INPLASY PROTOCOL

To cite: Lekhanya et al. Exploring the effectiveness of vitamin B12 complex and alpha-lipoic acid as a treatment for diabetic neuropathy. Protocol for systematic review. Inplasy protocol 202250167. doi: 10.37766/inplasy2022.5.0167

Received: 31 May 2022

Published: 31 May 2022

Corresponding author:
Kabelo Mokgalaboni

mokgak@unisa.ac.za

Author Affiliation:
University of South Africa

Support: **N/A.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Exploring the effectiveness of vitamin B12 complex and alpha-lipoic acid as a treatment for diabetic neuropathy. Protocol for systematic review

Lekhanya, PK[1]; Mokgalaboni, K[2].

Review question / Objective: **Does Alpha-Lipoic acid increase the uptake of glucose for better glycaemic control? Does vitamin B12 and Alpha-Lipoic acid improve inflammation? The aim of the study is to explore the effectiveness of Vitamin B12 and Alpha-Lipoic Acid as a possible treatment for diabetic neuropathy with major emphasis on markers of inflammation and glucose metabolism.**
Condition being studied: **Diabetic Neuropathy (DN) is a heterogeneous type of nerve damage associated with diabetes mellitus, the condition most often damages nerves in the legs and feet. It presents both clinically and sub-clinically affecting the peripheral nervous system as a result of an increase in glucose concentration which interferes with nerve signalling. After the discovery of insulin as a treatment for Diabetes Mellitus (DM), the prevalence of DN has since increased significantly due to DM patients having a longer life expectancy. It has been estimated that atleast 50% of DM patients will develop DN in their life, with approximately 20% of these patients experiencing neuropathic pain. Nerves are susceptible to changes in glucose concentrations and insulin makes it impossible for neurons to continue regulating glucose uptake.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 May 2022 and was last updated on 31 May 2022 (registration number INPLASY202250167).

INTRODUCTION

Review question / Objective: **Does Alpha-Lipoic acid increase the uptake of glucose for better glycaemic control? Does vitamin B12 and Alpha-Lipoic acid improve inflammation? The aim of the study is to explore the effectiveness of Vitamin B12 and Alpha-Lipoic Acid as a possible treatment for diabetic neuropathy with**

major emphasis on markers of inflammation and glucose metabolism.

Rationale: Diabetic Neuropathy (DN) is a heterogeneous type of nerve damage associated with diabetes mellitus, the condition most often damages nerves in the legs and feet. It presents both clinically and sub-clinically affecting the peripheral nervous system as a result of an increase in glucose concentration which interferes with nerve signalling . After the discovery of insulin as a treatment for Diabetes Mellitus (DM), the prevalence of DN has since increased significantly due to DM patients having a longer life expectancy. It has been estimated that atleast 50% of DM patients will develop DN in their life, with approximately 20% of these patients experiencing neuropathic pain. Nerves are susceptible to changes in glucose concentrations and insulin makes it impossible for neurons to continue regulating glucose uptake. For many years, Vitamin B12 and Alpha-Lipoic Acid (ALA) have been regarded as components that can treat pain and reduce oxidative stress. Vitamin B12 plays an important role in the metabolism of essential fatty acids involved in the maintenance of nerve myelin and direct scavenging of reactive oxygen species (ROS). However, patients with DN on metformin treatment have been shown to have low levels of Vitamin B12; this is because metformin on its own impairs Vitamin B12 absorption. When Vitamin B12 deficiency is prolonged, it leads to nerves degeneration, causing irreversible nerve damage. Previous researchers have explored the benefits of Vitamin B12 in nerve regeneration and have shown that it promotes nerve regeneration by promoting axon growth of neural cells after peripheral nerve damage. On the other hand, the naturally occurring ALA, an organosulfur compound derived from octanoic acid, is required to generate energy in the mitochondria by various enzymes. Most importantly, ALA serves as a potent antioxidant agent that can neutralize reactive oxygen species (ROS) and nerve blood flow, resulting in improved distal nerve conductions. Additionally, ALA act as a scavenger for free radicals both intra- and extracellularly to repair oxidative damage. Furthermore, ALA has been shown to increase the uptake of glucose to control glucose metabolism (3,4,10). However, it is still unclear how these compounds impact the markers of inflammation and related glucose parameters in patients with diabetic neuropathy. Therefore, this study is aimed at exploring the effectiveness of Vitamin B12 and Alpha-Lipoic Acid as a possible treatment for Diabetic Neuropathy with major emphasis on markers of inflammation and glucose metabolism.

Condition being studied: Diabetic Neuropathy (DN) is a heterogeneous type of nerve damage associated with diabetes mellitus, the condition most often damages nerves in the legs and feet. It presents both clinically and sub-clinically affecting the peripheral nervous system as a result of an increase in glucose concentration which interferes with nerve signalling. After the discovery of insulin as a treatment for Diabetes Mellitus (DM), the prevalence of DN has since increased significantly due to DM patients having a longer life expectancy. It has been estimated that atleast 50% of DM patients will develop DN in their life, with approximately 20% of these patients experiencing neuropathic pain. Nerves are susceptible to changes in glucose concentrations and insulin makes it impossible for neurons to continue regulating glucose uptake.

METHODS

Search strategy: Search will incluse MesH terms and text words such as vitamin B, alpha-lipoic acid, diabetes, diabetic neuropathy. PubMed, Google Scholar, Web of Science and Science direct will be searched in order to identify suitable sources for this review. Additionally, refernce list will also be searched mannually for eligible studies.

Participant or population: Adult pateints with diabetes/diabetic neuropathy.

Intervention: Vitamin B12 complex and alpha-lipoic acid.

Comparator: Patients on placebo or control.

Study designs to be included: Randomosed controlled trials.

Eligibility criteria: INCLUSIONS All studies will be reviewed for inclusions and where there may be uncertainty the studies in the review will required to meet the following criteria.· The study that focuses on the effects of vitamin B12 and/or Alpha-Lipoic Acid in Diabetic Neuropathy.· The study that uses human subjects with diabetes.· The study was published in English. EXCLUSION Animal studies and studies that are non-English will be excluded from this review. This is partially because translating studies from other languages end up losing the exact results obtained from such studies. Reviews will not be considered.

Information sources: Studies will be searched using online databases including PubMed, Google Scholar, Web of Sciences, Science direct, Embase and grey literature.

Main outcome(s): Markers of Inflammation (standardized mean difference and mean difference); Glucose parameters (standardized mean difference and mean difference).

Data management: Based on the characteristics of the study, we will prepare an excel form for data collection before data extraction. Outcomes and effect measures for eligible studies will be extracted and filled in the data extraction form by 2 independent reviewers. If there is any disagreement, it can be resolved by discussing it between the 2 reviewers or seeking a third reviewer's opinion. The main data extracted are as follows: The first authors of the article, year of publication, the country where the study was conducted, source of funding, interventions in experimental group, interventions in control group, time of treatment, number of patients in each group, ages, and sex of patients, outcomes and effect measures. To seek for clarity about the study, corresponding authors will be contacted.

Quality assessment / Risk of bias analysis: All the included studies will be evaluated in accordance with the Cochrane guidelines. Two reviewers will independently evaluate the design. Bias risk through 7 assessment trials: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias. Each item is classified as "Low risk", "High risk" or "Unclear risk". The disagreement of bias risk will be resolved through further discussion or consultation with the third independent reviewer.

Strategy of data synthesis: We will use the Review Manager software V5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark) to analyze all data. For continuous data, the mean difference (MD) or standardized MD (SMD) with 95% CI will be estimated. If we use the same scale to measure an outcome in different studies, we will use MD. Similarly, if we use different scales to measure the same outcome, we will use SMD. If an outcome measure contains less than 2 trials, we will summarize the results descriptively Statistical heterogeneity among studies will be evaluated using the Cochran Q test (x2) and the I2 statistical value. We will categorize the heterogeneity using the following rules. I2 of 0% to 25% indicates low heterogeneity. I2 of 25% to 50% represents moderate heterogeneity. And I2 of 75% to 100% represents high heterogeneity. When the P value from a x2 test is more than .10 or I2 50%, we will use the fixed-effects model. When a meta-analysis is not possible, a descriptive summary of individual studies will be made.

Subgroup analysis: Subgroup analysis If the results of the study are heterogeneous, we will conduct a subgroup analysis for different reasons. Heterogeneity is manifested in the following several

aspects, such as race, age, gender, different forms of intervention, drug dosage, duration of treatment.

Sensitivity analysis: Sensitivity analysis will be performed to investigate the stability of the results, we will conduct a sensitivity analysis for all outcomes. We will perform leave one study procedure and then re-analyze and pooled the data and compare the difference between the reobtained effects and the original effects. In this way, we will be able to assess the impact of individual studies on the overall results and whether the results are reliable.

Language: Search will be limited to studies published in English this is partially because translating studies from other languages end up losing the exact results obtained from such studies.

Country(ies) involved: South Africa.

Keywords: Vitamin B 12 , Alpha-lipoic acid, Diabetic neuropathy, Tyupe 2 diabetes.

Dissemination plans: The findings will be presented in seminars, journal clubs and published in peer reviewed journals.

Contributions of each author:

Author 1 - Portia Keabetswe Lekhanya - PKL conceptualized, designed and drafted the manuscript. PKL approved the final manuscript.
Email: 69744513@mylife.unisa.ac.za
Author 2 - Kabelo Mokgalaboni - KM conceptualized, designed and drafted the manuscript. KM approved the final manuscript. KM supervised the review.
Email: mokgak@unisa.ac.za