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Exploring the effectiveness of vitamin B_{12} complex and alpha-lipoic acid as a treatment for diabetes mellitus/neuropathy: a protocol for systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Diabetic neuropathy (DN) is common in patients diagnosed with diabetes mellitus. This often causes peripheral nerve damage. For many years vitamin B_{12} and alpha-lipoic acid (ALA) have been regarded as components that can be used in reducing markers of inflammation and oxidative stress. In this study, we will explore the effectiveness of vitamin B_{12} and ALA as a possible treatment for diabetic mellitus/neuropathy, emphasising markers of inflammation, lipid profile, and glucose metabolism.

Methods and analysis We will conduct a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P). The search strategies and information sources for the literature will be PubMed, Google Scholar, Web of Science and Science direct. The literature search will include studies published from inception until 30 June 2022. All included studies will be evaluated for quality and risk of bias according to the Cochrane guidelines. To investigate the stability of the results, we will conduct a sensitivity analysis of the outcomes. All data analysis will be performed using Review Manager V.5. 4.

Ethical and dissemination This systematic review and meta-analysis will not require ethical approval from an institution committee as it does not have direct participants. We will obtain all our data from previous studies. The findings will be disseminated through publications in peer-reviewed journals and presented at local and international seminars and conferences.

INTRODUCTION

Diabetic neuropathy (DN) is a heterogeneous type of nerve damage associated with diabetes mellitus (DM), the condition most often damages nerves in the legs and feet.[1] It presents both clinically and subclinically affecting the peripheral nervous system due to an increase in glucose concentration which interferes with nerve signalling.[1 2]

Following the discovery of insulin as a treatment for DM, the prevalence of DN has since increased significantly due to patients with DM having a longer life expectancy.[2] It has been estimated that at least 50% of patients with DM will develop DN in their life, with approximately 20% experiencing neuropathic-related pains.[1 2] Nerves are susceptible to changes in glucose concentrations, and insulin treatment makes it impossible for neurons to continue regulating glucose uptake.[3 4]

For many years, vitamin B_{12} and alpha-lipoic acid (ALA) have been regarded as components that reduce pain and oxidative stress. Vitamin B_{12} is essential 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 vitamin B_{12}; this is because metformin on its own impairs vitamin B_{12} absorption. When vitamin B_{12} deficiency is prolonged, it leads to nerve degeneration, causing irreversible nerve damage.[5] Previous researchers have explored the benefits of vitamin B_{12} and have discovered that it stimulates nerve regeneration by promoting axon growth of neural cells after peripheral nerve damage.[6]

On the other hand, the naturally occurring ALA, an organosulfur compound derived from octanoic acid,[7] is required to generate energy in the mitochondria by various enzymes. Most importantly, ALA is a potent antioxidant agent that can neutralise ROS and nerve blood flow, resulting in improved distal nerve conductions[1]. Additionally, ALA acts as a scavenger for free radicals

intracellularly and extracellularly to repair oxidative damage.[8 9] Furthermore, ALA has been shown to increase the uptake of glucose to control glucose metabolism.[7–9] Moreover, another study showed an improvement in glucose level and insulin sensitivity following the use of ALA treatment in patients with type 2 diabetes mellitus.[10] In metabolic syndromes, a previous meta-analysis demonstrated that treatment of ALA improves the marker of inflammation.[11] However, it is still unclear how these compounds impact the markers of inflammation and related glucose parameters in patients with diabetes/DN. A previous meta-analysis assessing the effect of ALA on lipid profiles revealed a significant decrease in lipid profiles; however, this was conducted in patients with various conditions, including diabetes, schizophrenia, obesity, renal disease and hyperthyroidism.[12] Therefore, this systematic review and meta-analysis aim to explore the effectiveness of vitamin B_{12} and ALA as either monotherapy or dual treatment for DM/neuropathy with major emphasis on markers of inflammation, lipid profile, and glucose metabolism.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This proposed review will comprehensively assess published randomised controlled trials on the primary research question, focusing on glycaemic control, inflammation and lipid profile in patients with diabetes on either monotherapy or dual treatment of vitamin B_{12} and alpha-lipoic acid.
⇒ A comprehensive search for literature will be conducted on the database to source out and retrieve studies relevant to our research question.
⇒ This will be the primary systematic review and meta-analysis conducted to evaluate the single or dual supplementation of these treatments in diabetes mellitus.
⇒ The anticipated limitation includes heterogeneity that may arise due to different dosages, forms of diabetes, dual or monotherapy and also the duration of intervention.
⇒ However, subgroup and sensitivity analysis will be performed to source the exact cause of heterogeneity.

METHODOLOGY

This protocol for a systematic review and meta-analysis is aimed at evaluating the beneficial impact of vitamin B_{12} and ALA in DM with a major focus on markers of inflammation, lipid profile and glucose metabolism. The review will follow the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocol (PRISMA-P;[13] online supplemental file 1).

Patient and public involvement

No patient involved.

Aim

The study's main aim is to explore the effectiveness of vitamin B_{12} and ALA as a possible treatment for DM/DN with major emphasis on markers of inflammation, lipid profile, and glucose metabolism.

Questions

Does ALA increase the uptake of glucose for better glycaemic control?
Do vitamin B_{12} and ALA improve markers of inflammation?
What is the impact of vitamin B_{12}/ALA on lipid profile among patients with diabetes?

Participants/population

We will consider studies conducted in patients with diabetes/DN on either vitamin B_{12} or ALA as supplements.

Intervention

We will consider studies conducted on patients living with DM/DN on Vitamin B_{12} and ALA supplementations. If vitamin B_{12} and ALA are used in the same trial, and there is a comparator/control, such studies will be analysed as dual treatment versus placebo/control. However, if one treatment is used in a trial, it will be subgrouped as monotherapy versus placebo/control.

Design

Randomised controlled trials.

Comparator

The comparator will be divided into two:
Patients with DM/DN on placebo.
Healthy participants not on any treatment (control).

Outcomes

Improved markers of inflammation such as tumour necrosis factor-alpha, interleukin-6 and C reactive protein.
Improved glucose parameters, fasting blood glucose and insulin.
Improved lipid profile, total cholesterol, triglyceride, low-density lipoprotein, andhigh-density lipoprotein.

Eligibility criteria

Inclusion

All studies will be reviewed for inclusions, and where there may be uncertainty, the studies in the review will be required to meet the following criteria.
The randomised controlled trials focus on the effects of vitamin B_{12} and ALA in DM/DN.
The studies that use human subjects with diabetes/DN.
The studies 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. Cohorts, case–control, case studies and experimental studies will all be excluded. Those studies that use other drugs will be deemed irrelevant to the current study.

Search strategy and information sources

PubMed, Google Scholar, Scopus, Web of Science and Science direct databases will be searched to identify suitable sources for this review. Two independent investigators (PKL and KM) will conduct the literature search. MesH terms and text words will be used, including 'vitamin B12' and synonyms, 'alpha-lipoic acid', 'diabetes mellitus', and 'diabetic neuropathy'. The search will be divided into two to source out studies on vitamin B_{12} and ALA in diabetes. The search will seek studies published in English from inception until 30 June 2022 (online supplemental file 2). Furthermore, studies that meet the inclusion criteria will be screened, and data will be extracted and presented in a tabular format.

Study selection

The screening of studies will be conducted by two independent investigators (PKL and KM) to avoid inconsistency in terms of eligibility of studies. First, studies will be screened by the titles, abstracts, keywords and synonyms, followed by identifying the full-text articles, if available. In case of discrepancies between two investigators (PKL and KM), the resolution will be reached through discussion and reviewing the study in question. Mendeley desktop reference manager (V.1.19.4) will be used to save extracted data, saving relevant and excluded studies. Furthermore, reference lists of included studies will be screened to identify other relevant studies. Studies meeting the inclusion criteria will then be subjected to data collection, critical appraisal, risk, and quality evaluation.

Data extraction and management

Reference manager (Mendeley desktop V.1.19.4) will be used to store retrieved studies from databases. Review Manager software V.5.4 will be sued to analyse all data and creation of forest and funnel plots. 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 two independent investigators (PKL and KM). Any disagreement can be resolved by discussing it between the two investigators (PKL and KM) or seeking a third investigators opinion. The primary data to be extracted are as follows: the first authors and year of publication of the study, the country where the study was carried out, source of funding, interventions in the experimental group (monotherapy or dual therapy), interventions in the control group, time of treatment, number of participants in each group, age and sex of participants, outcomes and effect measures. To seek clarity about the study, corresponding authors will be contacted.

Risk of bias assessment

All relevant studies will be evaluated following the Cochrane guidelines.[14 15] Two investigators (PLK and KM) will independently evaluate the methodological design by assessing these seven bias items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Individual items will be categorised as 'Low risk,' 'High risk' or 'Unclear risk'. The disagreement between the two investigators (PLK and KM) in terms of bias risk will be resolved through further discussion and re-evaluation of such an item and the study in question.

Sensitivity analysis

To assess the stability of the results, we will conduct a sensitivity analysis for the outcomes[16] with the use of RevMan V.5.4. We will exclude one study included in the analysis, then re-analyse the pooled estimates and compare effect size with the size of the initial effect.

Publication bias

Suppose studies greater than 10 are included in the meta-analysis. In that case, the symmetry of the funnel plot will be evaluated to examine publication bias,[17] and the results will be interpreted with care.

Strength of the quality of evidence

In this planned, systematic review and meta-analysis, the study's evidence quality will be investigated following the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[18 19] This is classified into four levels: high, medium, low and very low. We will use the GRADE profiler 3.2 for analysis.[20]

Subgroup analysis

If the obtained results are heterogeneous, we will perform a subgroup analysis to find the source of heterogeneity,[21 22] which can arise from study design, race, age, sex, different intervention forms, drug dosage, forms of diabetes, monotherapy or dual therapy and duration of treatment.

Statistical analysis

We will use the Review Manager software V.5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark) to analyse all data. The mean difference (MD) or standardised MD (SMD) and 95% CI will be estimated for continuous data. If the same scale is used to measure an outcome in different studies, MD will be used. Similarly, we will use SMD if different scales are used to measure the same outcome. If an outcome measure contains less than two trials, we will summarise the results descriptively. Meta-analysis will be carried out if at least two or more studies report the same outcome. However, in case of an insufficient number of studies to perform a meta-analysis, a qualitative synthesis will be performed.[23] The statistical level of heterogeneity among included studies will be assessed using the Cochran Q test (x^2) and the I^2 statistical tests. We will classify the heterogeneity using the predefined rules.[22] An I^2 of 0%–25% will be classified as low heterogeneity, I^2 of 25%–50% represents moderate heterogeneity[24] and an I^2 of 75%–100% represents high heterogeneity. We will use the fixed-effects model when the p value from an χ^2 test is more than 0.10 or $I^2 \leq 50\%$. A subgroup analysis will be conducted

to identify possible sources for statistical heterogeneity, considering prespecified factors. A descriptive summary of individual studies will be made when a meta-analysis is not possible.

DISCUSSION

DN has no existing medical cure, and prevention will be crucial. With tight glucose control, we can see a decrease in the progression of nerve damage. However, this warrants for effective medical intervention. This systematic review and meta-analysis focus on vitamin B_{12} and ALA as monotherapy or dual treatments in DM/DN. These components have shown properties that decrease oxidative stress and increase nerve myelination. A previous meta-analysis assessing the effect of ALA on lipid profiles revealed a significant decrease in lipid profiles; however, this was conducted in patients with various conditions, including diabetes, schizophrenia, obesity, renal disease and hyperthyroidism.[12] So, there is a need for evaluation of the effects of both ALA and vitamin B_{12} on lipid profile, glycaemia and inflammation in DM.

Collaborators Not applicable.

Contributors KM and PKL conceptualised, designed and initiated the protocol. PLK and KM drafted the original manuscript. KM revised and edited the final version of the protocol. All authors approved the final version of the manuscript submitted for publication. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the	10, 11

		guarantor of the review	
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	9
Sponsor	#5b	Provide name for the review funder and / or sponsor	9
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	9
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4-5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Study records -	#11b	State the process that will be used for selecting studies (such	6

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

PubMed on the 30 June 2022

Item	MesH terms	Hits
1	Alpha-lipoic acid	4,509
2	Type 2 diabetes	159398
3	Alpha-lipoic acid AND type 2 diabetes mellitus	36

Item	MesH terms	Hits
1	Vitamin B12	23248
2	Cobalamin	23248
3	cyanocobalamin	23248
4	Type 2 diabetes mellitus	159398
5	1,2,3, and 4	30