INPLASY PROTOCOL

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Corresponding author:
Wenjing Wei

243091968@qq.com

Author Affiliation:
Chengdu University of traditional Chinese Medicine

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Conflicts of interest:
There may be some conflicts of interest in the use of research funds.

The efficacy of vitamin D supplementation on Painful diabetic neuropathy，protocol for a systematic review and meta-analysis

Wei, W[1]; Zhang, Y[2]; Chen, R[3]; Gao, Y[4]; Chen, Q[5].

Review question / Objective: **Painful diabetic neuropathy (PDN) is one of the main and serious complications of diabetic patients, which not only accelerates the occurrence of ulcers of diabetic foot and even amputation of lower extremities but also seriously affects the quality of life.It is common that vitamin D deficiency in diabetic patients and especially in these patients diagnosed with DPN. vitamin D supplementation can effectively improve patients' pain symptoms and improve neurological function. However, the evidence of these studies is unconvincing. Therefore,This article focuses on the systematic evaluation and meta analysis of the efficacy and safety of vitamin D supplementation in patients with PDN, in order to provide a new choice for the prevention and treatment of early PDN patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 May 2020 and was last updated on 15 May 2020 (registration number INPLASY202050065).

INTRODUCTION

Review question / Objective: **Painful diabetic neuropathy (PDN) is one of the main and serious complications of diabetic patients, which not only accelerates the occurrence of ulcers of diabetic foot and even amputation of lower extremities but also seriously affects the quality of life.It is common that vitamin D deficiency in diabetic patients and especially in these patients diagnosed with DPN. vitamin D supplementation can effectively improve patients' pain symptoms and improve**

neurological function. However, the evidence of these studies is unconvincing. Therefore,This article focuses on the systematic evaluation and meta analysis of the efficacy and safety of vitamin D supplementation in patients with PDN, in order to provide a new choice for the prevention and treatment of early PDN patients.

Rationale: Studies have shown that vitamin D deficiency is common in PDN patients, and improving vitamin D levels may be beneficial to the improvement of pain symptoms and the recovery of nerve conduction function in PDN patients, but the existing clinical evidence in this regard is not comprehensive.

Condition being studied: Painful diabetic neuropathy (PDN), a chronic pain syndrome in peripheral neuropathic , is estimated that the incidence of diabetes is more than 20%. It has something to do with Sleep disorder, weight loss, and neuropsychiatric symptoms including anxiety and depression that affect people's quality of life.The causes of pain in DPN patients are very complicated.the clinical application of these drugs is often limited by unbearable adverse reactions.More and more studies have shown that vitamin deficiency may play a special role in the long-term chronic complications of diabetes mellitus, especially in patients with PDN. Due to the general lack of tendency and the advantages of low side effects, vitamin D therapy is considered to be a promising intervention for the treatment of PDN.

METHODS

Search strategy: We will include randomized controlled trials on vitamin D supplementation in the treatment of PDN. And we will retrieval 8 electronic databases with respect to this theme, the English databases mainly retrieval PubMed, Web of Science ,Embase and the Cochrane Library, while CNKI, VIP, CBM, and Wanfang database Will be used to retrieve the Chinese Literature. There is no clear time limit for retrieval conditions and the languages will be limited to Chinese and English. Besides, some clinical registrated tests and grey literatures are also researched by us. We will draw up a search strategy for each database , including MeSH headings: Diabetic Neuropathies, Vitamin D and Randomized controlled trial, Broad free terms such as Diabetic Neuropathy, Painful; Diabetic Neuropathies, Painful; Neuropathies, Painful; vitamin d; 25(OH)D; 25-HydroxyvitaminD; hypovitaminosisD; ControlledClinicalTrial, randomized ,placebo. Finally, we use the integration of subject words and free words.

Participant or population: Participants who meet the following three criteria will be included: 1.Diabetic patients under 75 years old, whether patients with type 1 or type 2 diabetes; 2.Diagnosis of diabetic peripheral neuropathy 3.Have symptoms of pain and symmetrical pain in the distal lower extremities lasted at least three weeks. Participants who meet one or more of these items will be excluded: 1.HbA1c > 11%; 2.There is a diagnosis of diabetic foot and foot ulcers occur; 3.Neuropathic pain that is not caused by PDN (e.g., malignant tumors, vitamin B12 deficiency, hypothyroidism, neurotoxic drug therapy, etc.); Diabetic patients with serious acute and chronic complications, such as diabetic ketoacidosis, etc. 4.Oral and injection of vitamin D and calcium or multivitamins in the past 3 months.

Intervention: No matter the experimental group or the control group also were cured with routine basic treatment of diabetes, including diet, exercise or drug therapy to control the level of blood glucose. In addition, all kinds of symptomatic analgesic drugs also are used to relieve symptoms. On this basis, vitamin D supplementation on Painful diabetic neuropathy is used for experimental group, without limitation about dosage and form of vitamin D.

Comparator: While the control group is limited to basic treatment. In addition, neither group took any drugs that affect the outcome indicators.

Study designs to be included: Only randomized controlled trials of vitamin D supplementation on PDN can be included.

Eligibility criteria: Type of study:Only randomized controlled trials of vitamin D supplementation on PDN can be included. Participants who meet the following three criteria will be included: 1.Diabetic patients under 75 years old, whether patients with type 1 or type 2 diabetes; 2.Diagnosis of diabetic peripheral neuropathy 3.Have symptoms of pain and symmetrical pain in the distal lower extremities lasted at least three weeks. Intervention:vitamin D supplementation on Painful diabetic neuropathy is used for experimental group.

Information sources: We will retrieval 8 electronic databases with respect to this theme, the English databases mainly retrieval PubMed, Web of Science ,Embase and the Cochrane Library, while CNKI, VIP, CBM, and Wanfang database Will be used to retrieve the Chinese Literature. There is no clear time limit for retrieval conditions and the languages will be limited to Chinese and English. Besides, some clinical registered tests and grey literatures are also researched by us.

Main outcome(s): The primary outcomes with respect to the Improvement of pain symptoms and assessment of peripheral nerve function. the degree of Improvement of pain symptoms is measured by different pain score scales. Peripheral nerve function includes the score of neurological symptoms and the examination of nerve conduction function.All symptom survey scores are reported by patients.

Additional outcome(s): Some changes of biochemical Indicators including fasting blood glucose (FBG), 2 hours postprandial blood glucose, glycated hemoglobin (HbA1C), calcium and Serum vitamin D level are included in secondary outcomes. Besides, adverse events in the study are also included.There outcome measured was the difference from pre-intervention and post-intervention.

Data management: We will design an appropriate data extraction table according to the characteristics of the included study, and the data extraction process will be completed separately by two researchers. The two researchers fill in each of the raw materials included in the study according to the requirements in the data extraction form, and if any dispute occurs in the process, we will discuss it or consult a third researcher to resolve it.The data extraction table mainly includes the following contents: research title, first author, year of publication, sample size (including experimental group and control group), course of disease, intervention measures, outcome indicators (including main and secondary results), adverse reactions and so on. If we find that there is a lack of key information in the process of filling in, we can solve it by contacting the author of the article, but if we can not find the relevant important information in various ways, we may want to consider excluding the study.

Quality assessment / Risk of bias analysis: According to the guidance of Cochrane Handbook for Systematic Reviews of Interventions, we will conduct a bias risk assessment for inclusion in the study. The evaluation of each study mainly includes the following seven aspects: whether random sequence generation, allocation hiding, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data , incomplete outcome data , selective outcome reporting and other bias .In the end, the bias of the study will be rated on three levels: "low bias", "high bias" and "ambiguous bias".

Strategy of data synthesis: According to the guidance of Cochrane Handbook for Systematic Reviews of Interventions, we will conduct a bias risk assessment for inclusion in the study. The evaluation of each study mainly includes the following seven aspects: whether random sequence generation, allocation hiding, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data , incomplete outcome data , selective

outcome reporting and other bias. In the end, the bias of the study will be rated on three levels: "low bias", "high bias" and "ambiguous bias".

Subgroup analysis: If the heterogeneity is relative large in our study, we will be advised to use subgroup analysis for different reasons. Heterogeneity may mainly come from the following several aspects: duration of intervention in study , vitamin D dosage form, dosage, etc. If a sufficient number of studies are included, we can further conduct meta regression to explore the heterogeneity between studies.

Sensibility analysis: In order to evaluate the quality and robustness of the merger results of the whole study, a sensitivity analysis according to the recommendations of the Cochrane Handbook will be conducted by us. The way is to eliminate literature that is rated as low-quality in turn and recombine the effects to evaluate the influence of the elimination of a single study on the overall results.

Language: The languages will be limited to Chinese and English.

Country(ies) involved: The countries that may be involved are China and the United States.

Keywords: vitamin D; painful diabetic neuropathy; systematic review; meta-analysis.

Dissemination plans: If some relevant important information are not available in the included original study, we will get in touch with the author of the article directly by e-mail or phone to obtain the information. If the missing information is still not obtain, then we can conduct a sensitivity analysis of the missing information to determine the impact of the missing data on the results of the whole study.

Contributions of each author:
Author 1 - Wenjing Wei - The title, methodology and writing of the thesis.
Author 2 - Yanli Zhang - Methodology of papers.
Author 3 - Rumeng Chen - Methodology of papers.
Author 4 - Yang Gao - Methodology of papers.
Author 5 - Qiu Chen - Methodology of papers.