuropathy'. No language restrictions were applied. Additional sources were identified through reference lists of the included studies and clinical trial registries, ensuring the comprehensiveness of the search. The detailed search strategy is provided in Supplementary Table S1.

Participant or population This systematic review focuses on patients diagnosed with Type 2 Diabetes Mellitus (T2DM) who also suffer from Diabetic Peripheral Neuropathy (DPN).

Intervention Studies where the intervention consisted of dapagliflozin combined with methylcobalamin.

Comparator Comparator consisted of Metformin and Mecobalamin.

Study designs to be included Only randomized controlled trials (RCTs) were selected to ensure high-quality evidence.

Eligibility criteria Inclusion and Exclusion Criteria

The systematic review included studies based on the following criteria: (1) only RCTs were selected to ensure high-quality evidence; (2) studies that involved patients diagnosed with T2DM complicated by DPN; (3) studies where the intervention consisted of dapagliflozin combined with methylcobalamin; and (4) studies that reported outcomes related to neuropathic symptom improvement, nerve conduction velocity, blood glucose levels, and adverse events.

Exclusion criteria were: (1) studies that did not employ a randomized controlled design; (2) studies that did not include both dapagliflozin and methylcobalamin as part of the treatment regimen; and (3) studies with incomplete or unavailable data.

Information sources A thorough literature search was conducted across several databases, including PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure (CNKI), covering studies from the inception of each database to the September 30, 2024. Additional sources were identified through reference lists of the included studies and clinical trial registries, ensuring the comprehensiveness of the search.

Main outcome(s) The main outcome are overall effective rate (OER), motor nerve conduction velocity (MNCV), sensory nerve conduction velocity (SNCV), and blood glucose levels. Specific measurements for nerve conduction velocity included common peroneal motor nerve conduction velocity (CPMNCV), common peroneal sensory nerve conduction velocity (CPSNCV), median motor nerve conduction velocity (MMNCV), and median sensory nerve conduction velocity

(MSNCV). Blood glucose measurements included fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), and glycosylated hemoglobin (HbA1c)overall effective rate (OER).

Additional outcome(s) Safety outcomes were assessed based on the reported rate of adverse events (RAE).

Data management In this systematic review, data management was conducted meticulously to ensure the accuracy, consistency, and reliability of the findings. The following mechanisms were employed to manage records and data:

1.Literature Search and Record Keeping: A comprehensive search strategy was implemented across multiple databases (PubMed, Embase, Cochrane Library, CNKI, and Wanfang) to identify relevant studies. All search results were recorded and stored using reference management software to organize and track the retrieved articles. Duplicates were removed, and the remaining records were screened based on titles and abstracts.

2.Data Extraction: A standardized data extraction form was developed to systematically collect data from the included studies. The form captured key information such as study details (authors, publication year, journal), patient characteristics (age, gender, diabetes duration), intervention details (dosage, duration), and outcomes (nerve conduction velocity, glycemic control, adverse events). This ensured consistency in data collection across all studies.

3.Data Storage and Security: All extracted data were stored in a secure, password-protected database. Access to the data was restricted to the research team to maintain confidentiality and prevent unauthorized access. Regular backups were performed to prevent data loss.

4.Quality Assessment: The methodological quality and risk of bias of the included studies were assessed using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool. The results of the quality assessment were documented and used to inform the interpretation of the findings.

5.Statistical Analysis: Data were pooled using appropriate statistical methods, with heterogeneity assessed using the I^2 statistic. Both fixed-effects and random-effects models were applied based on the level of heterogeneity. All statistical analyses were performed using specialized software, and the results were carefully documented.

6.Data Verification: To ensure accuracy, the extracted data and statistical analyses were independently reviewed by at least two researchers. Any discrepancies were resolved through discussion and consensus.

7.Reporting: The findings were reported in accordance with the PRISMA guidelines, ensuring transparency and reproducibility. All data, including search strategies, extracted data, and analysis results, were made available for review upon request.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias in the included RCTs were systematically evaluated using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool, a widely recognized and validated framework for bias assessment in clinical research. This tool provides a structured approach to evaluate potential biases across five core domains, each addressing critical aspects of trial design and conduct. First, the randomization process was assessed to determine whether the allocation sequence was generated and implemented appropriately, ensuring comparable baseline characteristics between groups. Second, deviations from intended interventions were examined to identify any systematic differences in care provided apart from the intervention under investigation. Third, missing outcome data were analyzed to evaluate the extent and potential impact of participant attrition or exclusion on the study results. Fourth, the measurement of outcomes was scrutinized to assess the validity and reliability of outcome assessment methods, including the adequacy of blinding procedures. Finally, the selection of reported results was reviewed to detect any potential bias arising from selective reporting of outcomes or analyses. For each domain, a series of signaling questions guided the evaluation, and an overall risk of bias judgment (low risk, some concerns, or high risk) was assigned based on predefined criteria. This comprehensive assessment framework not only enhances the transparency and reproducibility of our evaluation but also provides a more nuanced understanding of the methodological strengths and limitations of the included studies, thereby strengthening the validity of our findings.

Strategy of data synthesis The data synthesis for this systematic review will be conducted using a meta-analytic approach to pool the results from the included randomized controlled trials (RCTs). The following steps outline the strategy for data synthesis:

Data Extraction and Preparation: Data from each included study will be extracted using a standardized form, capturing key outcomes such as the overall effective rate (OER), nerve conduction velocities (CPMNCV, CPSNCV, MMNCV, MSNCV), blood glucose levels (FPG, 2hPG, HbA1c), and adverse events (RAE). Continuous outcomes will be recorded as mean differences (MD) with standard deviations (SD), while dichotomous outcomes will be recorded as odds ratios (OR) with 95% confidence intervals (CI).

Assessment of Heterogeneity: Heterogeneity among the studies will be assessed using the I^2 statistic. An I^2 value greater than 50% will indicate substantial heterogeneity, prompting the use of a random-effects model. If heterogeneity is low ($I^2 \leq 50\%$), a fixed-effects model will be applied.

Meta-Analysis: For continuous outcomes (e.g., nerve conduction velocities, blood glucose levels), the mean difference (MD) with 95% CI will be calculated. For dichotomous outcomes (e.g., OER, adverse events), the odds ratio (OR) with 95% CI will be computed. The pooled effect sizes will be calculated using the inverse-variance method for continuous data and the Mantel-Haenszel method for dichotomous data.

Subgroup Analysis: If substantial heterogeneity is observed, subgroup analyses will be conducted based on factors such as treatment duration, dosage, and baseline severity of neuropathy to explore potential sources of variability.

Sensitivity Analysis: Sensitivity analyses will be performed by excluding studies with a high risk of bias or those that significantly contribute to heterogeneity to assess the robustness of the results.

Publication Bias: Publication bias will be assessed using funnel plots and Egger's test if a sufficient number of studies (≥10) are included.

Statistical Software: All analyses will be performed using Review Manager (RevMan) version 5.4, ensuring accurate and reproducible results.

Subgroup analysis If substantial heterogeneity is observed, subgroup analyses will be conducted based on factors such as treatment duration, dosage, and baseline severity of neuropathy to explore potential sources of variability.

Sensitivity analysis Sensitivity analyses will be performed by excluding studies with a high risk of bias or those that significantly contribute to heterogeneity to assess the robustness of the results.

Language restriction English and Chinese.

Country(ies) involved China.

Keywords Diabetic peripheral neuropathy; type 2 diabetes mellitus; dapagliflozin; methylcobalamin; systematic review.

Dissemination plans This study will be published in a peer-reviewed journal.

Contributions of each author

Author 1 - Xiao-long Deng.
Email: dengxiao-long@outlook.com
Author 2 - Ren Wu.
Email: wuren007@hotmail.com
Author 3 - Xuan-xia Lin.
Email: xuan-xialin@hotmail.com
Author 4 - Jia-jian Liang.
Email: liangjia-jian@outlook.com
Author 5 - Han-wei Huang.
Email: han-weihuang@outlook.com