BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834
Article Type:	Original research
Date Submitted by the Author:	03-Dec-2021
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Lord, Heidi; Saint George Hospital, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and metaanalysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Lord[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.gov.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and metaanalysis

ABSTRACT

Objective: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose levels and prevent complications. This systematic review was done to evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods: *Design:* RCTs and quasi-experimental studies that assessed effect of thiamine supplementation in adults with T2DM were considered. Trials which measured the glcemic outcomes - glycated haemoglobin (HbA1C), fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included. Relevant studies were searched in PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar. Studies obtained were uploaded in to Endnote X8. Two independent reviewers assessed methodological quality and data extracted. Studies, where possible, were pooled in a meta-analysis. Results are presented in a narrative format if statistical pooling was not possible.

Results: Total six trials involving 364 participants were included. No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for upto 3 months. However, significant increase in HDL was seen (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) when given in 120mg/day dose as compared to placebo 150mg/day, but not in higher doses.

Conclusions: Thiamine supplementation doesn't affect glycemic outcomes but reduces triglycerides while increasing HDL. Multicentre well designed randomised controlled trial

with higher doses of thiamine and1-2 years follow up will give better idea regarding effect of thiamine on glycemic outcomes in T2DM.

Strengths: This systematic review addresses an important topic of control of diabetes with thiamine supplementation and includes a few important secondary outcomes as well like LDL and triglyceride levels. This is a systematic review of good quality RCTs, hence the results can be relied upon to give direction to future research.

Limitations: This review includes single-centre trials published only in the English language. Sample sizes of the included studies were small although some had addressed this issue using statistical power. Furthermore, there was a lack of trials investigating the outcomes for some comparisons. The follow-up period also varied and was short lasting that is, only for upto three months.

Summary:

- Thiamine supplementation does not have any beneficial effect on sugar levels in patients of Type 2 DM.
- Significant increase in HDL level is seen at three months follow-up.
- Triglyceride levels also reduce significantly with 120 mg/day compared to 150 mg/day benfotiamine.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045.[1]Type 2 diabetes mellitus was the cause of 4.2 million fatalities in 2019 globally .[1]

Numerous complications have been associated with T2DM which have an impact on the quality of life of those affected and imposes a high economic burden on the individuals and community. T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2]T2DM is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG) having T2DM.[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and a-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7]Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a type of thiamine, a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives. It has been

reported that benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. Benfotiamine also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11,14,122] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[133]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23]

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C) and various vitamins

(including thiamine) and minerals[13,15,17-25] but with inconsistent results. Some studies reported significant inverse association for thiamine supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,26]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[30]by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[31] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy that was carried out in December 2019. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and

blood glucose was undertaken. Text words contained in the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L).Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies

were resolved by discussion with a third author (HL). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HL) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality was assessed using the standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs. [30]An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[32]. The continuous data

extracted from the cross-over RCTs were treated as if from a parallel trial[33]. All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as weighted mean differences and corresponding 95% confidence intervals (CI) were calculated. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if I^2>50% and P value <0.10 in the chi-square test for heterogeneity.[34]A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 145 potential trials, with 127 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials were identified for potential inclusion in the review. (Appendix II) The reference lists of the 11 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded after examination of the full text against the inclusion criteria (see Appendix III). Thus, finally six trials were included in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[35] or non-diabetic[36], in vitro study[37], did not assess the outcome of interest [28,38,39] and study done on rats.[40]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q1 0	Q1 1	Q1 2	Q1 3	Total
Winkler 1999[24]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[34]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[25]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[48]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[32]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22 [16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way.

Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[41]an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	Q1	Q2	Q3	Q4	Score
1	Shahmiri 2013[48]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallelRCTs[15,16,19,27,29]and one was cross-over RCT.[41] The six trials were conducted in six different countries – Germany [29], Pakistan [19], Netherlands [27], Australia [41], Mexico/USA [15]and Hungary [16]. The number of participants in parallel RCTs varied from 12[41] to 165[29]while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,27]One trial [27] had male predominance (77% vs 33%) while the other [16]had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16]to 65.3 ± 5.9 years.[27]

Five of the six trials compared the intervention to placebo and one trial [16]compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from

100 mg/day[41]to 300mg/day [19]and the dosage for benfotiamine ranged from 120mg/ day [16] to 900mg/day.[27]. The follow-up period ranged from 1 month[15]to 3 months.[19,27]

Fasting blood glucose was reported in four trials,[15,16,19,41] PPG in two trials,[16,41]HbA1c in five trials,[15,16,19,27,29] HDL in four trials,[15,16,19,27] LDL in three trials,[15,19,27] triglycerides in four trials,[15,16,19,27], systolic and diastolic BP in three trials [15,19,27]and BMI in two trials. [15,41]Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,27]that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD-0.02, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,27,29]investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study [29]reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16]that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,41]demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20; CI -0.69, 0.29) (Fig 3).The absolute effect with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine onFBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day

benfotiamine (MD 0.60; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [41]investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16]compared 320mg/day and 120mg/day of Benfotiamine onPPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10; CI 0.10, 0.30) (Fig 4) but a statistically significant difference was seen (MD 0.10; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16]compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine(MD -0.20, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14; CI -0.17, 0.45) (Fig 5) as well as the 3 month follow-up period (MD 0.25; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22; 95% CI -2.23, 1.79).

Discussion

Plasma thiamine levels have been reported to be 75% lower in patients with T2DM.[14] Given that thiamine is vital for intracellular glucose metabolism, this systematic review was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable with the assessment criteria regarding the method of randomization and allocation concealment not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG[42,43] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [44].

The results of the review also demonstrated no significant differences in FBG, , LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations and the presence of underlying health conditions which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [45].Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

Despite summarising the evidence, several limitations of this review should be noted. Firstly, the review includes single-centre trials published only in the English language which limits

the generalizability of the results. Sample sizes of the included studies were small although some had addressed this issue using statistical power. Furthermore, there was a lack of trials investigating the outcomes for some comparisons. The follow-up period also varied and was short lasting that is, only for upto three months.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100mg/day to 900mg/day for up to 3 months. Until further research is available practices will be dictated by existing policies and available resources.However, some important points are identified like - the studies published this far have all been single centric studies, with small sample size, using varying doses and follow-up for only 3 months. Therefore, more robust multicentre well designed randomised controlled trial with higher doses of thiamine for long enough follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: All authors contributed to the study

AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data acquisition and analysis; PM: Data collection, manuscript preparation.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. IDF Diabetes Atlas 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H, Hadian M. Cost effectiveness of type 2 diabetes screening: A systematic review. Med J Islam Repub Iran. 2016;30(326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. Clin Nutr. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. Diabetes Care. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. Cell Mol Life Sci. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, Subramanian VS, Maedler K, Said HM. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, Pierzynowska J, Drywień M. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. J Anim Physiol Anim Nutr (Berl). 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. Stem Cells Dev. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. Nat Med. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. Diab Vasc Dis Res. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. Diabetologia. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, Chen G, Zhang M. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. PLoS One. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. Proceedings of the Society for Experimental Biology and Medicine: Minireviews. 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, Ramírez-Ramírez V, Ramos-Zavala MG. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. Eur J Nutr. 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, Porochnavec M, Kempler P. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. Arzneimittelforschung. 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. The American Journal of Clinical Nutrition. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. Diabet Med. 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. Diabetologia. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, Incampa S, Jaiyen S, Khaithong W. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Res Clin Pract. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. Int J Clin Pract. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. Ann Nutr Metab. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, Ali W, Reddy HD, Mishra A. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. J Nat Sci Biol Med. 2013;4(2):336.

24. Rafat D, Rabbani T, Ahmad J, Ansari M. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect

of Iron Supplementation. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2012;6(2):102-5.

25. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. Am J Ther. 2014;21(6):491-5.

26. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. Free Radic Res. 2010;44(12):1445-53.

27. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. Diabetes Care. 2010;33(7):1598-601.

28. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. Int J Clin Pharmacol Ther. 2005;43(2):71-7.

29. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel R. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. Experimental and clinical endocrinology & diabetes. 2008;116(10):600-5.

30. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic Reviews of Effectiveness. Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute. 2017.

31. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. The Joanna Briggs Institute. 2017;299(

32. Review Manager. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014.

33. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002;31(1):140-9.

34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring Inconsistency in Meta-Analyses. BMJ. 2003;327(7414):557-60.

35. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.

36. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PLoS One. 2015;10(10).

37. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.

38. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).

39. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metab Brain Dis. 1996;11(1):95-106.

40. Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.

41. Shahmiri FA, Soares M, Zhao Y, Sherriff J. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. Eur J Nutr. 2013;52(7):1821-4.

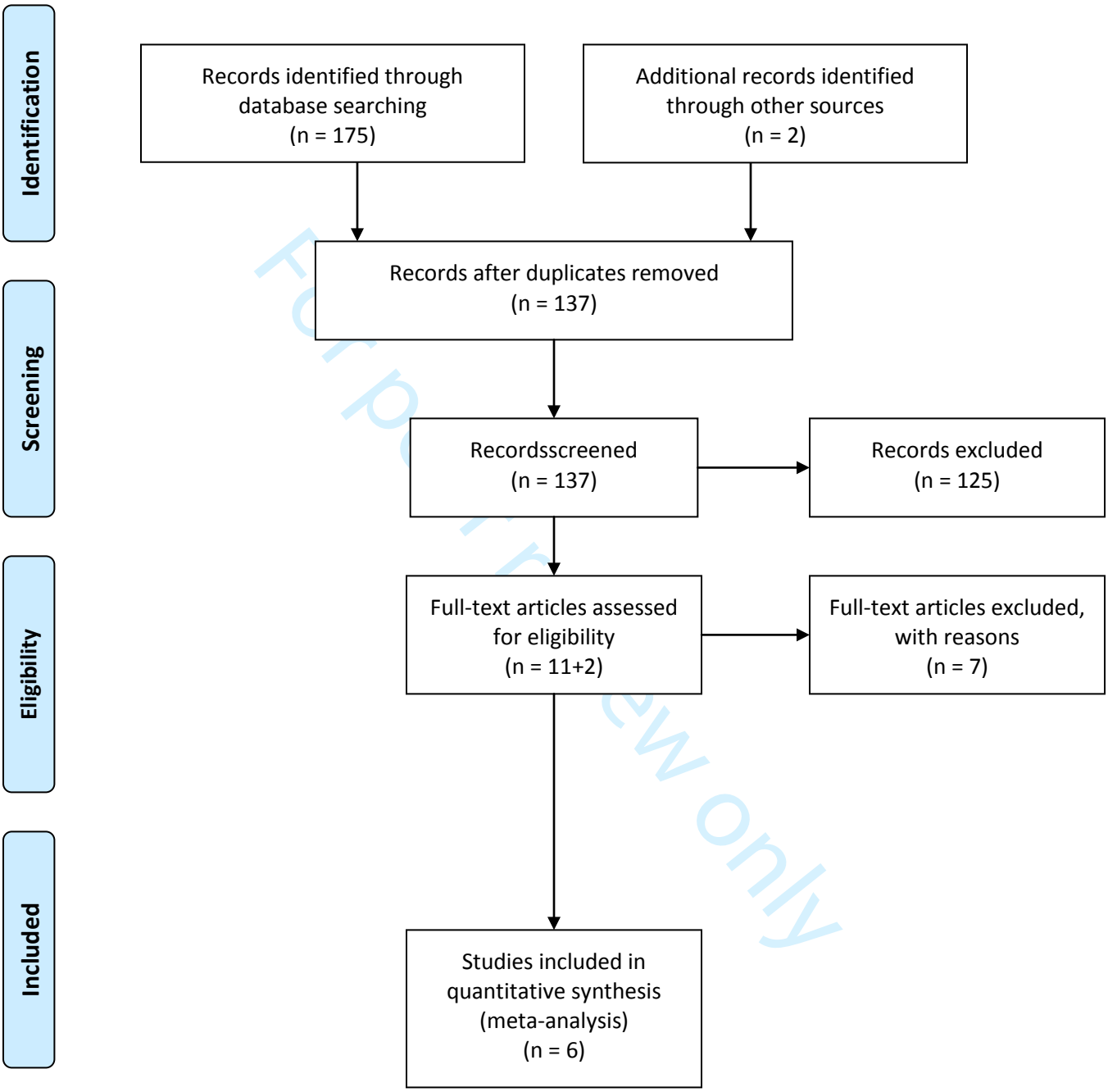
42. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. Prehosp Disaster Med. 2019;34(5):506-9.

43. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care. 2009;32(12):2245-50.

44. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. Arch Intern Med. 2003;163(11):1306-16.

45. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2014;37(Supplement 1):S120-S43.

PRISMA 2009 Flow Diagram[57]



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visitwww.prisma-statement.org.

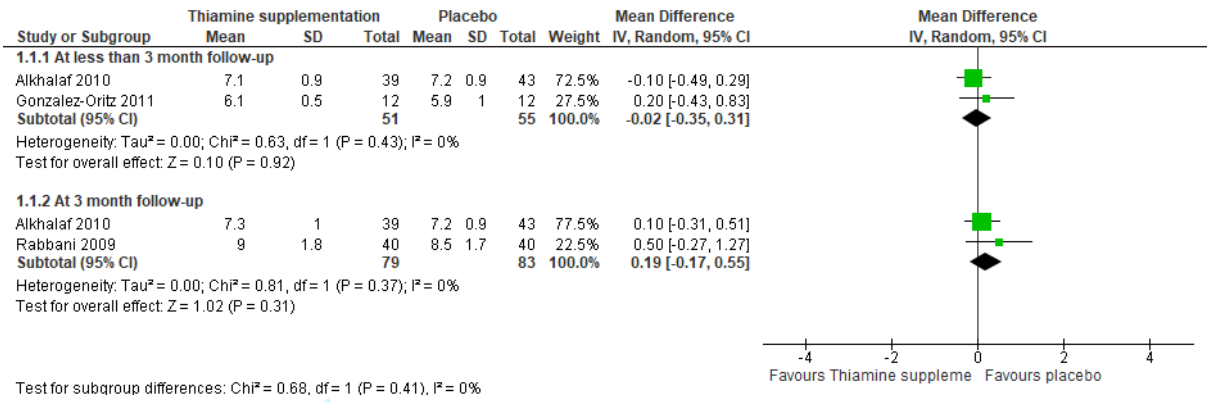


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

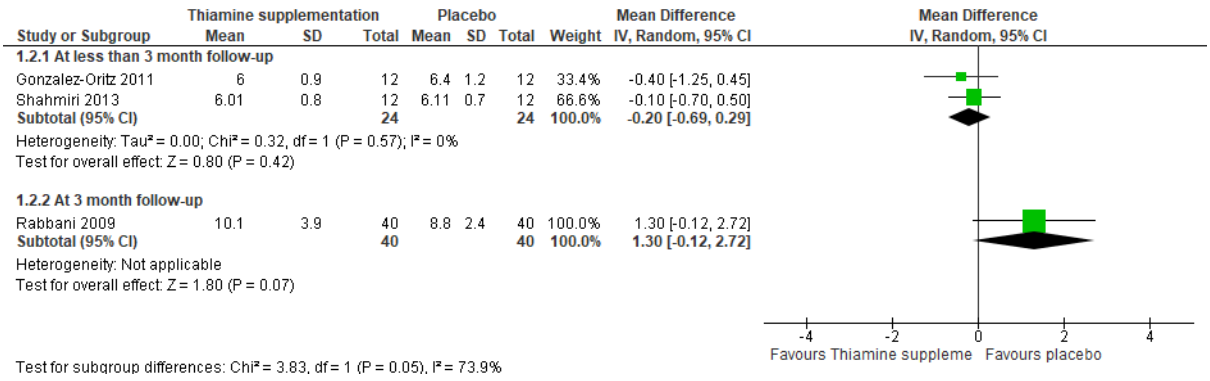


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

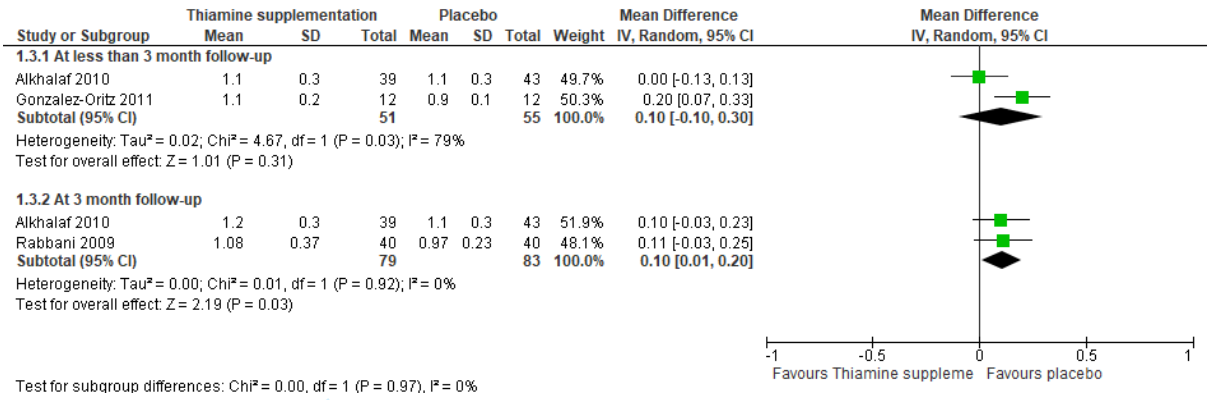


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

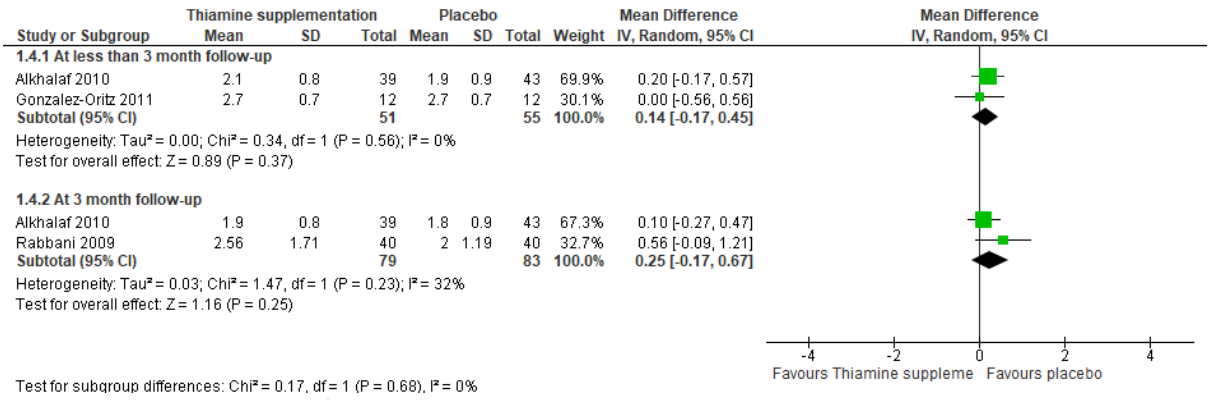


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

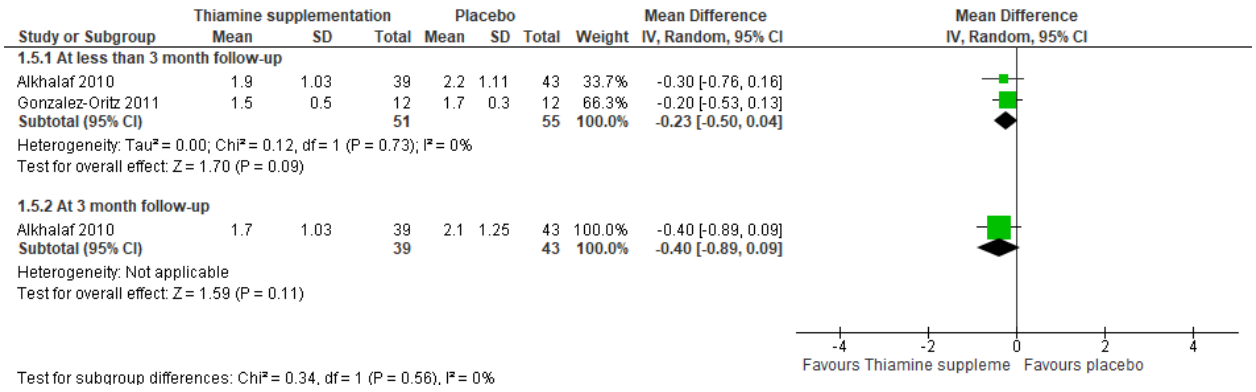


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride, at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride, at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

Review title

Effect of thiamine or benfotiamine on blood sugar and HBA1C in adults: A systematic review protocol.

Review question

The question for this review is: what is the effectiveness of thiamine or benfotiamine supplementation on blood sugar and HBA1C in adults?

Introduction

Type 2 Diabetes mellitus (T2DM) is a major global health problem. It is a chronic metabolic disease with high prevalence in both developed and developing countries. Over the past decade, the prevalence of T2DM has risen faster in low and middle-income countries than in high-income countries.[1] The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is also higher in low and middle-income countries than in high-income countries.[1] In the adult population, its prevalence has almost doubledfrom 4.7% to 8.5% in the last four decades.[1]In 1980, 108 million adults were reported to have diabetes. The figure increased to about 422 million in 2014[1]which is expected to be more than 592 million by 2035.[2]

T2DM has many complications which significantly affect the quality of life and impose a high economic burden on the individuals and community. Approximately 20% to 30% of the patients undergoing coronary artery bypass graft (CABG) have T2DM.[5-7]In 2012, it lead to 59,258,034 disability adjusted life years (DALYs) and became the third most common cause of fatal complications.[3]From 1990 to 2013, the mortalities due to T2DM increased by 89.7% to make it the seventh leading cause of death.[4] Hence it is vital that prevention and/or optimal management strategies are implemented to reduce the effect of the this global epidemic.

Thiamine (vitamin B1) was identified in 1926 by Jansen et al.[8]Thiamine diphosphate (TDP) is its metabolically active form which acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and a-ketoglutarate dehydrogenase complexes, which are the fundamental enzymes required for intracellular glucose metabolism. It thus, plays a significant role in the intracellular glucose metabolism at various stages (glycolysis, Krebs cycle, pentose-phosphate cycle).[9]The pancreas also has high concentration of thiamine.[10] Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[11]As a result, vitamin B1 deficiency leads to a marked decrease in synthesis and secretion of insulin.[12-13]In addition, high thiamine level is found in high fiber foods which have been reported to decrease postprandial glycemia in diabetic patients.[14]

Benfotiamine is a type of allithiamine, a lipid soluble thiamine derivative which more efficiently raises thiamine level in blood as compared to the water soluble thiamine derivatives.It has been proved thatit reduces glucose toxicity caused by hyperglycemia in DM by activating glucose metabolism and insulin synthesis.[15]It also has a role in blocking many pathways responsible for hyperglycaemia induced damage,e.g; the hexosamine pathway, formation of AGEs andactivation of protein kinase C.It also worksby activating transketolase which is the rate limiting enzyme of the non-oxidativebranch of the pentose phosphate pathway.[16]

It was observed that although relatively low doses of thiamine saturate the thiamine transporter in intestine, at high concentration of thiamine, there is continuous slow passive diffusion.[17]Based on this observation, recently, many evidenceshave been published to prove the role of high dose thiamine and thiamine derivative therapy inreducing blood sugar levels and diabetic complications. In a study, the authors reported the maximum TPP-saturated transketolase activity with high dose thiamine supplementation with (20-50-fold the normal daily requirement).[18] Another study reported that thiamine supplementationprevented the hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[19]It has also been reported that in Streptozotocin-induced diabetic rats, 6 months' therapy of thiamnie or benfotiamine, halted advanced glycationand delayed the development of diabetic neuropathy.[20-22]In women, thiamine intake has been shown to have a strong association with glucose tolerance .[23] In other studies, it was reported that thiamine decreased blood glucose and leptin concentration in one month.[24]and glycosylated hemoglobin decreasedsignificantly with benfotiamine therapy in 45 days.[25]

Interestingly in various studies it was observed that diabetic patients had low blood thiamine level, erythrocyte Tk activity and high erythrocyte thiamine pyrophosphate (TPP) activity[26-30] with an increased renal clearance and fractional excretion of thiamine[31,32], as compared to healthy controls. In a study, plasma thiamine level was reported to be 75% lower in type 2 diabetes patients.[31]Reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine have been suggested as the reasons for these observations.[33]In a study of diabetic subjects (type not specified), 76% had a thiamine concentration lower than the lower limit of the normal range.[34] In another study of Type 2 diabetes, 18% of the participants showed lower thiamine concentration as compared to the lower limit of the normal range.[35]It has been suggested that in such individuals, inability of endothelial cells and pericytes to regulate glucose transport leads to high levels of intracellular glucose concentrations.[36] Similar effects of Benfotiamine have been found in hyperglycaemia on RBC metabolism.[22]

Many studies have investigated association between FBS, PP2BS, HBA1C and various vitamins (including thiamine) and minerals[32-44]but with inconsistent results. Some studies reported significant inverse association for vitamin B1 supplementation[37-41] while other intervention studies did not find any significant association forvitamin B1.[32-36,38]

32.

As dietary supplementation can be an easily feasible and economic strategy to control sugar levels and prevent hyperglycemia related complications, we aimtodo a systematic review and metaanalysis to find out therelationship of supplementation of vitamin B1 or Benfotiamine with FBS, PP2BS and HbA1c concentrations in adults.During the initial search, about 10 RCTs which addressed the study question were identified. However, no systematic review has addressed this question as yet. Considering the relevance of this topic, this systematic review will provide updated evidence for the effect of thiamine supplementation on glycemic outcomes.

Keywords

Type 2 diabetes mellitus, vitamin B1, benfotiamine, glycemic control, HBA1C.

Inclusion criteria

Participants

The review will consider studies in whichparticipants aged more than 18 yearsreceived thiamine or benfotiamine supplementation and effect of this supplementation on FBS or PP2BS or HBA1C was assessed as an outcome. Studies with be included irrespective of the prediabetic ordiabetic status of their population.

Intervention(s)

This review will consider studies that evaluate the effect of thiamine supplementation on levels of blood glucose in adults.

Comparator(s)

This review will compare the studies that compare the intervention to any other treatments, placebo or control products such as other dietary supplements.

Outcomes

Studies that have reported outcome in terms of fasting blood sugar (FBS), postprandial blood sugar (PP2BS) and/or glycated hemoglobin (HbA1C) will be included.

Types of studies

This review will include only experimental studies that are randomized controlled trials. Studies complying with the inclusion criteria, published in English, and published as far back as possible in will be included.

Methods

Search strategy

A search strategy will be formed so as to find both published and unpublished articles in English. To start with, the MEDLINE, CINAHL, EMBASE, and Cochrane Central Register of Controlled Trials databases will be searched electronically. Type 2 diabetes mellitus, T2DM, FBS, PP2BS, HBA1C, glycosylated hemoglobin, blood sugar, thiamine, benfotiamine andvitamin B1 will be used as keywords for searching. Clinicaltrials.gov, ProQuest, MEDNAR and reference list of all studies selected for critical appraisal will be searched for retrieving unpublished studies.

Information sources

The databases MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane library will be searched for identifying relevant published studies. Google Scholar, Dissertation Abstracts International, ProQuest Dissertations and Theses and MedNar will be searched for unpublished studies.

The trial register to be searched will include clinicaltrials.gov.

Study selection

After completing the search, titles and abstracts of the identified studies will be organized and uploaded into Zotero and duplicates will be removed. The irrelevant articles based on titles and abstract will also be removed. The articles thus left will be taken up for full text reading. Two independentreviewers will thenscreen the articles to justify the reason for their inclusion in the review. Full text of the studies thus identified, will be assessed for satisfaction of inclusion criteria and their details will be imported into SUMARI. Full text studies that do not meet the inclusion criteria will be excluded and names of these studies with reasons for exclusion will be given in an appendix in the final systematic review report. Included studies will be critically appraised. The PRISMA flow diagram will be used in the final report to report the results of searching.[45] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Assessment of methodological quality

The methodological quality of the articles retrieved in full text will be assessed by three reviewers using the standardized critical appraisal instruments from the Joanna Briggs Institute for randomized control trials[46]to find good quality studies to be include in the review. The three reviewers will discuss the points of disagreements to reach a concensus. Data will be extracted from all the studies irrespective of their quality.

Data extraction

The standardized data extraction tool of JBI SUMARI will be used for extraction of data from the included studies. The details of the participants of the studies, interventions used, study methodology and outcomes relevant to the review question will be collected and collated in the data extraction sheet. Any disagreements that arise between the reviewers will be resolved through discussion. Authors of articles will be contacted for details of missing or additional data wherever required.

Data synthesis

Wherever feasible, the results will be pooled in statistical meta-analysis using JBI SUMARI. Odds ratio or mean differences and their 95% confidence intervals will be calculated to present effect sizes. Odds ratios will be used to express dichotomous data while continuous data will be presented as weighted (or standardized) mean differences. Heterogeneity will be assessed statistically using the standard chi-squared and I squared tests. The suggestions from Tufunaru et al 2015[46]will be used to decide whether random or fixed effects model will be used for meta-analysis.[7] If sufficient data is available for investigating subgroups, subgroup analyses will also be conducted.Where statistical pooling is not possible, the results will be presented with the help of tables and figures. If more than 10 studies are included in a meta-analysis, a funnel plot will be used to assess publication bias. Egger test will be used to look for funnel plot asymmetry. [47]

Assessing certainty in the findings

A 'summary of findings' table will be created using GRADEPro GDT software.[48] We will use the GRADE system for grading the quality and reliability of evidence. The SoF will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on risk of bias in the included studies, indirectness, heterogeneity, inconsistency, imprecision and publication bias.The following outcomes will be included in the 'Summary of Findings' table: Effect of ingestion of nuts on control of fasting blood sugar, post prandial blood sugar and HbA1C.

Acknowledgments

None

Funding

None

Conflicts of interest

None

References

1. International Diabetes Federation. IDF Diabetes Atlas. 62013. http://www.idf.org/diabetesatlas.
2. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, et al.Projection of diabetes burden through 2050. Diabetes Care. 2001;24(11):1936.
3. Najafi B, Farzadfar F, Ghaderi H, Hadian M., et al. Cost effectiveness of type 2 diabetes screening: a systematic review. Med J Islamic Repub Iran. 2016;30:326.
4. Wu JH, Micha R, Imamura F, et al. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr. 2012; 107(Suppl 2):S214–S27. [PubMed: 22591895]
5. Campmans-Kuijpers MJ, Sluijs I, Nothlings U, Freisling H, Overvad K, Boeing H, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. Clin Nutr. 2015 doi:10.1016/j.clnu.2015.08.003. [PubMed: 26342536].
6. Jenkins DJ, Kendall CW, Banach MS, Srichaikul K, Vidgen E, Mitchell S, et al. Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes Care. 2011;34(8):1706–11. doi: 10.2337/dc11-0338. [PubMed: 21715526].
7. Rajaram S, Sabate J. Nuts, body weight and insulin resistance. Br J Nutr.2006;96 Suppl 2:S79–86.
8. Jansen B, Donath W (1926) Geneeskundig Tijdschrift voor Nederlandsch-Indie 66:1–2 (Reprinted as (1982) The isolation of the anti beri beri vitamin. Nutr Rev 40:53–55)
9. Frank RAW, Leeper FJ, Luisi BF (2007) Structure, mechanism and catalytic duality of thiamine-dependent enzymes. Cell Mol Life Sci 64:892–905.
10. Prasannan KG, Sundaresan R, Venkatesan D. Thiamine deficency and protein secretion by pancreatic slices in vitro. Experientia. 1977;33(2):169-170.
11. Mee L, Nabokina SM, Sekar VT, Subramanian VS, Maedler K, Said HM. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. Am J Physiol Gastrointest Liver Physiol. 2009;297(1):G197- 206.
12. Rathanaswami P, Pourany A, Sundaresan R. Effects of thiamine deficiency on the secretion of insulin and the metabolism of glucose in isolated rat pancreatic islets. Biochem Int. 1991;25(3):577-583.

13. Debski B, Kuryl T, Gralak MA, Pierzynowska J, Drywien M. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. J Anim Physiol Anim Nutr (Berl). 2011;95(3):335-342.
14. Anderson JW. Dietary fiber and diabetes: what else do we need to know? Diabetes Res Clin Pract. 1992;17(2):71- 73.
15. Oh SH, Witek RP, Bae SH, Darwiche H, Jung Y, Pi L, Brown A, et al. Detection of transketolase in bone marrow-derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. Stem Cells Dev. 2009;18(1):37-46.
16. Hammes HP , Du X , Edelstein D , Taguchi T , Matsumura T , Ju Q , Lin J , Bierhaus A , Nawroth P , Hannak D , Neumaier M , Bergfeld R , Giardino I , Brownlee M . Benfotiamine blocks three major pathways of hyperglycaemic damage and prevents experimental diabetic retinopathy. Nature Medicine 2003;9(3):294 – 299.
17. Rindi G, Lafarenza U (2000) Thiamine intestinal transport and related issues: recent aspects. PSEBM 224:246–255.
18. Saito, N., Kimura, M., Kuchiba, A., and Itokawa, Y. (1987) Blood thiamine levels in outpatients with diabetes mellitus. J. Nutr. Sci. Vitaminol 33, 421-430.
19. LaSelva, M., Beltrano, E., Pagnozzi, F., Bena, E., Molinatti, P.A., Molinatti, G.M., and Porta, M. (1997) Thiamine corrects delayed replication and decreases production of lactate and ad vanced glycation end -products in bovine retinal and human umbilical vein endothelial cells cultured under high glucose conditions. Diabetologia 39, 1263-1268
20. Hammes, H.-P., Bretzel, R.G., Federlin, K., Horiuchi, S., Niwa, T., and Stracke, H. (1998) Benfotiamin inhibits the formation of advanced glycation end products in diabetic rats. Diabetologia 41,1164
21. Lin, J., Alt, A., Liersch, J., Bretzel, R.G., Brownlee, M., and Hammes, H. P. (2000) Benfotiamine inhibits intracellular formation of advanced glycation endproducts in vivo. Diabetes 49, A143
22. Winkler, G., Pal, B., Nagybeganyi, E., Ory I., Porochnavec, M.,and Kempler, M. (1999) Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. Arzneimittel-forschung Drug Res. 49, 220-224.
23. Bakker SJ, Hoogeveen EK, Nijpels G, Kostense PJ, Dekker JM, Gans RO, Heine RJ. The association of dietary fibres with glucose tolerance is partly explained by concomitant intake of thiamine: the Hoorn Study. Diabetologia. 1998;41(10):1168-1175.
24. Gonzalez-Ortiz M, Martinez-Abundis E, Robles-Cervantes JA, Ramirez-Ramirez V, Ramos-Zavala MG. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naive patients with type 2 diabetes. Eur J Nutr. 2011;50(2):145-149.
25. Nikolic A, Kacar A, Lavrnic D, Basta I, Apostolski S. [The effect of benfothiamine in the therapy of diabetic polyneuropathy]. Srp Arh Celok Lek. 2009;137(11- 12):594-600.

26. Kjosen B, Seim SH. The transketolase assay of thiamine in some diseases. Am J Clin Nutr. 1977;30(10):1591- 1596.
27. Valerio G, Franzese A, Poggi V, Patrini C, Laforenza U, Tenore A (1999) Lipophilic thiamine treatment in long-standing insulindependent diabetes mellitus. Acta Diabetol 36:73–76
28. Jermendy G (2006) Evaluating thiamine deficiency in patients with diabetes. Diab Vasc Dis Res 3:120–121
29. Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, Ahmed A, et al. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. Diabetologia. 2007;50(10):2164-2170.
30. Patrini C, Lafarenza U, Gastaldi G, Verri A, Ferrari G, Rindi G (1996) Effects of insulin on thiamine intestinal transport in rat everted jejunal sacs. J Physiol (Lond) 493:100S–101S
31. Havivi, E., Bar, On H., Reshef, A., and Raz, I. (1991) Vitamins and trace metals status in non insulin dependent diabetes mellitus. Int. J. Vit. Nutr. Res. 61, 328-333 Vol. 129,
32. Xu R, Zhang S, Tao A, Chen G, Zhang M. Influence of vitamin E supplementation on glycaemic control: a meta-analysis of randomised controlled trials. PLoS One. 2014 9: e95008. doi: 10.1371/journal.pone.0095008 PMID: 24740143
33. Rytter E, Vessby B, Asgard R, Ersson C, Moussavian S, Sjodin A, et al. Supplementation with a combination of antioxidants does not affect glycaemic control, oxidative stress or inflammation in type 2 diabetes subjects. Free Radic Res. 2010 44: 1445–1453. doi: 10.3109/10715762.2010.515219 PMID: 20942575
34. Oosterwerff MM, Eekhoff EM, Van Schoor NM, Boeke AJ, Nanayakkara P, Meijnen R, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D-deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. Am J Clin Nutr. 2014 100: 152– 160. doi: 10.3945/ajcn.113.069260 PMID: 24898240
35. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabet Med. 2012 29: e142–150. doi: 10. 1111/j.1464-5491.2012.03672.x PMID: 22486204
36. Gonzalez-Ortiz M, Martinez-Abundis E, Robles-Cervantes JA, Ramirez-Ramirez V, Ramos-Zavala MG. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drugnaive patients with type 2 diabetes. Eur J Nutr. 2011 50: 145–149. doi: 10.1007/s00394-010-0123-x PMID: 20652275
37. Rabbani N, Alam SS, Riaz S, Larkin JR, Akhtar MW, Shafi T, et al. High-dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a randomised, double-blind placebo-controlled pilot study. Diabetologia. 2009 52: 208–212. doi: 10.1007/s00125-008-1224-4 PMID: 19057893
38. Sudchada P, Saokaew S, Sridetch S, Incampa S, Jaiyen S, Khaithong W. Effect of folic acid supplementation on plasma total homocysteine levels and glycemic control in patients with type 2

diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2012 98: 151–158. doi: 10.1016/j. diabres.2012.05.027 PMID: 22727498

39. Sabherwal S, Bravis V, Devendra D. Effect of oral vitamin D and calcium replacement on glycaemic control in South Asian patients with type 2 diabetes. Int J Clin Pract. 2010 64: 1084–1089. doi: 10. 1111/j.1742-1241.2010.02372.x PMID: 20642708
40. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. Ann Nutr Metab. 1995 39: 217–223. PMID: 8546437 Vitamin/Mineral Supplements and Long-Term HbA1cPLOS ONE | DOI:10.1371/journal.pone.0139244 October 16, 2015 15 / 17
41. Khan MI, Siddique KU, Ashfaq F, Ali W, Reddy HD, Mishra A. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. J Nat Sci Biol Med. 2013 4: 336–340. doi: 10.4103/0976-9668.117002 PMID: 24082728
42. Rafat D, Rabbani TK, Ahmad J, Ansari MA. Influence of iron metabolism indices on HbA1c in non-diabetic pregnant women with and without iron-deficiency anemia: effect of iron supplementation. Diabetes Metab Syndr. 2012 6: 102–105. doi: 10.1016/j.dsx.2012.05.011 PMID: 23153978
43. Faghihi T, Radfar M, Barmal M, Amini P, Qorbani M, Abdollahi M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. Am J Ther. 2014 21: 491–495. doi: 10.1097/MJT. 0b013e318269175f PMID: 23633679
44. Boeing H, Weisgerber UM, Jeckel A, Rose HJ, Kroke A. Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. Am J Clin Nutr. 2000 71: 1115–1122. PMID: 10799373
45. Mattes RD & Dreher ML (2010) Nuts and healthy body weight maintenance mechanisms. Asia Pac J Clin Nutr 19, 137–141.
46. Allen LH (2008) Priority areas for research on the intake, composition, and health effects of tree nuts and peanuts. J Nutr 138, 1763S–1765S.
47. Jenkins DJ, Kendall CW, Banach MS, Srichaikul K, Vidgen E, Mitchell S, Parker T, Nishi S, Bashyam B, de Souza R, Ireland C, Josse RG: Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes Care 2011, 34:1706–1711.
48. Caio E. G. Reis1, Daniela N. Ribeiro et al. Acute and second-meal effects of peanuts on glycaemic response and appetite in obese women with high type 2 diabetes risk: a randomized cross-over clinical trial. British Journal of Nutrition. 2013:10;:2015–2023.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction 2nd para, Pg 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction last 4 lines, Pg 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods – inclusion, exclusion criteria, Pg 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods – literature search strategy, Pg 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods-screening, Pg7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods – Data extraction, Pg 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods – inclusion criteria, Pg 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods – data extraction, Pg 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – quality assessment Pg 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods data synthesis and analysis, Pg 7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods data synthesis and analysis, Pg 7-8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods data synthesis and analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods data synthesis and analysis, Pg 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods data synthesis and analysis, Pg 7-8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods – quality assessment, Pg7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods data synthesis and analysis, Pg 7-8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results – Para 1, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results – Para2 , AppendixII
Study characteristics	17	Cite each included study and present its characteristics.	Appendix III
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1, Pg 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1, Pg 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, Pg 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig 2-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Fig 2-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-

.136/bmjopen-2021-059834 on 25 August 2022. Downloaded from

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion – Para 2-4, Pg 16
	23b	Discuss any limitations of the evidence included in the review.	Discussion – Limitations of review, Pg 17
	23c	Discuss any limitations of the review processes used.	Discussion – Limitations of review, Pg 17
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods – Para 1, Pg 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods – Para 1, Pg 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding, Pg 18
Competing interests	26	Declare any competing interests of review authors.	Diclosure of interests, Pg 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	No additional data available

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.doi: 10.1136/bmj.n71

For more information, visit:http://www.prisma-statement.org/

BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834.R1
Article Type:	Original research
Date Submitted by the Author:	16-May-2022
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Lord, Heidi; Saint George Hospital, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Green[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

ABSTRACT

Objective: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose levels and prevent complications. The aim of this systematic review was to evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods: A three-step search strategy to locate RCTs was conducted in PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar from database inception until December 2019. Studies that assessed effect of thiamine supplementation in adults with T2DM were considered for inclusion. Studies that measured glycemic outcomes - glycated haemoglobin (HbA1C), fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included. Two independent reviewers assessed methodological quality and data extracted. Where possible, studies were pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling was not possible.

Results: Six trials involving 364 participants were included. No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). However, there was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) when given in 120mg/day dose as compared to placebo 150mg/day, however this was not demonstrated in higher doses.

Conclusions: Thiamine supplementation was found to not affect glycemic outcomes, however reduces triglycerides while increasing HDL. Multicentre well designed randomised controlled trial with higher doses of thiamine and with a follow-up period of 1-2 will provide further evidence regarding the effect of thiamine on glycemic outcomes in T2DM.

Strengths: This systematic review addresses an important topic on the control of diabetes with thiamine supplementation, including important secondary outcomes such as LDL and triglyceride levels. The inclusion of good quality RCTs ensures the results are robust and provide evidence for diabetes management and direction of future research.

Limitations: This review includes single-centre trials published only in the English language. Sample sizes of the included studies were small although some had addressed this issue with statistical power. Furthermore, there was a lack of trials investigating the outcomes for some comparisons. The follow-up periods also varied among trials with some trials having a limited follow-up period of only up to three months.

Summary:

- Thiamine supplementation does not have any beneficial effect on sugar levels in patients of Type 2 DM.
- Significant increase in HDL level is seen at three months follow-up.
- Triglyceride levels also reduce significantly with 120 mg/day compared to 150 mg/day benfotiamine.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045. T2DM was the cause of 4.2 million fatalities in 2019 globally .[1]

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7] Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives Benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for

hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. It also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11-14] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[13]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23]

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL, HDL, triglycerides and various vitamins (including thiamine) and minerals[13,15,17-25] but with inconsistent results. Some studies reported significant inverse association for thiamine

supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,26]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[30]by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[31] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy to include all relevant articles published till 31st December 2019.. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in

the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined based on ADA (American Diabetes Association) guidelines as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies were resolved by

discussion with a third author (HG). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality was assessed using the standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs. [30]An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[32]. The continuous data

extracted from the cross-over RCTs were treated as if from a parallel trial[33]. All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as mean differences and corresponding 95% confidence intervals (CI) were calculated. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if $I^2>50\%$ and P value <0.10 in the chi-square test for heterogeneity.[34]A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 145 potential trials, with 127 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials were identified for potential inclusion in the review. (Appendix II) The reference lists of the 11 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded after examination of the full text against the inclusion criteria (see Appendix III). Thus, finally six trials were included in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[35] or non-diabetic[36], in vitro study[37], did not assess the outcome of interest [28,38,39] and study done on rats.[40]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q1 0	Q1 1	Q1 2	Q1 3	Total
Winkler 1999[24]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[34]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[25]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[48]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[32]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22 [16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way.

Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[41]an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	Q1	Q2	Q3	Q4	Score
1	Shahmiri 2013[48]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallel RCTs[15,16,19,27,29]and one was cross-over RCT.[41] The six trials were conducted in six different countries – Germany [29], Pakistan [19], Netherlands [27], Australia [41], Mexico/USA [15]and Hungary [16]. The number of participants in parallel RCTs varied from 12[41] to 165[29]while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,27]One trial [27] had male predominance (77% vs 33%) while the other [16]had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16]to 65.3 ± 5.9 years.[27]

Five of the six trials compared the intervention to placebo and one trial [16]compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from

100 mg/day[41]to 300mg/day [19]and the dosage for benfotiamine ranged from 120mg/ day [16] to 900mg/day.[27]. The follow-up period ranged from 1 month[15]to 3 months.[19,27]

Fasting blood glucose was reported in four trials,[15,16,19,41] PPG in two trials,[16,41]HbA1c in five trials,[15,16,19,27,29] HDL in four trials,[15,16,19,27] LDL in three trials,[15,19,27] triglycerides in four trials,[15,16,19,27], systolic and diastolic BP in three trials [15,19,27]and BMI in two trials. [15,41]Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

Heterogeneity among studies

Heterogeneity measured was insignificant (I^2<50%) for all parameters except FBG which was accounted for by using random effects model for meta-analysis.

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,27]that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,27,29]investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study [29]reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16]that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,41]demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine on FBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [41]investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16]compared 320mg/day and 120mg/day of Benfotiamine onPPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those

who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10 mmol/l; CI 0.10, 0.30) (Fig 4) but a statistically significant difference was seen (MD 0.10 mmol/l; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16]compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14 mmol/l; CI -0.17, 0.45) (Fig 5) as well as the 3 month follow-up period (MD 0.25 mmol/l; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the

HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,27]investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22 kg/m^2; 95% CI -2.23, 1.79).

Systolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,25,32] investigated the effect of thiamine supplementation vs placebo on systolic BP levels. Pooled results demonstrated no statistically significant differences in the systolic BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).

Diastolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,25,32]investigated the effect of thiamine supplementation vs placebo on diastolic BP levels. Pooled results demonstrated no statistically significant differences in the diastolic BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).

Discussion

Plasma thiamine levels have been reported to be 75% lower in patients with T2DM.[14] Given that thiamine is vital for intracellular glucose metabolism, this systematic review was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable as the assessment criteria regarding the method of randomization and allocation concealment was not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG[42,43] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [44].

The results of the review also demonstrated no significant differences in FBG, , LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level

is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore, trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations in different studies (with different diabetes risk) and the presence of underlying health conditions (like presence of autoimmune diseases) which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [45]. Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

Despite summarising the evidence, several limitations of this review should be noted. Firstly, the review includes single-centre trials published only in the English language which limits the generalizability of the results. Sample sizes of the included studies were small although some had addressed this issue using statistical power. Furthermore, there was a lack of trials investigating the outcomes for a variety of comparisons, further trials are needed to investigate multiple comparisons. Additionally, the follow-up period varied among trials

with some having a short period of only up to three months, which may limit the effect of the intervention and results.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to change practices. Therefore, existing practices will be dictated by current policies. However, some important points have been identified such as, the studies published to date have been single centric studies, with small sample size, varying doses and follow-up for only 3 months. Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Data availability: No additional data available.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: All authors contributed to the study

AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data acquisition and analysis; PM: Data collection, manuscript preparation.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H et al. Cost effectiveness of type 2 diabetes screening: A systematic review. *Med J Islam Repub Iran.*. 2016;30:326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. *Clin Nutr*. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. *Diabetes Care*. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. *Cell Mol Life Sci*. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, et al.. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, et al. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. *J Anim Physiol Anim Nutr (Berl)*. 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. *Stem Cells Dev*. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. *Nat Med*. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. *Diabetologia*. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, et al. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine: Minireviews.* 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, et al. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr.* 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, et al. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. *Arzneimittelforschung.* 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western

immigrants in the Netherlands: a randomized placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabet Med.* 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia*. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, et al. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res Clin Pract*. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab*. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, et al. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. *J Nat Sci Biol Med*. 2013;4(2):336.

24. Rafat D, Rabbani T, Ahmad J, et al. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect of Iron Supplementation. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*. 2012;6(2):102-5.

25. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491-5.

26. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. *Free Radic Res*. 2010;44(12):1445-53.

27. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care*. 2010;33(7):1598-601.

28. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *Int J Clin Pharmacol Ther*. 2005;43(2):71-7.

29. Stracke H, Gaus W, Achenbach U, et al. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Experimental and clinical endocrinology & diabetes*. 2008;116(10):600-5.

30. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Effectiveness. *Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute*. 2017.

31. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. *The Joanna Briggs Institute*. 2017;299(

32. Review Manager. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. 2014.

33. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-9.

34. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring Inconsistency in Meta-Analyses. *BMJ*. 2003;327(7414):557-60.

35. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care*. 2012;35(5):1095-7.

36. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

37. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

38. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

39. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis*. 1996;11(1):95-106.

40. Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

41. Shahmiri FA, Soares M, Zhao Y, et al. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. *Eur J Nutr*. 2013;52(7):1821-4.

42. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. *Prehosp Disaster Med*. 2019;34(5):506-9.

43. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-50.

44. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-16.

45. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.

Figure Legends:

Fig 1: PRISMA 2009 Flow Diagram for searching

Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

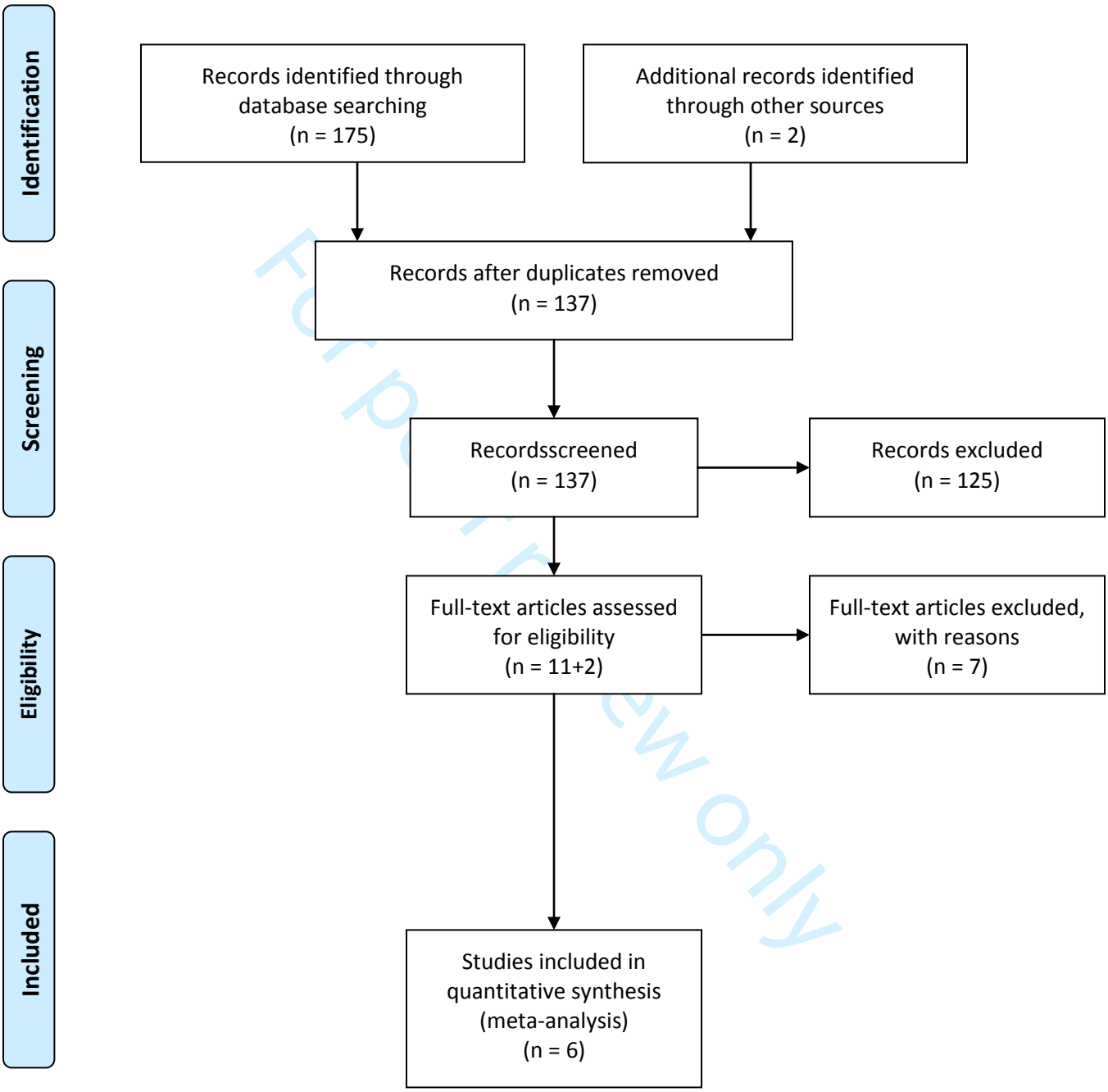
Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.

Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.

Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.

Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

PRISMA 2009 Flow Diagram[57]



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visitwww.prisma-statement.org.

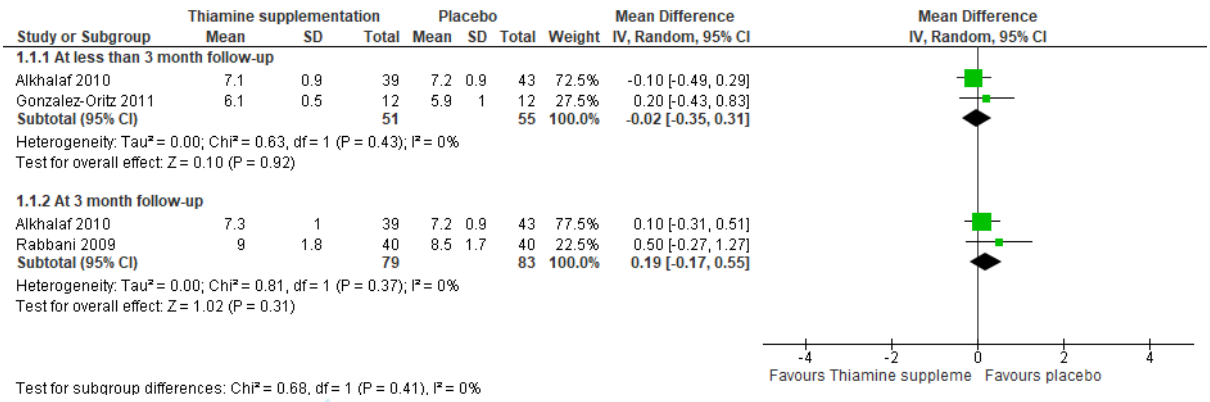


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

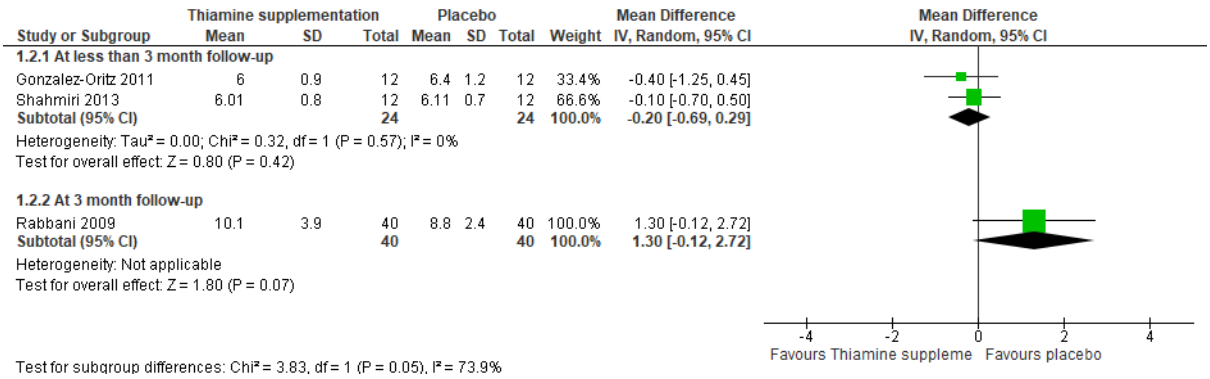


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

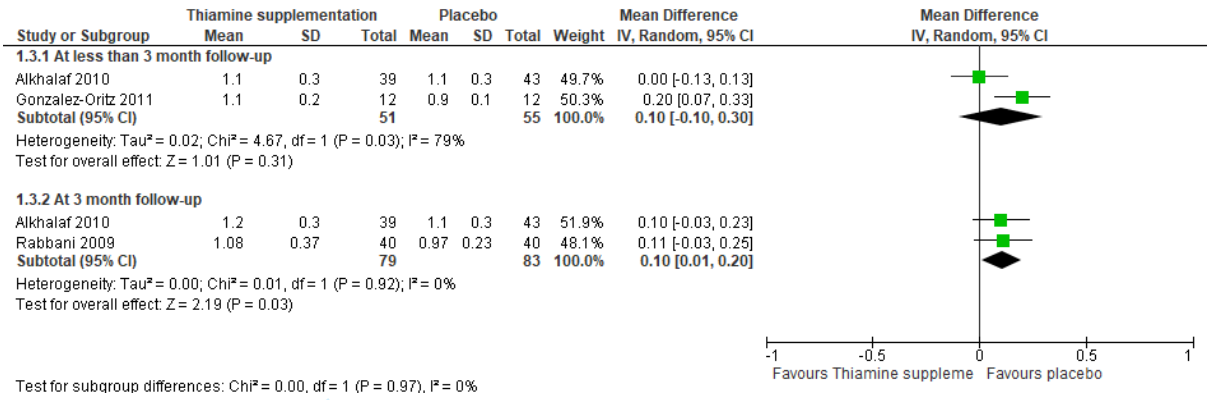


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

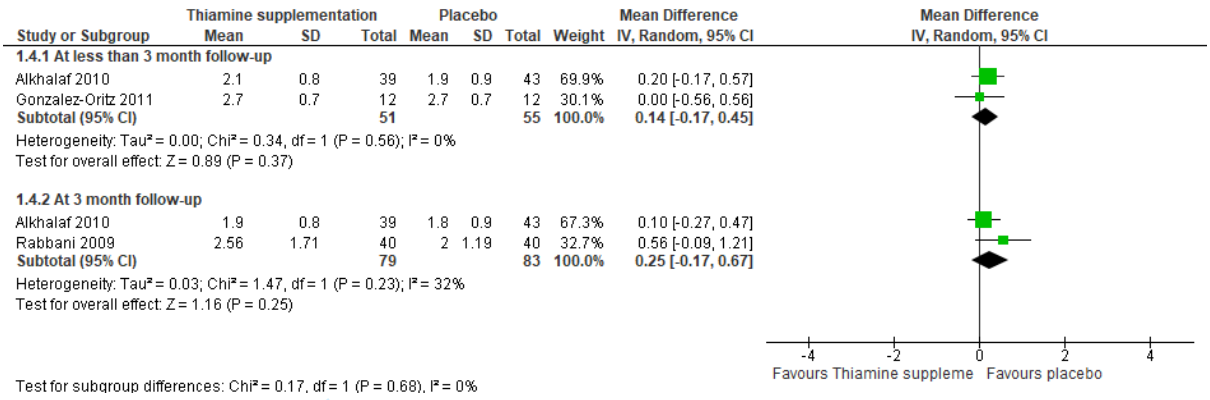


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

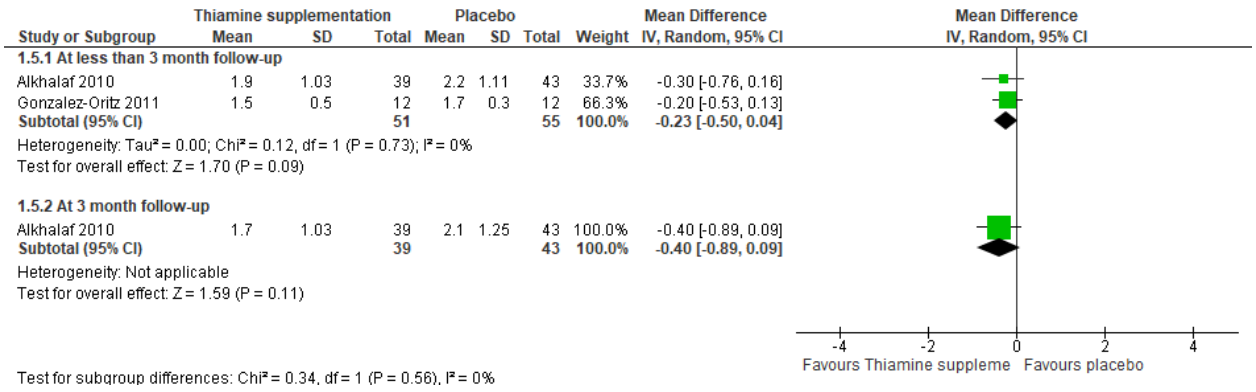


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction 2nd para, Pg 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction last 4 lines, Pg 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods – inclusion, exclusion criteria, Pg 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods – literature search strategy, Pg 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods-screening, Pg7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods – Data extraction, Pg 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods – inclusion criteria, Pg 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods – data extraction, Pg 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – quality assessment Pg 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods data synthesis and analysis, Pg 7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods data synthesis and analysis, Pg 7-8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods data synthesis and analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods data synthesis and analysis, Pg 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods data synthesis and analysis, Pg 7-8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods – quality assessment, Pg7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods data synthesis and analysis, Pg 7-8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results – Para 1, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results – Para2 , AppendixII
Study characteristics	17	Cite each included study and present its characteristics.	Appendix III
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1, Pg 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1, Pg 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, Pg 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig 2-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Fig 2-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion – Para 2-4, Pg 16
	23b	Discuss any limitations of the evidence included in the review.	Discussion – Limitations of review, Pg 17
	23c	Discuss any limitations of the review processes used.	Discussion – Limitations of review, Pg 17
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods – Para 1, Pg 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods – Para 1, Pg 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding, Pg 18
Competing interests	26	Declare any competing interests of review authors.	Diclosure of interests, Pg 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	No additional data available

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.doi: 10.1136/bmj.n71

For more information, visit:http://www.prisma-statement.org/

BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834.R2
Article Type:	Original research
Date Submitted by the Author:	10-Jun-2022
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Lord, Heidi; Saint George Hospital, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Green[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

ABSTRACT

Background: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods:

Eligibility criteria: Studies that assessed effect of thiamine supplementation in adults with T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included.

Information sources: PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar were searched until December 2021 for RCTs.

Risk of bias: It was assessed using standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs.

Synthesis of results: Where possible, studies were pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling was not possible.

Results:

Included studies: Six trials involving 364 participants.

Synthesis of results: No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02

%, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in higher doses.

Discussion:

Limitations of evidence: Inclusion of single-centre trials published only in English, small sample sizes of included studies, lack of trials investigating outcomes for same comparisons and varying follow-up periods.

Interpretation: Thiamine supplementation doesn't affect glycemic outcomes, however reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher doses of thiamine and a follow-up period of 1-2 years will provide better evidence.

Strengths:

- Addresses an important topic of control of diabetes with thiamine supplementation including secondary outcomes as well like LDL and triglyceride levels.
- Included only good quality RCTs, hence the results can be relied upon to give direction to future research.
- **Limitations:** The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.
- There was a lack of trials investigating the outcomes for a variety of comparisons,

- The follow-up period varied among trials.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045. T2DM was the cause of 4.2 million fatalities in 2019 globally .[1]

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7] Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives Benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for

hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. It also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11-14] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[13]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23] Gestational diabetes has also been reported to be associated with thiamine mishandling.[24] Another study showed that thiamine supplementation reduced inflammatory and oxidative markers in women with gestational diabetes.[25] Unfortunately, these timid approaches were never followed by proper randomized controlled clinical trials (RCTs).

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL, HDL, triglycerides and various vitamins (including thiamine) and minerals[13,15,17-28] but with inconsistent results. Some studies reported significant inverse association for thiamine supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,29-31]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[32] by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[33] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy to include all relevant articles published till 31st December 2021. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined based on ADA (American Diabetes Association) guidelines as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the

outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies were resolved by discussion with a third author (HG). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality was assessed using the standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs.[32] An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[34] The continuous data extracted from the cross-over RCTs were treated as if from a parallel trial.[35] All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as mean differences and corresponding 95% confidence intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if I^2>50% and P value <0.10 in the chi-square test for heterogeneity.[36] A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 145 potential trials, with 127 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials were identified for potential inclusion in the review. (Appendix II) The reference lists of the 11 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded after examination of the full text against the inclusion criteria (see Appendix III). Thus, finally six trials were included in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[37] or non-diabetic[38], in vitro study[39], did not assess the outcome of interest [30,40,41] and study done on rats.[42]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q1 0	Q1 1	Q1 2	Q1 3	Total
Winkler 1999[16]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[31]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[19]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[43]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[29]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22[16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way. Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[43] an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Score**
1	Shahmiri 2013[43]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallel RCTs[15,16,19,29,31]and one was cross-over RCT.[43] The six trials were conducted in six different countries – Germany [31], Pakistan [19], Netherlands[29], Australia [43], Mexico/USA [15] and Hungary [16]. The number of participants in parallel RCTs varied from 12[43] to 165[31] while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,29] One trial [29] had male

predominance (77% vs 33%) while the other [16] had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16] to 65.3 ± 5.9 years.[29]

Five of the six trials compared the intervention to placebo and one trial [16] compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from 100 mg/day[43] to 300mg/day [19] and the dosage for benfotiamine ranged from 120 mg/ day [16] to 900mg/day.[29] The follow-up period ranged from 1 month[15] to 3 months.[19,29]

Fasting blood glucose was reported in four trials,[15,16,19,43] PPG in two trials,[16,43] HbA1c in five trials,[15,16,19,29,31] HDL in four trials,[15,16,19,29] LDL in three trials,[15,19,29] triglycerides in four trials,[15,16,19,29], systolic and diastolic BP in three trials [15,19,29] and BMI in two trials. [15,43] Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

Heterogeneity among studies:

There was no heterogeneity among studies for HbA1C (I^2 = 0%, p=0.41), HDL (I^2 = 0%, p=0.97), LDL (I^2 = 0%, p=0.88) and triglycerides (I^2 = 0%, p=0.56). Heterogeneity measured for FBG was significant (I^2 = 79%; p=0.05), which was accounted for by using random effects model for meta-analysis.

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,29] that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,29,31] investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study[31] reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,43] demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect

with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine on FBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [43] investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16] compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10 mmol/l; CI 0.10, 0.30) (Fig 4) but a statistically significant difference was seen (MD 0.10 mmol/l; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16] compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those

who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14 mmol/l; CI -0.17, 0.45) (Fig 5) as well as the 3 months follow-up period (MD 0.25 mmol/l; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22 kg/m^2; 95% CI -2.23, 1.79).

Systolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on systolic BP levels. Pooled results demonstrated no statistically significant differences in the systolic BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).

Diastolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on diastolic BP levels. Pooled results demonstrated no statistically significant differences in the diastolic BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).

Discussion

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable as the assessment criteria regarding the method of randomization and allocation concealment was not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG [44,45] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [46].

The results of the review also demonstrated no significant differences in FBG, LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore, trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations in different studies (with different diabetes risk) and the presence of underlying health conditions (like presence of autoimmune diseases) which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [47]. Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.
- There was a lack of trials investigating the outcomes for a variety of comparisons,
- The follow-up period varied among trials.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to change practices. Therefore, existing practices will be dictated by current policies. However, some important points have been identified such as, the studies published to date have been single centric studies, with small sample size, varying doses and follow-up for only 3 months. Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Data availability: No additional data available.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: All authors contributed to the study

AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data acquisition and analysis; PM: Data collection, manuscript preparation.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H et al. Cost effectiveness of type 2 diabetes screening: A systematic review. *Med J Islam Repub Iran.*. 2016;30:326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. *Clin Nutr*. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. *Diabetes Care*. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. *Cell Mol Life Sci*. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, et al.. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, et al. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. *J Anim Physiol Anim Nutr (Berl)*. 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. *Stem Cells Dev*. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. *Nat Med*. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. *Diabetologia*. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, et al. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine: Minireviews.* 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, et al. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr.* 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, et al. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. *Arzneimittelforschung.* 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabet Med.* 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia*. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, et al. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res Clin Pract*. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab*. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, et al. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. *J Nat Sci Biol Med*. 2013;4(2):336.

24. Bartakova V, Pleskačova A, Kuricova K et al (2016) Dysfunctional protection against advanced glycation due to thiamine metabolism abnormalities in gestational diabetes. Glycoconj J 33(4):591–598. https:// doi. org/ 10. 1007/ s10719- 016- 9688-9

25. Amirani E, Aghadavod E, Shafabakhsh R et al (2020) Antiinflammatory and antioxidative effects of thiamin supplements in patients with gestational diabetes mellitus. J Matern Fetal Neonatal Med. https:// doi. org/ 10. 1080/ 14767 058. 2020. 17792 12

26. Rafat D, Rabbani T, Ahmad J, et al. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect of Iron Supplementation. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*. 2012;6(2):102-5.

27. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491-5.

28. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. *Free Radic Res*. 2010;44(12):1445-53.

29. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care*. 2010;33(7):1598-601.

30. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *Int J Clin Pharmacol Ther*. 2005;43(2):71-7.

31. Stracke H, Gaus W, Achenbach U, et al. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Experimental and clinical endocrinology & diabetes*. 2008;116(10):600-5.

32. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Effectiveness. *Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute*. 2017.

33. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. *The Joanna Briggs Institute*. 2017;299(

34. Review Manager. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. 2014.

35. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-9.

36. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring Inconsistency in Meta-Analyses. *BMJ*. 2003;327(7414):557-60.

37. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care*. 2012;35(5):1095-7.

38. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

39. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

40. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

41. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis*. 1996;11(1):95-106.

42. Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes.* 2003;52(8):2110-20.

43. Shahmiri FA, Soares M, Zhao Y, et al. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. *Eur J Nutr*. 2013;52(7):1821-4.

44. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. *Prehosp Disaster Med*. 2019;34(5):506-9.

45. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-50.

46. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-16.

47. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.

Figure Legends:

Fig 1: PRISMA 2009 Flow Diagram for searching

Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.

Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.

Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.

Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

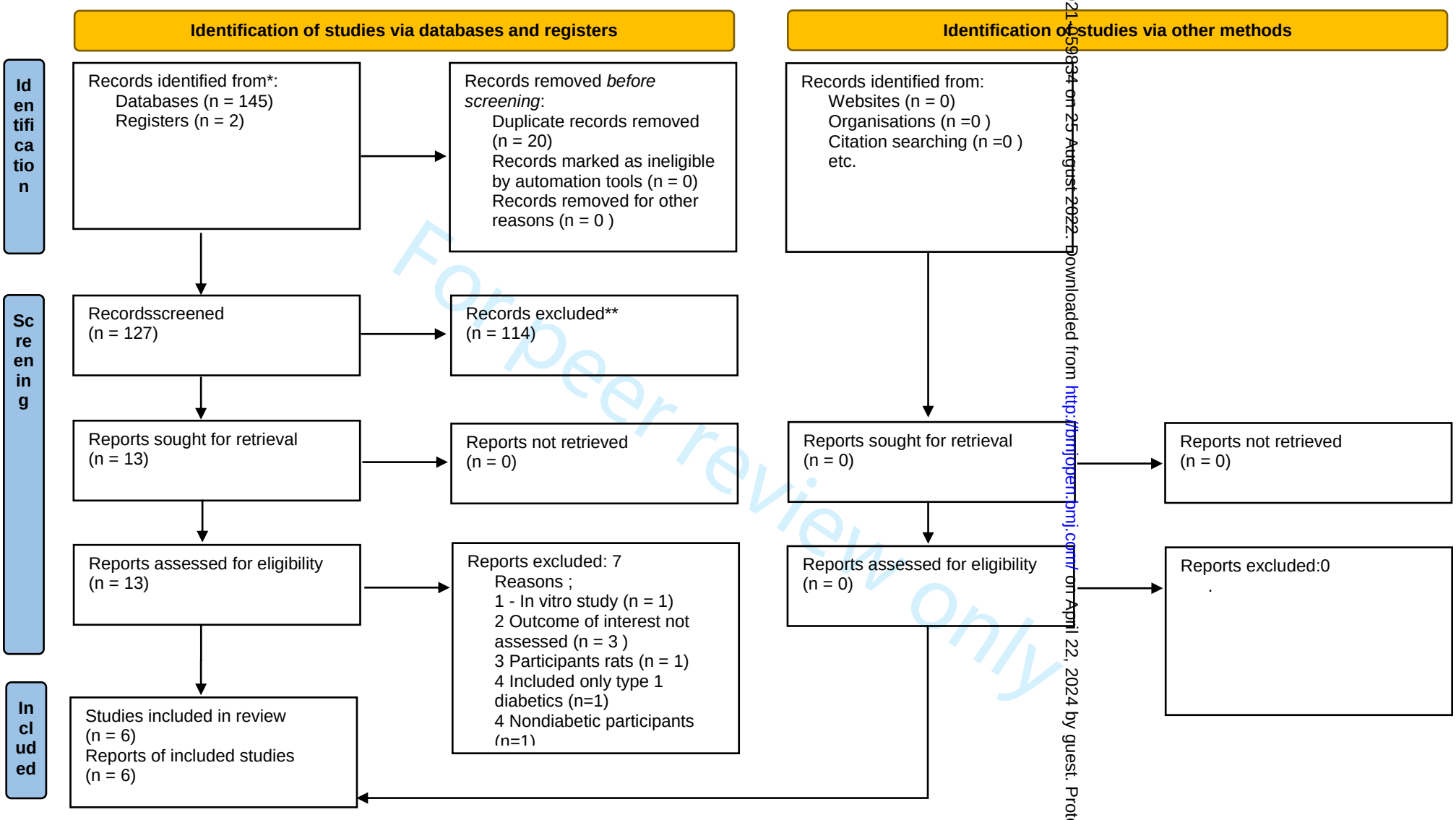


Fig 1: **PRISMA 2020 Flow diagram showing searching results**

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit:http://www.prisma-statement.org/

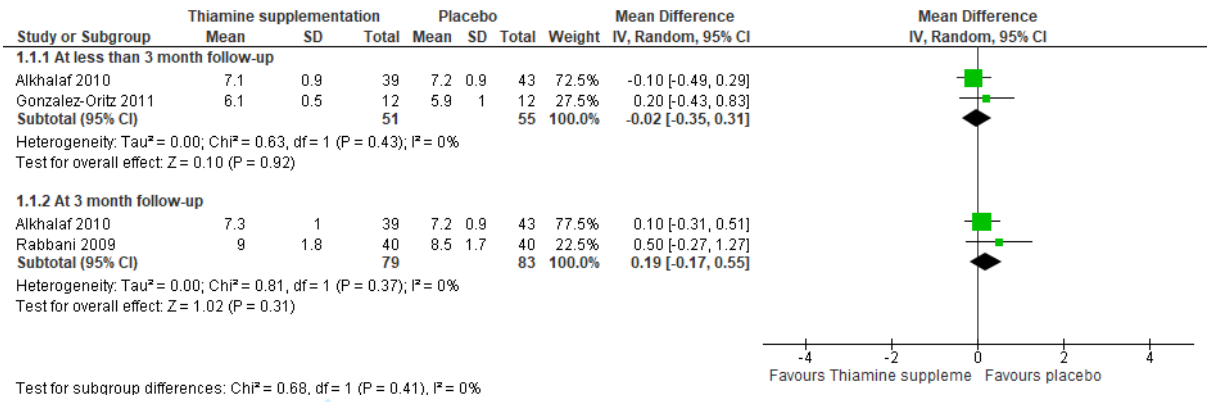


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

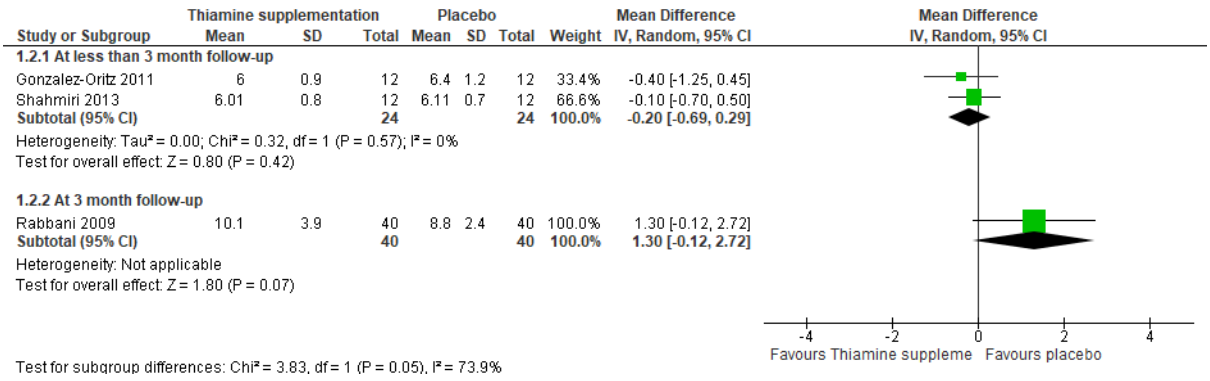


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

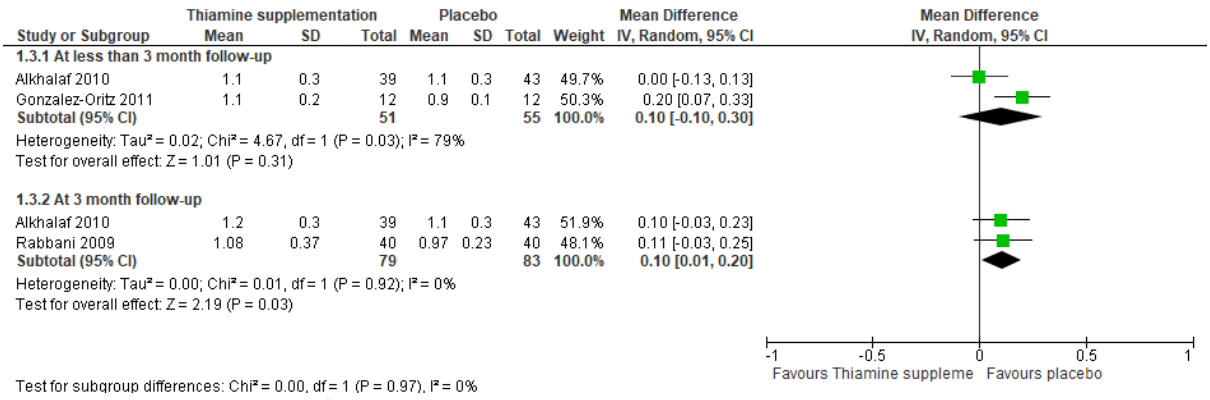


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

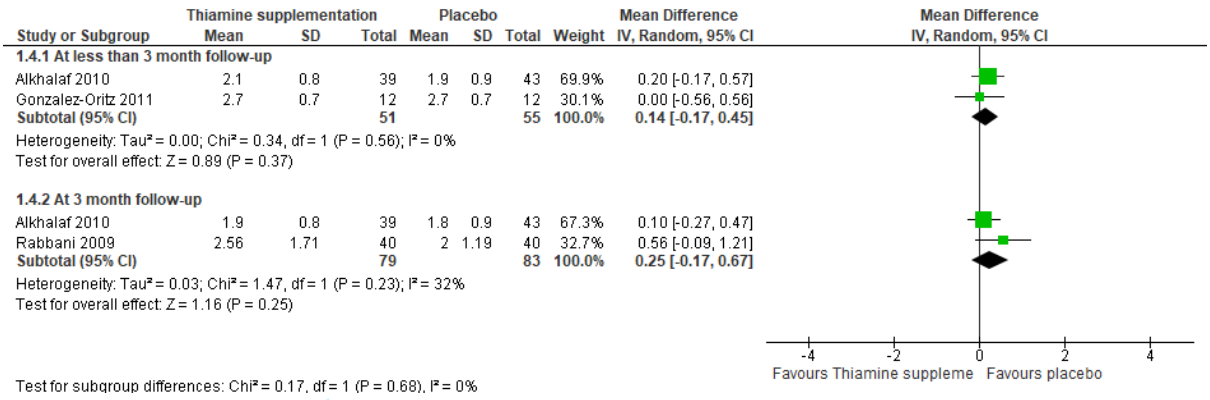


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

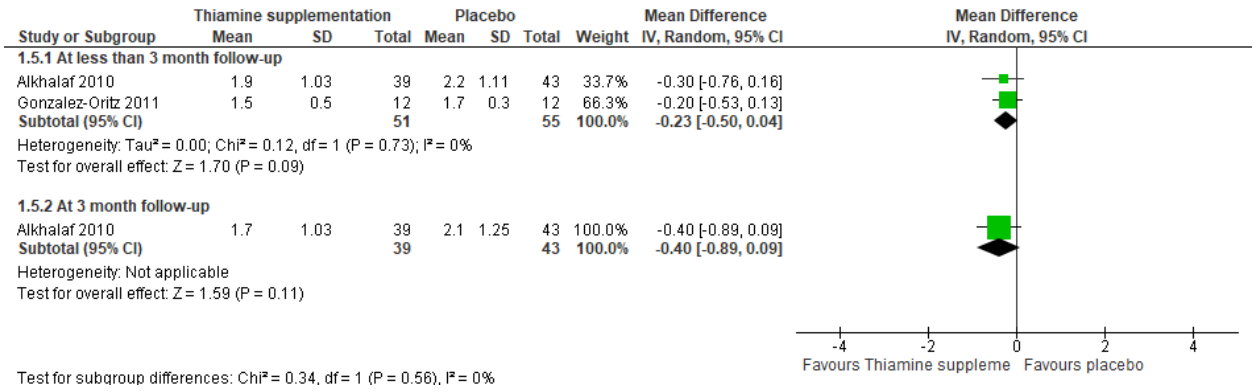


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834.R3
Article Type:	Original research
Date Submitted by the Author:	07-Jul-2022
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Green, Heidi; Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Green[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

ABSTRACT

Background: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods:

Eligibility criteria: Studies that assessed effect of thiamine supplementation in adults with T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included.

Information sources: PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar were searched until December 2021 for RCTs.

Risk of bias: It was assessed using standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs.

Synthesis of results: Where possible, studies were pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling was not possible.

Results:

Included studies: Six trials involving 364 participants.

Synthesis of results: No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02

%, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in higher doses.

Discussion:

Limitations of evidence: Inclusion of single-centre trials published only in English, small sample sizes of included studies, lack of trials investigating outcomes for same comparisons and varying follow-up periods.

Interpretation: Thiamine supplementation doesn't affect glycemic outcomes, however reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher doses of thiamine and a follow-up period of 1-2 years will provide better evidence.

Strengths:

- Addresses an important topic of control of diabetes with thiamine supplementation including secondary outcomes as well like LDL and triglyceride levels.
- Included only good quality RCTs, hence the results can be relied upon to give direction to future research.

Limitations:

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.

- There was a lack of trials investigating the outcomes for a variety of comparisons and the follow-up period also varied among trials.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045. T2DM was the cause of 4.2 million fatalities in 2019 globally .[1]

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7] Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives Benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for

hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. It also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11-14] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[13]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23] Gestational diabetes has also been reported to be associated with thiamine mishandling.[24] Another study showed that thiamine supplementation reduced inflammatory and oxidative markers in women with gestational diabetes.[25] Unfortunately, these timid approaches were never followed by proper randomized controlled clinical trials (RCTs).

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL, HDL, triglycerides and various vitamins (including thiamine) and minerals[13,15,17-28] but with inconsistent results. Some studies reported significant inverse association for thiamine supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,29-31]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[32] by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[33] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy to include all relevant articles published till 31st December 2019 and updated later till 31st December 2021. A final update search was done till 30th June 2022. No additional article was found in the updated search. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined based on ADA (American Diabetes Association) guidelines as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the

review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies were resolved by discussion with a third author (HG). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality of parallel group RCTs was assessed using the widely used critical JBI checklist for randomised controlled trials. [32] This checklist comprises of 13 items that assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored as '2' when the criteria were found adequately reported for the study, '1' when the

information was unclear and '0' when there was no reporting based on the criteria. The minimal obtainable score was 0 and the maximum 26. For unclear information, authors were contacted for more information and a decision made accordingly. An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[34] The continuous data extracted from the cross-over RCTs were treated as if from a parallel trial.[35] All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as mean differences and corresponding 95% confidence intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if I^2>50% and P value <0.10 in the chi-square test for heterogeneity.[36] A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 145 potential trials, with 127 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials were identified for potential inclusion in the review. (Appendix II) The reference lists of the 11 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded after examination of the full text against the inclusion criteria (see Appendix III). Thus, finally six trials were included in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[37] or non-diabetic[38], in vitro study[39], did not assess the outcome of interest [30,40,41] and study done on rats.[42]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	**Q 1**	**Q 2**	**Q 3**	**Q 4**	**Q 5**	**Q 6**	**Q 7**	**Q 8**	**Q 9**	**Q1 0**	**Q1 1**	**Q1 2**	**Q1 3**	**Total**
Winkler 1999[16]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[31]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[19]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[43]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[29]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22[16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way. Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[43] an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Score**
1	Shahmiri 2013[43]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallel RCTs[15,16,19,29,31]and one was cross-over RCT.[43] The six trials were conducted in six different countries – Germany [31], Pakistan [19], Netherlands[29], Australia [43], Mexico/USA [15] and Hungary [16]. The number of participants in parallel RCTs varied from 12[43] to 165[31] while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,29] One trial [29] had male predominance (77% vs 33%) while the other [16] had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16] to 65.3 ± 5.9 years.[29]

Five of the six trials compared the intervention to placebo and one trial [16] compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from 100 mg/day[43] to 300mg/day [19] and the dosage for benfotiamine ranged from 120 mg/ day [16] to 900mg/day.[29] The follow-up period ranged from 1 month[15] to 3 months.[19,29]

Fasting blood glucose was reported in four trials,[15,16,19,43] PPG in two trials,[16,43] HbA1c in five trials,[15,16,19,29,31] HDL in four trials,[15,16,19,29] LDL in three trials,[15,19,29] triglycerides in four trials,[15,16,19,29], systolic and diastolic BP in three trials [15,19,29] and BMI in two trials. [15,43] Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

Heterogeneity among studies:

There was no heterogeneity among studies for HbA1C (I^2 = 0%, p=0.41), HDL (I^2 = 0%, p=0.97), LDL (I^2 = 0%, p=0.88) and triglycerides (I^2 = 0%, p=0.56). Heterogeneity measured for FBG was significant (I^2 = 79%; p=0.05), which was accounted for by using random effects model for meta-analysis.

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,29] that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,29,31] investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study[31] reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among

those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,43] demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine on FBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [43] investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16] compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10 mmol/l; CI 0.10, 0.30) (Fig 4) but a

statistically significant difference was seen (MD 0.10 mmol/l; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16] compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14 mmol/l; CI -0.17, 0.45) (Fig 5) as well as the 3 months follow-up period (MD 0.25 mmol/l; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22 kg/m^2; 95% CI -2.23, 1.79).

Systolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on systolic BP levels. Pooled results demonstrated no statistically significant differences in the systolic BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).

Diastolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on diastolic BP levels. Pooled results demonstrated no statistically significant differences in the diastolic BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).

Discussion

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people

with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable as the assessment criteria regarding the method of randomization and allocation concealment was not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG [44,45] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [46].

The results of the review also demonstrated no significant differences in FBG, LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore, trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased

as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations in different studies (with different diabetes risk) and the presence of underlying health conditions (like presence of autoimmune diseases) which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [47]. Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.
- There was a lack of trials investigating the outcomes for a variety of comparisons,
- The follow-up period varied among trials.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to change practices. Therefore, existing practices will be dictated by current policies. However, some important points have been identified such as, the studies published to date have been

single centric studies, with small sample size, varying doses and follow-up for only 3 months. Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Data availability: No additional data available.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data acquisition, manuscript preparation and analysis; PM: Data collection, manuscript preparation and analysis.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H et al. Cost effectiveness of type 2 diabetes screening: A systematic review. *Med J Islam Repub Iran.*. 2016;30:326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. *Clin Nutr*. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. *Diabetes Care*. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. *Cell Mol Life Sci*. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, et al.. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, et al. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. *J Anim Physiol Anim Nutr (Berl)*. 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. *Stem Cells Dev*. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. *Nat Med*. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. *Diabetologia*. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, et al. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine: Minireviews.* 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, et al. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr.* 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, et al. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. *Arzneimittelforschung.* 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabet Med.* 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia*. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, et al. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res Clin Pract*. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab*. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, et al. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. *J Nat Sci Biol Med*. 2013;4(2):336.

24. Bartakova V, Pleskačova A, Kuricova K et al (2016) Dysfunctional protection against advanced glycation due to thiamine metabolism abnormalities in gestational diabetes. Glycoconj J 33(4):591–598. https:// doi. org/ 10. 1007/ s10719- 016- 9688-9

25. Amirani E, Aghadavod E, Shafabakhsh R et al (2020) Antiinflammatory and antioxidative effects of thiamin supplements in patients with gestational diabetes mellitus. J Matern Fetal Neonatal Med. https:// doi. org/ 10. 1080/ 14767 058. 2020. 17792 12

26. Rafat D, Rabbani T, Ahmad J, et al. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect of Iron Supplementation. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*. 2012;6(2):102-5.

27. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491-5.

28. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. *Free Radic Res*. 2010;44(12):1445-53.

29. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care*. 2010;33(7):1598-601.

30. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *Int J Clin Pharmacol Ther*. 2005;43(2):71-7.

31. Stracke H, Gaus W, Achenbach U, et al. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Experimental and clinical endocrinology & diabetes*. 2008;116(10):600-5.

32. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Effectiveness. *Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute*. 2017.

33. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. *The Joanna Briggs Institute*. 2017;299(

34. Review Manager. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. 2014.

35. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-9.

36. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring Inconsistency in Meta-Analyses. *BMJ*. 2003;327(7414):557-60.

37. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care*. 2012;35(5):1095-7.

38. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

39. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

40. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

41. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis*. 1996;11(1):95-106.

42. Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes.* 2003;52(8):2110-20.

43. Shahmiri FA, Soares M, Zhao Y, et al. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. *Eur J Nutr*. 2013;52(7):1821-4.

44. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. *Prehosp Disaster Med*. 2019;34(5):506-9.

45. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-50.

46. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-16.

47. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.

Figure Legends:

Fig 1: PRISMA 2009 Flow Diagram for searching

Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.

Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.

Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.

Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

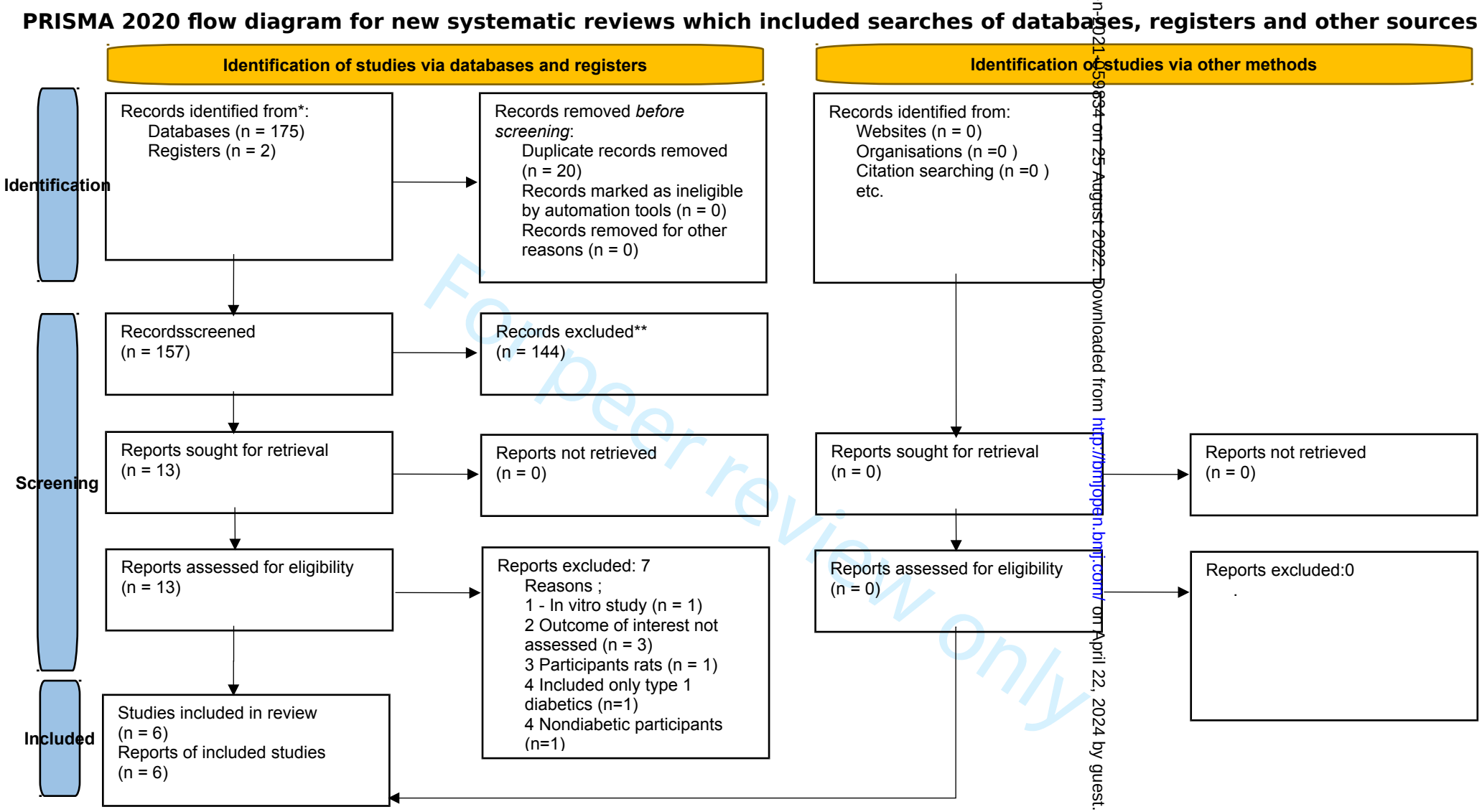


Fig 1: **PRISMA 2020 Flow diagram showing searching results**

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit:http://www.prisma-statement.org/

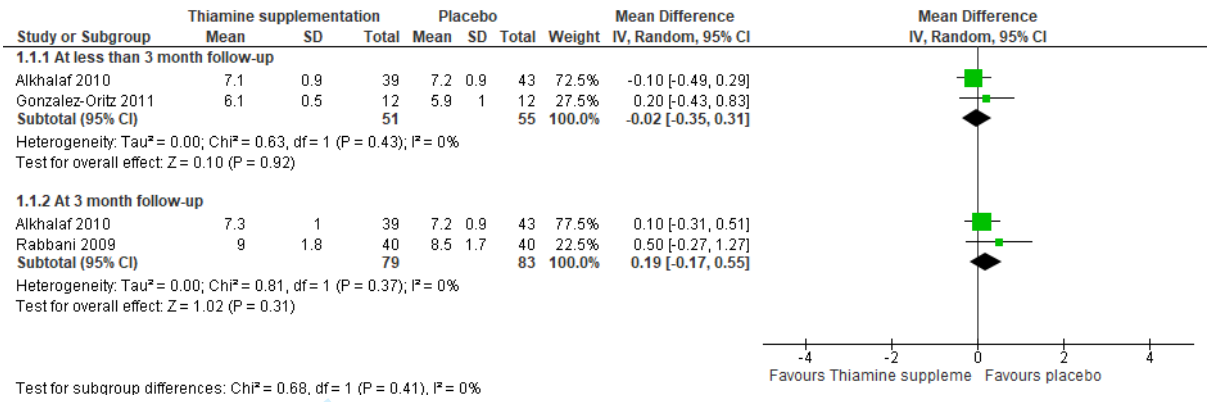


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

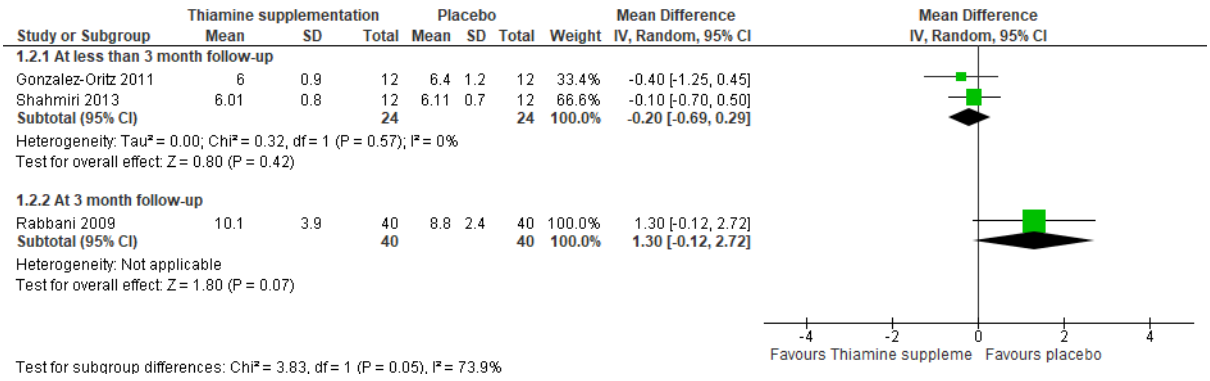


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

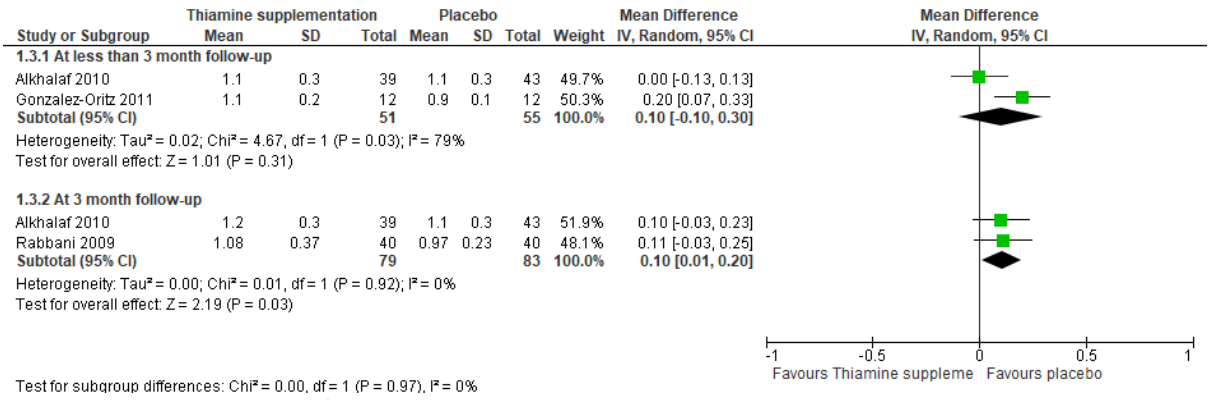


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

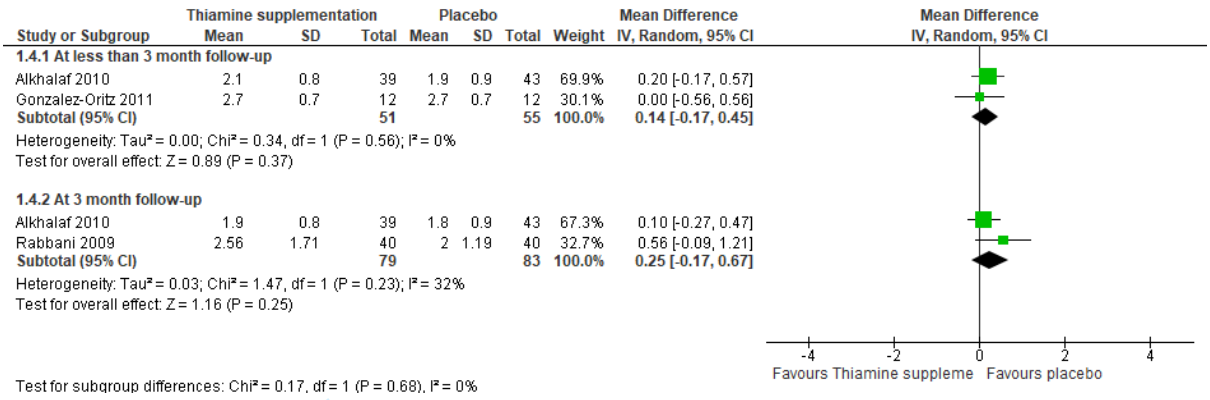


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

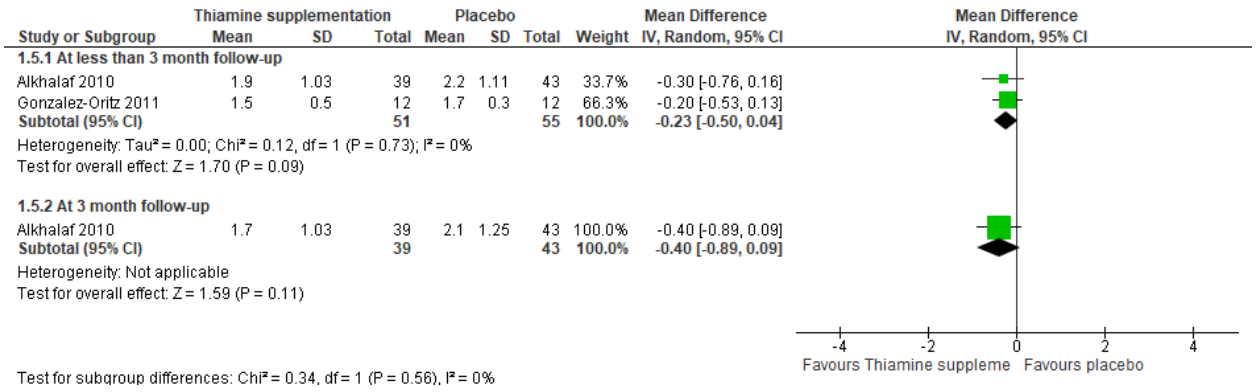


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834.R4
Article Type:	Original research
Date Submitted by the Author:	25-Jul-2022
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Green, Heidi; Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Green[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

ABSTRACT

Background: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods:

Eligibility criteria: Studies that assessed effect of thiamine supplementation in adults with T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included.

Information sources: PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar were searched until December 2021 for RCTs.

Risk of bias: It was assessed using standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs.

Synthesis of results: Where possible, studies were pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling was not possible.

Results:

Included studies: Six trials involving 364 participants.

Synthesis of results: No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02

%, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in higher doses.

Discussion:

Limitations of evidence: Inclusion of single-centre trials published only in English, small sample sizes of included studies, lack of trials investigating outcomes for same comparisons and varying follow-up periods.

Interpretation: Thiamine supplementation doesn't affect glycemic outcomes, however reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher doses of thiamine and a follow-up period of 1-2 years will provide better evidence.

Strengths:

- Addresses an important topic of control of diabetes with thiamine supplementation including secondary outcomes as well like LDL and triglyceride levels.
- Included only good quality RCTs, hence the results can be relied upon to give direction to future research.

Limitations:

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.

- There was a lack of trials investigating the outcomes for a variety of comparisons and the follow-up period also varied among trials.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045. T2DM was the cause of 4.2 million fatalities in 2019 globally .[1]

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7] Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives Benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for

hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. It also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11-14] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[13]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23] Gestational diabetes has also been reported to be associated with thiamine mishandling.[24] Another study showed that thiamine supplementation reduced inflammatory and oxidative markers in women with gestational diabetes.[25] Unfortunately, these timid approaches were never followed by proper randomized controlled clinical trials (RCTs).

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL, HDL, triglycerides and various vitamins (including thiamine) and minerals[13,15,17-28] but with inconsistent results. Some studies reported significant inverse association for thiamine supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,29-31]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[32] by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[33] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy to include all relevant articles published till 31st December 2019 and updated later till 31st December 2021. A final update search was done till 30th June 2022. No additional article was found in the updated search. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined based on ADA (American Diabetes Association) guidelines as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the

review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies were resolved by discussion with a third author (HG). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality of parallel group RCTs was assessed using the widely used critical JBI checklist for randomised controlled trials. [32] This checklist comprises of 13 items that assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored as '2' when the criteria were found adequately reported for the study, '1' when the

information was unclear and '0' when there was no reporting based on the criteria. The minimal obtainable score was 0 and the maximum 26. For unclear information, authors were contacted for more information and a decision made accordingly. An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[34] The continuous data extracted from the cross-over RCTs were treated as if from a parallel trial.[35] All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as mean differences and corresponding 95% confidence intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if I^2>50% and P value <0.10 in the chi-square test for heterogeneity.[36] A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 175 potential trials, with 157 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 157 trials, 13 trials were identified for potential inclusion in the review. (Appendix II) The reference lists of the 13 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded after examination of the full text against the inclusion criteria (see Appendix III). Thus, finally six trials were included in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[37] or non-diabetic[38], in vitro study[39], did not assess the outcome of interest [30,40,41] and study done on rats.[42]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	**Q 1**	**Q 2**	**Q 3**	**Q 4**	**Q 5**	**Q 6**	**Q 7**	**Q 8**	**Q 9**	**Q1 0**	**Q1 1**	**Q1 2**	**Q1 3**	**Total**
Winkler 1999[16]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[31]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[19]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[43]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[29]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22[16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way. Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[43] an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Score**
1	Shahmiri 2013[43]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallel RCTs[15,16,19,29,31]and one was cross-over RCT.[43] The six trials were conducted in six different countries – Germany [31], Pakistan [19], Netherlands[29], Australia [43], Mexico/USA [15] and Hungary [16]. The number of participants in parallel RCTs varied from 12[43] to 165[31] while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,29] One trial [29] had male predominance (77% vs 33%) while the other [16] had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16] to 65.3 ± 5.9 years.[29]

Five of the six trials compared the intervention to placebo and one trial [16] compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from 100 mg/day[43] to 300mg/day [19] and the dosage for benfotiamine ranged from 120 mg/ day [16] to 900mg/day.[29] The follow-up period ranged from 1 month[15] to 3 months.[19,29]

Fasting blood glucose was reported in four trials,[15,16,19,43] PPG in two trials,[16,43] HbA1c in five trials,[15,16,19,29,31] HDL in four trials,[15,16,19,29] LDL in three trials,[15,19,29] triglycerides in four trials,[15,16,19,29], systolic and diastolic BP in three trials [15,19,29] and BMI in two trials. [15,43] Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

Heterogeneity among studies:

There was no heterogeneity among studies for HbA1C (I^2 = 0%, p=0.41), HDL (I^2 = 0%, p=0.97), LDL (I^2 = 0%, p=0.88) and triglycerides (I^2 = 0%, p=0.56). Heterogeneity measured for FBG was significant (I^2 = 79%; p=0.05), which was accounted for by using random effects model for meta-analysis.

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,29] that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,29,31] investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study[31] reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among

those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,43] demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine on FBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [43] investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16] compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10 mmol/l; CI 0.10, 0.30) (Fig 4) but a

statistically significant difference was seen (MD 0.10 mmol/l; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16] compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14 mmol/l; CI -0.17, 0.45) (Fig 5) as well as the 3 months follow-up period (MD 0.25 mmol/l; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22 kg/m^2; 95% CI -2.23, 1.79).

Systolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on systolic BP levels. Pooled results demonstrated no statistically significant differences in the systolic BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).

Diastolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on diastolic BP levels. Pooled results demonstrated no statistically significant differences in the diastolic BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).

Discussion

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people

with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable as the assessment criteria regarding the method of randomization and allocation concealment was not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG [44,45] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [46].

The results of the review also demonstrated no significant differences in FBG, LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore, trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased

as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations in different studies (with different diabetes risk) and the presence of underlying health conditions (like presence of autoimmune diseases) which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [47]. Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.
- There was a lack of trials investigating the outcomes for a variety of comparisons,
- The follow-up period varied among trials.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to change practices. Therefore, existing practices will be dictated by current policies. However, some important points have been identified such as, the studies published to date have been

single centric studies, with small sample size, varying doses and follow-up for only 3 months. Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Data availability: No additional data available.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data acquisition, manuscript preparation and analysis; PM: Data collection, manuscript preparation and analysis.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H et al. Cost effectiveness of type 2 diabetes screening: A systematic review. *Med J Islam Repub Iran.*. 2016;30:326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. *Clin Nutr*. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. *Diabetes Care*. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. *Cell Mol Life Sci*. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, et al.. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, et al. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. *J Anim Physiol Anim Nutr (Berl)*. 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. *Stem Cells Dev*. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. *Nat Med*. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. *Diabetologia*. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, et al. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine: Minireviews.* 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, et al. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr.* 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, et al. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. *Arzneimittelforschung.* 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabet Med.* 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia*. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, et al. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res Clin Pract*. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab*. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, et al. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. *J Nat Sci Biol Med*. 2013;4(2):336.

24. Bartakova V, Pleskačova A, Kuricova K et al (2016) Dysfunctional protection against advanced glycation due to thiamine metabolism abnormalities in gestational diabetes. Glycoconj J 33(4):591–598. https:// doi. org/ 10. 1007/ s10719- 016- 9688-9

25. Amirani E, Aghadavod E, Shafabakhsh R et al (2020) Antiinflammatory and antioxidative effects of thiamin supplements in patients with gestational diabetes mellitus. J Matern Fetal Neonatal Med. https:// doi. org/ 10. 1080/ 14767 058. 2020. 17792 12

26. Rafat D, Rabbani T, Ahmad J, et al. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect of Iron Supplementation. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*. 2012;6(2):102-5.

27. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491-5.

28. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. *Free Radic Res*. 2010;44(12):1445-53.

29. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care*. 2010;33(7):1598-601.

30. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *Int J Clin Pharmacol Ther*. 2005;43(2):71-7.

31. Stracke H, Gaus W, Achenbach U, et al. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Experimental and clinical endocrinology & diabetes*. 2008;116(10):600-5.

32. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Effectiveness. *Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute*. 2017.

33. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. *The Joanna Briggs Institute*. 2017;299(

34. Review Manager. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. 2014.

35. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-9.

36. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring Inconsistency in Meta-Analyses. *BMJ*. 2003;327(7414):557-60.

37. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care*. 2012;35(5):1095-7.

38. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

39. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

40. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

41. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis*. 1996;11(1):95-106.

42. Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes.* 2003;52(8):2110-20.

43. Shahmiri FA, Soares M, Zhao Y, et al. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. *Eur J Nutr*. 2013;52(7):1821-4.

44. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. *Prehosp Disaster Med*. 2019;34(5):506-9.

45. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-50.

46. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-16.

47. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.

Figure Legends:

Fig 1: PRISMA 2009 Flow Diagram for searching

Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.

Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.

Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.

Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

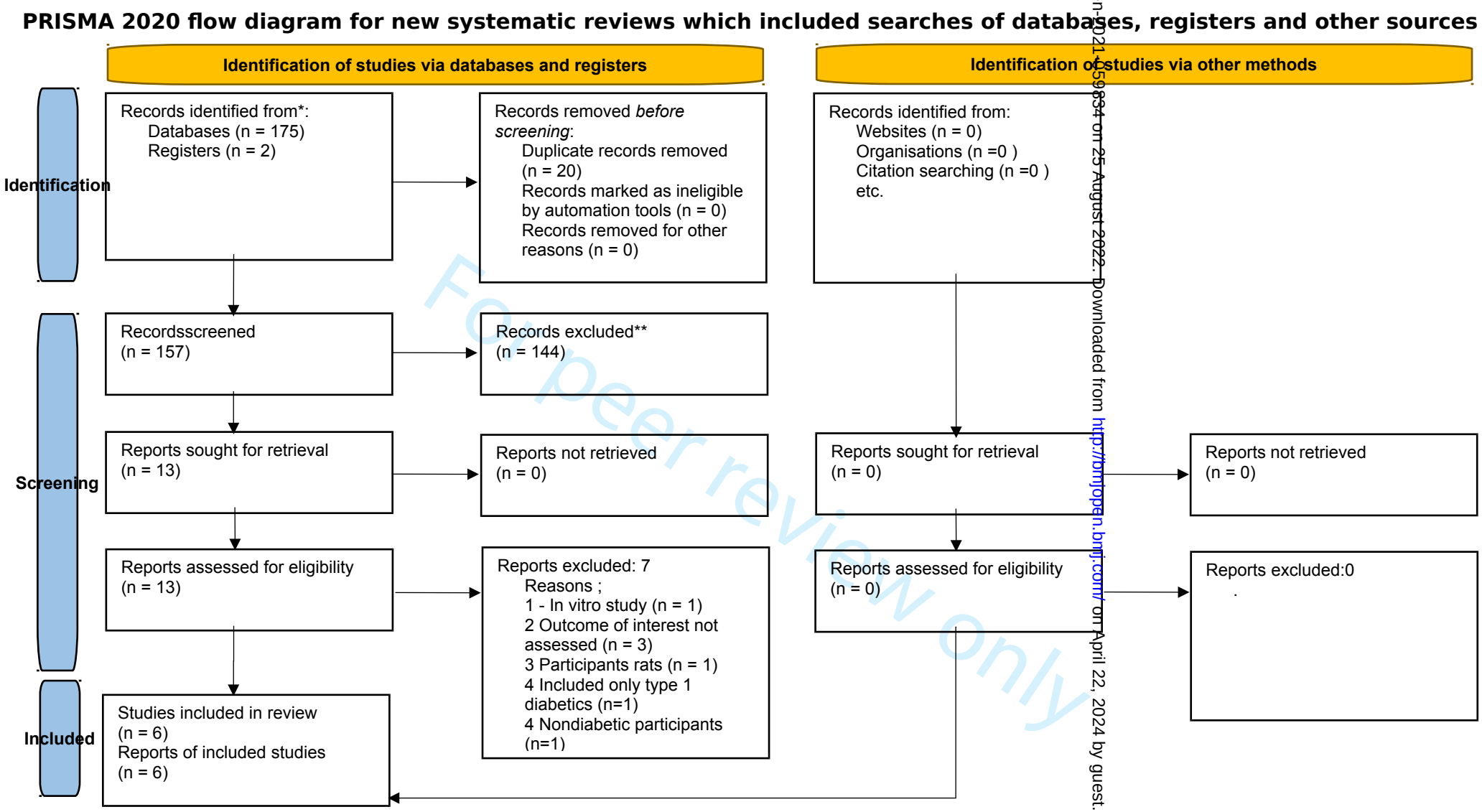


Fig 1: **PRISMA 2020 Flow diagram showing searching results**

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit:http://www.prisma-statement.org/

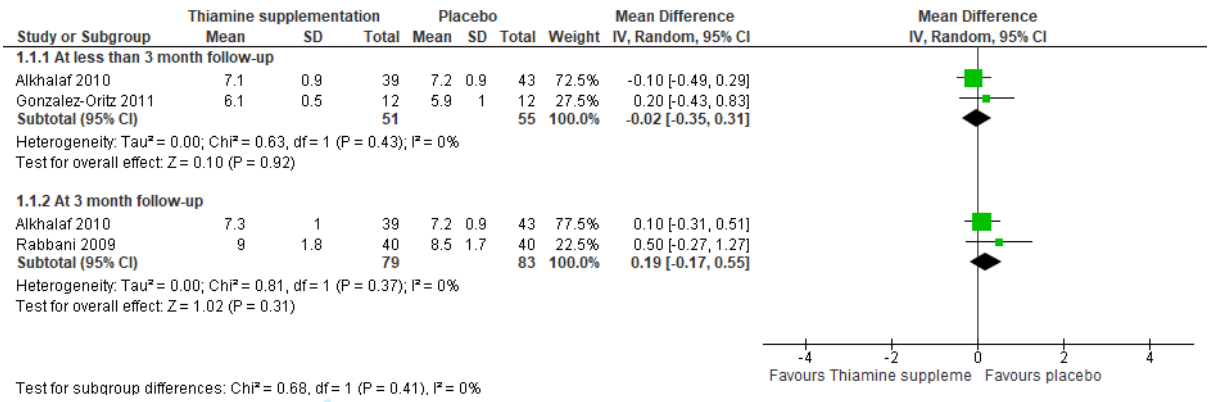


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

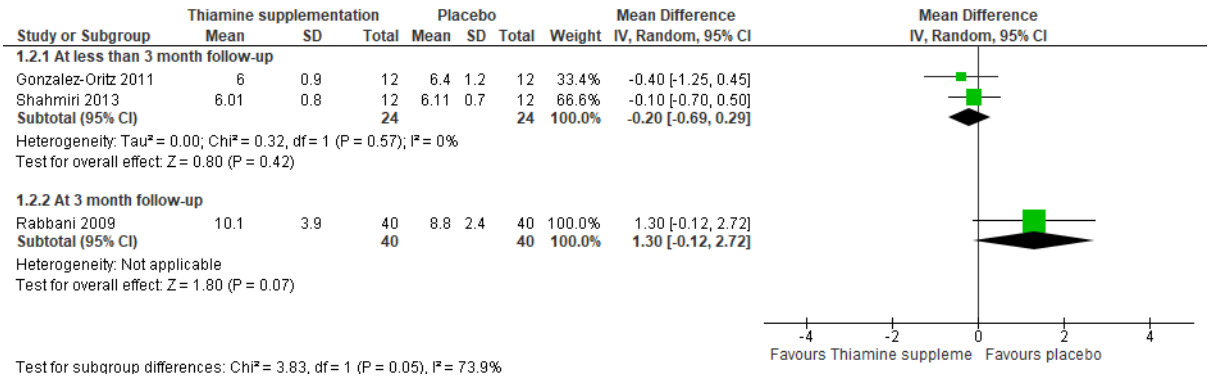


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

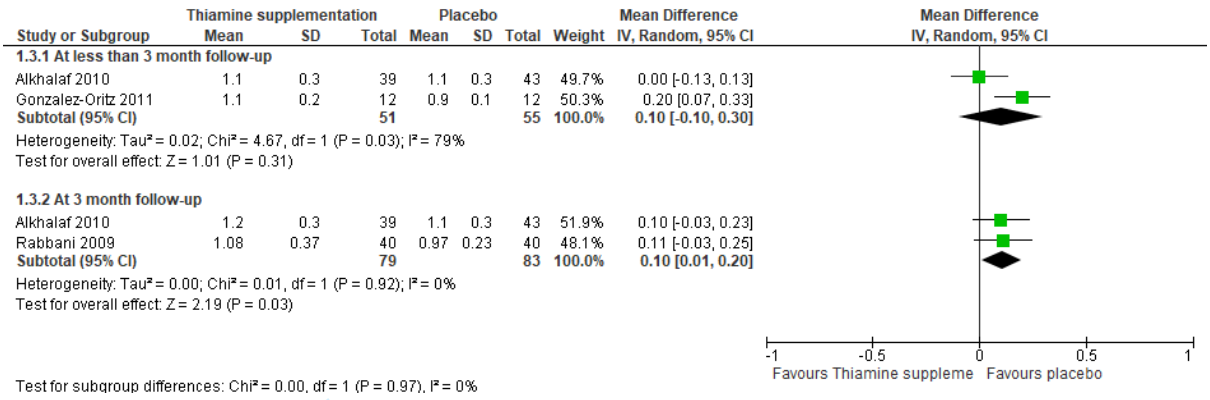


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

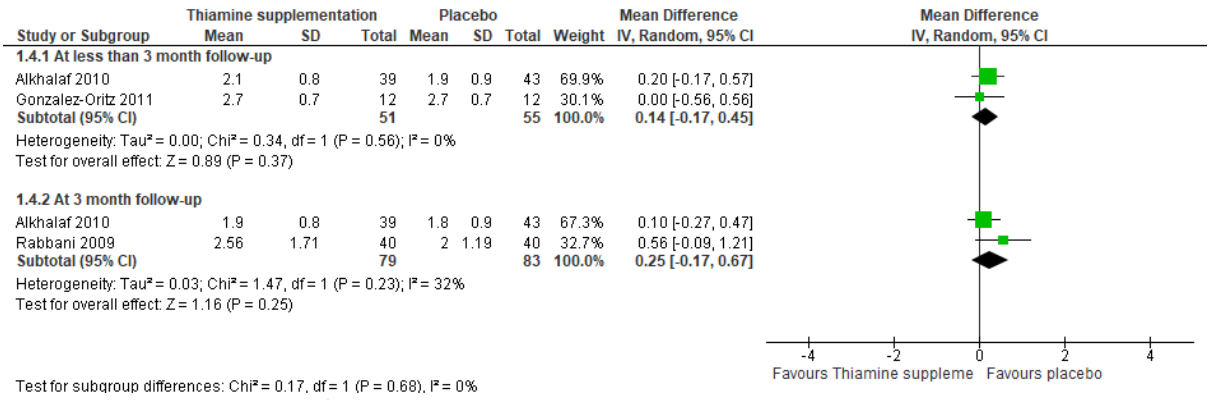


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

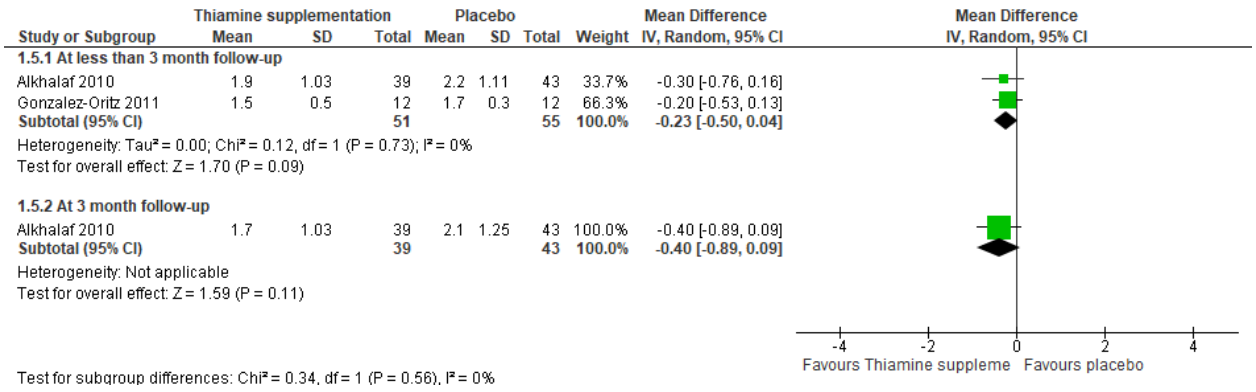


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

BMJ Open

Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059834.R5
Article Type:	Original research
Date Submitted by the Author:	29-Jul-2022
Complete List of Authors:	Muley, Arti; Parul University, Medicine, PIMSR Fernandez, Ritin; University of Wollongong Faculty of Science Medicine and Health, Nursing Green, Heidi; Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia, Nursing Muley, Prasad; Parul University, Pediatrics, PIMSR
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

Running title: Type 2 Diabetes and thiamine

Authors:

Arti Muley[1]

Ritin Fernandez[2,3,4]

Heidi Green[3]

Prasad Muley[1]

1. PIMSR, Parul University, Waghodia, Vadodara, Gujarat, India.
2. Centre for Evidence Based Initiatives in Health Care: a Joanna Briggs Centre of Excellence, NSW, Australia
3. Centre for Research in Nursing and Health, St George Hospital, Sydney, Australia
4. School of Nursing, University of Wollongong, Sydney, Australia.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Word count:

Abstract: 244

Main text: 4868

No. of references: 52

Corresponding author:

Ritin Fernandez
Professor, School of Nursing
Faculty of science, Medicine and Health
University of Wollongong
email: Ritin.Fernandez@health.nsw.au

TITLE: Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2 diabetes: A systematic review and meta-analysis

ABSTRACT

Background: Patients with Type 2 diabetes mellitus (T2DM) have been shown to have thiamine deficiency. Dietary supplementation is an economic strategy to control blood glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic outcomes in patients with T2DM.

Methods:

Eligibility criteria: Studies that assessed effect of thiamine supplementation in adults with T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or post prandial blood glucose (PPG) were included.

Information sources: PUBMED, Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database and Google Scholar were searched until December 2021 for RCTs.

Risk of bias: It was assessed using standardized critical appraisal instruments from the Joanna Briggs Institute for RCTs.

Synthesis of results: Where possible, studies were pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling was not possible.

Results:

Included studies: Six trials involving 364 participants.

Synthesis of results: No significant beneficial effects were observed on glycemic outcomes with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02

%, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in higher doses.

Discussion:

Limitations of evidence: Inclusion of single-centre trials published only in English, small sample sizes of included studies, lack of trials investigating outcomes for same comparisons and varying follow-up periods.

Interpretation: Thiamine supplementation doesn't affect glycemic outcomes, however reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher doses of thiamine and a follow-up period of 1-2 years will provide better evidence.

Strengths:

- Addresses an important topic of control of diabetes with thiamine supplementation including secondary outcomes as well like LDL and triglyceride levels.
- Included only good quality RCTs, hence the results can be relied upon to give direction to future research.

Limitations:

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.

- There was a lack of trials investigating the outcomes for a variety of comparisons and the follow-up period also varied among trials.

Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health problem in both developed and developing countries. In 2019 there were approximately 463 million adults with diabetes in the world and the number is expected to rise to 700 million by 2045. T2DM was the cause of 4.2 million fatalities in 2019 globally .[1]

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).[3,4] Hence, it is vital that prevention and or optimal management strategies are implemented to reduce the effect of this global epidemic.

Vitamin supplementation has been reported to improve glycemic outcomes in patients with T2 DM. One vitamin extensively investigated is Thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen et al.[5] Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. These complexes are the fundamental enzymes required at the various stages (glycolysis, citric acid cycle, pentose-phosphate cycle) for intracellular glucose metabolism.[6] The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.[7] Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.[8]

Benfotiamine is a lipid soluble thiamine derivative that efficiently raises thiamine levels in the blood compared to the water soluble thiamine derivatives Benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes mellitus (DM) by activating glucose metabolism and insulin synthesis.[9]It also has a role in blocking pathways responsible for

hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein kinase C. It also works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway.[10]

How the intervention might work

Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM patients[11-14] due to reduction in absorption of thiamine from the intestine and decreased membrane transport of thiamine[15,16] with an increased renal clearance and fractional excretion of thiamine[13]. In another study 18% of the participants showed lower thiamine concentration compared to the lower limit of the normal range.[17]

Although relatively low doses of thiamine saturate the thiamine transporter in the intestine, there is continuous slow passive diffusion at high concentration.[18] Based on this observation it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily requirement) leads to the maximum TPP-saturated transketolase activity[19] and prevents hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial cells in vitro.[20] In women, thiamine intake has been shown to have a strong association with glucose tolerance.[21] Other studies have reported that thiamine decreased blood glucose concentration in one month[22] and glycosylated hemoglobin decreased significantly with benfotiamine therapy within 45 days.[23] Gestational diabetes has also been reported to be associated with thiamine mishandling.[24] Another study showed that thiamine supplementation reduced inflammatory and oxidative markers in women with gestational diabetes.[25] Unfortunately, these timid approaches were never followed by proper randomized controlled clinical trials (RCTs).

Many studies have investigated the association between fasting blood sugar (FBS), post prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL, HDL, triglycerides and various vitamins (including thiamine) and minerals[13,15,17-28] but with inconsistent results. Some studies reported significant inverse association for thiamine supplementation[19-21,23]while other intervention studies did not find any significant association with thiamine.[13,15,17,18,20,29-31]

As dietary supplementation can be an easily feasible and an economic strategy to control sugar levels and prevent hyperglycemia related complications, we aim to conduct a systematic review and meta-analysis to find out the relationship of supplementation of thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and no systematic reviews were identified. Therefore, the question for the review is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults with T2DM?

Methods

The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence[32] by two independent reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.[33] The proposed systematic review was registered in PROSPERO (Registration no. CRD42020170520).

Literature search strategy

The search strategy aimed to find both published and unpublished studies which included a three-step search strategy to include all relevant articles published till 31st December 2019 and updated later till 31st December 2021. A final update search was done till 30th June 2022. No additional article was found in the updated search. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in the title, abstract and index terms of the studies identified were used to inform the development of a search strategy for the second step which was tailored for each information source. Published studies were searched for including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in Appendix I. The following databases were searched to find any unpublished studies: the National Institute of Health Clinical Database (http://ClinicalTrials.gov) and Google Scholar. The final step of the search strategy included a review of the reference list of all trials selected for critical appraisal. The search was restricted to papers published in the English language.

Inclusion and exclusion criteria

We searched for randomised controlled trials and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets, capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined based on ADA (American Diabetes Association) guidelines as either: plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or HbA1c ≥ 6.5% (48 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma glucose of ≥ 200mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the

review. The following secondary outcomes were also included in the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the outcomes were measured in different units were included and results were converted to desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters to the editors, and conference abstracts were excluded. Any discrepancies were resolved by discussion with a third author (HG). The results of the search is presented in a PRISMA flow diagram (Figure 1).

Screening

The titles and abstracts of all the identified citations were independently screened by two authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data was extracted from all trials included in the review by two independent reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data extracted included specific details about the type of intervention, populations, context, study design and duration, study methods and other outcomes of significance to the review question and specific objectives.

Quality assessment

Methodological quality of parallel group RCTs was assessed using the widely used critical JBI checklist for randomised controlled trials. [32] This checklist comprises of 13 items that assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored as '2' when the criteria were found adequately reported for the study, '1' when the

information was unclear and '0' when there was no reporting based on the criteria. The minimal obtainable score was 0 and the maximum 26. For unclear information, authors were contacted for more information and a decision made accordingly. An additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the additional risk of bias exists in cross-over RCTs, therefore a further four questions were used to assess the methodological quality of these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

Data from included studies were pooled in a statistical meta-analysis model using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[34] The continuous data extracted from the cross-over RCTs were treated as if from a parallel trial.[35] All pooled statistics were subject to double data entry with two independent reviewers. For continuous data, effect sizes are expressed as mean differences and corresponding 95% confidence intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and chi-squared statistics, and heterogeneity was considered substantial if I^2>50% and P value <0.10 in the chi-square test for heterogeneity.[36] A random effects model was used in the meta-analysis. Subgroup-analysis according to type of intervention and length of intervention period were performed. For results which were not possible to present in a meta-analysis, the findings have been presented in a narrative form.

Patient and public involvement:

No patient involved.

Results

The search results identified 175 potential trials, with 157 potential trials remaining after duplicates were removed. After a review of the title and abstract of all 157 trials, 13 trials were identified for potential inclusion in the review. The reference lists of the 13 trials were examined and full texts of a further two trials were obtained. From a total of 13 trials, seven trials were excluded (see Appendix II) after examination of the full text against the inclusion criteria. Thus, finally six trials were included (Appendix III) in the systematic review. (Figure1)

Reasons for exclusion were: participants type 1 diabetic[37] or non-diabetic[38], in vitro study[39], did not assess the outcome of interest [30,40,41] and study done on rats.[42]

Insert Figure1 here

Quality assessment

The results of the methodological quality assessment for the six trials are presented in Table 1.

Table 1: Assessment of methodological quality

Study	**Q 1**	**Q 2**	**Q 3**	**Q 4**	**Q 5**	**Q 6**	**Q 7**	**Q 8**	**Q 9**	**Q1 0**	**Q1 1**	**Q1 2**	**Q1 3**	**Total**
Winkler 1999[16]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008[31]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009[19]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri[43]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010[29]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

N, No; NA, Not applicable; U, Unclear; Y, Yes; N=0, U=1, Y=2 points

JBI critical appraisal checklist for randomized controlled trials: Q1: Was true randomization used for assignment of participants to treatment groups?; Q2: Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering treatment blind to treatment assignment?; Q6: Were outcomes assessors blind to treatment assignment?; Q7: Were treatments groups treated identically other than the intervention of interest?; Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9: Were participants analyzed in the groups to which they were randomized?; Q10: Were outcomes measured in the same way for treatment groups?; Q11: Were outcomes measured in a reliable way?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Overall, the quality of the trials was high, with scores ranging from 18/22[16] to 26/26 [19] (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one [19] in which the random number method was used. All trials used the appropriate study design, and measured the outcomes in a reliable way. Following discussion, there was 100 per cent concordance between the two independent reviewers. For the one included cross-over trial,[43] an additional four questions were assessed (Table 2). The trial met all criteria for the four questions; appropriately used the cross-over trial design, reported that treatment schedules were randomized and that data provided was unbiased. There was a wash-out period of 14 weeks between the interventions.

Table 2: Critical appraisal for cross-over trials (additional four questions)

	Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Score**
1	Shahmiri 2013[43]	Y	Y	Y	Y	8/8

N: No, Y: Yes, U: Unclear, NA: Not Applicable
N=0; Y=2; U=1 points.
Additional four questions for cross-over RCTs: Q1: Was use of a cross-over design appropriate? Q2: Is it clear that the order of receiving treatments was randomized? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?

Characteristics of included studies

Of the six trials included in the review, five were placebo-controlled parallel RCTs[15,16,19,29,31]and one was cross-over RCT.[43] The six trials were conducted in six different countries – Germany [31], Pakistan [19], Netherlands[29], Australia [43], Mexico/USA [15] and Hungary [16]. The number of participants in parallel RCTs varied from 12[43] to 165[31] while in the cross-over RCT the number of participants were 40. The distribution of male and female participants in the trials was even in all except two trials.[16,29] One trial [29] had male predominance (77% vs 33%) while the other [16] had female predominance (61% vs 39%).The mean age of the patients ranged from 52 ± 8 years [16] to 65.3 ± 5.9 years.[29]

Five of the six trials compared the intervention to placebo and one trial [16] compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from 100 mg/day[43] to 300mg/day [19] and the dosage for benfotiamine ranged from 120 mg/ day [16] to 900mg/day.[29] The follow-up period ranged from 1 month[15] to 3 months.[19,29]

Fasting blood glucose was reported in four trials,[15,16,19,43] PPG in two trials,[16,43] HbA1c in five trials,[15,16,19,29,31] HDL in four trials,[15,16,19,29] LDL in three trials,[15,19,29] triglycerides in four trials,[15,16,19,29], systolic and diastolic BP in three trials [15,19,29] and BMI in two trials. [15,43] Data extracted from all trials is summarized in the table of included study characteristics (Appendix III).

Heterogeneity among studies:

There was no heterogeneity among studies for HbA1C (I^2 = 0%, p=0.41), HDL (I^2 = 0%, p=0.97), LDL (I^2 = 0%, p=0.88) and triglycerides (I^2 = 0%, p=0.56). Heterogeneity measured for FBG was significant (I^2 = 79%; p=0.05), which was accounted for by using random effects model for meta-analysis.

HbA1C

Comparison between Thiamine supplementation vs Placebo

Two trials [15,29] that investigated the effect of thiamine supplementation vs placebo on HbA1C levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with placebo was 5.9% and with thiamine was 5.88%.

Three trials [19,29,31] investigated the effect of thiamine supplementation vs placebo on HbA1C levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis. Pooled data demonstrated no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo (MD 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study[31] reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

Insert Figure 2

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level demonstrated no statistically significant differences in the HbA1C levels between the two groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10, 0.10). There were also no statistically significant differences in the HbA1C levels among

those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.30; 955 CI -1.09, 0.49).

FBG

Comparison between Thiamine supplementation vs Placebo

Pooled results from three trials [15,19,43] demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation vs placebo after less than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no statistically significant difference in the FBG level between the groups after 3 months follow-up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).

Insert Fig 3 here

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared 320mg/day and 120mg/day of benfotiamine on FBG levels demonstrated no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically significant differences in the FBG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).

PPG

Comparison between Thiamine supplementation vs Placebo

One trial [43] investigated the effect of thiamine supplementation vs placebo on PPG levels. However, due to the paucity of the reported data, the authors were contacted to obtain further information. No response was received from the authors hence we were unable to conclude the effect of thiamine supplementation vs placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

One trial[16] compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results demonstrated no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically significant differences in the PPG levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63, 1.23). There were also no statistically significant differences in the PPG levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).

HDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 month (MD 0.10 mmol/l; CI 0.10, 0.30) (Fig 4) but a

statistically significant difference was seen (MD 0.10 mmol/l; 95% CI 0.01, 0.20) at 3 month follow-up period (Fig 4).

Insert Fig 4 here

Comparisons between various dosages of Benfotiamine supplementation

One trial [16] compared two dosages of Benfotiamine demonstrated no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36). Similarly, there were no statistically significant differences in the HDL levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant differences in the HDL levels among those who received 120 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).

LDL

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on LDL levels. Pooled results demonstrated no statistically significant differences in the LDL levels between the groups at less than 3 month (MD 0.14 mmol/l; CI -0.17, 0.45) (Fig 5) as well as the 3 months follow-up period (MD 0.25 mmol/l; CI -0.17, 0.67) (Fig 5).

Insert Fig 5

Triglycerides

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on triglyceride levels. The results demonstrated no statistically significant differences in the triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04) (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) . The study by Rabbani provided Median and minimum and maximum scores and hence could not be included in the meta-analysis. The results however demonstrated no statistically significant differences in the triglyceride levels between the groups at the 3 month follow-up.

Insert Fig 6

Comparisons between various dosages of Benfotiamine supplementation

One trial[16] that compared various dosages of Benfotiamine demonstrated no statistically significant differences in the triglyceride levels among those who received 320 mg/day benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l; 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the HbA1C levels among those who received 320 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels among those who received 120 mg/day benfotiamine compared was significantly lower compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -1.90,-0.30)

BMI

Comparison between Thiamine supplementation vs Placebo

Three trials [15,19,29] investigated the effect of thiamine supplementation vs placebo on BMI levels. Pooled results demonstrated no statistically significant differences in the BMI levels between the groups at less than 3 month (MD -0.22 kg/m^2; 95% CI -2.23, 1.79).

Systolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on systolic BP levels. Pooled results demonstrated no statistically significant differences in the systolic BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).

Diastolic BP

Comparison between Thiamine supplementation vs Placebo

Three trials [15,27,34] investigated the effect of thiamine supplementation vs placebo on diastolic BP levels. Pooled results demonstrated no statistically significant differences in the diastolic BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).

Discussion

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and diastolic BP and BMI. Since this review only included trials that were undertaken in people

with T2DM, only six trials were eligible for inclusion of which one was a cross over trial. The overall methodological quality of the trials was variable as the assessment criteria regarding the method of randomization and allocation concealment was not reported in four trials.

For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG [44,45] is considered as clinically significant. In our review, the treatment effect sizes did not reach the point of clinical significance for both HbA1C and FBG which could be due to the small sample sizes in the included studies. Nevertheless, the small reductions identified in HbA1C and blood glucose levels can reduce the health impacts associated with T2DM [46].

The results of the review also demonstrated no significant differences in FBG, LDL, and BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation compared to those receiving placebo at less than three months or at three months follow-up. These results could be due the fact that the outcomes were assessed within three months of administration of thiamine. It has been established that plasma thiamine level is associated with increased fractional excretion of thiamine resulting in decreased thiamine concentration by about 75% in type 2 diabetic patients [7]. Therefore, trials with longer term follow-up are required to assess the effect of thiamine on glycemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120mg/day benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day dosage there were no differences in triglyceride levels [16] indicating that the benefit decreased

as the dose was escalated. This result should be interpreted with caution as these results are based on a single study with a sample size of 36 participants.

Various other factors could have influenced the results of the review including different populations in different studies (with different diabetes risk) and the presence of underlying health conditions (like presence of autoimmune diseases) which can cause high blood glucose despite thiamine supplementation. It has been shown that people with poorly controlled diabetes often experience micronutrient deficiencies [47]. Hence there is substantial interest globally to find easily accessible and inexpensive treatments such as thiamine supplementation for T2DM.

Limitations of this review

- The review includes single-centre trials published only in the English language.
- Sample sizes of the included studies were small although some had addressed this issue using statistical power.
- There was a lack of trials investigating the outcomes for a variety of comparisons,
- The follow-up period varied among trials.

Conclusions

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to change practices. Therefore, existing practices will be dictated by current policies. However, some important points have been identified such as, the studies published to date have been

single centric studies, with small sample size, varying doses and follow-up for only 3 months. Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer follow-up of 1-2 years using sample size based on power calculation should be undertaken to address the confusion regarding benefit of thiamine supplementation on glycemic outcomes in T2DM. One such study if undertaken would be able to give specific recommendations on whether or not to consider thiamine supplementation for improving glycemic outcomes in T2DM patients.

Ethics statement: This study does not involve any human or animal participant.

Funding: No additional sources of funding.

Data availability: No additional data available.

Disclosure of Interest: The authors declare that they have no competing interests.

Contribution: AM, RF formulated the study concept and design and contributed in data analysis and manuscript preparation; GH : did data acquisition, manuscript preparation and analysis; PM collected data and contributed inmanuscript preparation and analysis.

Acknowledgements: The authors would like to thank Ms Sofia Russo for secretarial support.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th Edition 2017.

2. Najafi B, Farzadfar F, Ghaderi H et al. Cost effectiveness of type 2 diabetes screening: A systematic review. *Med J Islam Repub Iran.*. 2016;30:326.

3. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U, et al. The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients. *Clin Nutr*. 2016;35(5):1096-102.

4. Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a Replacement for Carbohydrates in the Diabetic Diet. *Diabetes Care*. 2011;34(8):1706-11.

5. Jansen B, Donath W. The Isolation of Anti-Beriberi Vitamin. Geneeskundig Tijdschrift voor Nederlandsche-Indie. 1926;66(4).

6. Frank R, Leeper F, Luisi B. Structure, Mechanism and Catalytic Duality of Thiamine-Dependent Enzymes. *Cell Mol Life Sci*. 2007;64(7-8):892.

7. Mee L, Nabokina SM, Sekar VT, et al.. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;297(1):G197-G206.

8. Dębski B, Kurył T, Gralak M, et al. Effect of inulin and oligofructose enrichment of the diet on rats suffering thiamine deficiency. *J Anim Physiol Anim Nutr (Berl)*. 2011;95(3):335-42.

9. Oh S-H, Witek RP, Bae S-H, et al. Detection of transketolase in bone marrow–derived insulin-producing cells: benfotiamine enhances insulin synthesis and glucose metabolism. *Stem Cells Dev*. 2009;18(1):37-46.

10. Hammes H-P, Du X, Edelstein D, et al. Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy. *Nat Med*. 2003;9(3):294-9.

11. Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006;3(120-1.

12. Thornalley P, Babaei-Jadidi R, Al Ali H, et al. High Prevalence of Low Plasma Thiamine Concentration in Diabetes Linked to a Marker of Vascular Disease. *Diabetologia*. 2007;50(10):2164-70.

13. Xu R, Zhang S, Tao A, et al. Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2014;9(4).

14. Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine: Minireviews.* 2000;224(4):246-55.

15. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, et al. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr.* 2011;50(2):145-9.

16. Winkler G, Pál B, Nagybégányi E, Öry I, et al. Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy. *Arzneimittelforschung.* 1999;49(03):220-4.

17. Oosterwerff MM, Eekhoff EM, Van Schoor NM, et al. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2014;100(1):152-60.

18. George P, Pearson E, Witham M. Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabet Med.* 2012;29(8):e142-e50.

19. Rabbani N, Alam SS, Riaz S, et al. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia*. 2009;52(2):208-12.

20. Sudchada P, Saokaew S, Sridetch S, et al. Effect of Folic Acid Supplementation on Plasma Total Homocysteine Levels and Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Res Clin Pract*. 2012;98(1):151-8.

21. Sabherwal S, Bravis V, Devendra D. Effect of Oral Vitamin D and Calcium Replacement on Glycaemic Control in South Asian Patients with Type 2 Diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

22. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab*. 1995;39(4):217-23.

23. Khan MI, Siddique KU, Ashfaq F, et al. Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. *J Nat Sci Biol Med*. 2013;4(2):336.

24. Bartakova V, Pleskačova A, Kuricova K et al (2016) Dysfunctional protection against advanced glycation due to thiamine metabolism abnormalities in gestational diabetes. Glycoconj J 33(4):591–598. https:// doi. org/ 10. 1007/ s10719- 016- 9688-9

25. Amirani E, Aghadavod E, Shafabakhsh R et al (2020) Antiinflammatory and antioxidative effects of thiamin supplements in patients with gestational diabetes mellitus. J Matern Fetal Neonatal Med. https:// doi. org/ 10. 1080/ 14767 058. 2020. 17792 12

26. Rafat D, Rabbani T, Ahmad J, et al. Influence of Iron Metabolism Indices on HbA1c in Non-Diabetic Pregnant Women with and without Iron-Deficiency Anemia: Effect of Iron Supplementation. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*. 2012;6(2):102-5.

27. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491-5.

28. Rytter E, Vessby B, Åsgård R, et al. Supplementation with a Combination of Antioxidants does not affect Glycaemic Control, Oxidative Stress or Inflammation in Type 2 Diabetes Subjects. *Free Radic Res*. 2010;44(12):1445-53.

29. Alkhalaf A, Klooster A, Van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care*. 2010;33(7):1598-601.

30. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *Int J Clin Pharmacol Ther*. 2005;43(2):71-7.

31. Stracke H, Gaus W, Achenbach U, et al. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Experimental and clinical endocrinology & diabetes*. 2008;116(10):600-5.

32. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Effectiveness. *Joanna Briggs Institute Reviewer's Manual The Joanna Briggs Institute*. 2017.

33. Aromataris E, Munn Z. Joanna Briggs Institute reviewer's manual. *The Joanna Briggs Institute*. 2017;299(

34. Review Manager. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. 2014.

35. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-9.

36. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring Inconsistency in Meta-Analyses. *BMJ*. 2003;327(7414):557-60.

37. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care*. 2012;35(5):1095-7.

38. Schwab S, Zierer A, Heier M, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

39. Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

40. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

41. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis*. 1996;11(1):95-106.

42. Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes.* 2003;52(8):2110-20.

43. Shahmiri FA, Soares M, Zhao Y, et al. High-dose thiamine supplementation improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-over trial. *Eur J Nutr*. 2013;52(7):1821-4.

44. Topping J, Reardon M, Coleman J, et al. A Comparison of Venous versus Capillary Blood Samples when Measuring Blood Glucose Using a Point-of-Care, Capillary-Based Glucometer. *Prehosp Disaster Med*. 2019;34(5):506-9.

45. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-50.

46. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-16.

47. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.

Figure Legends:

Fig 1: PRISMA 2009 Flow Diagram for searching

Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.

Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.

Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.

Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

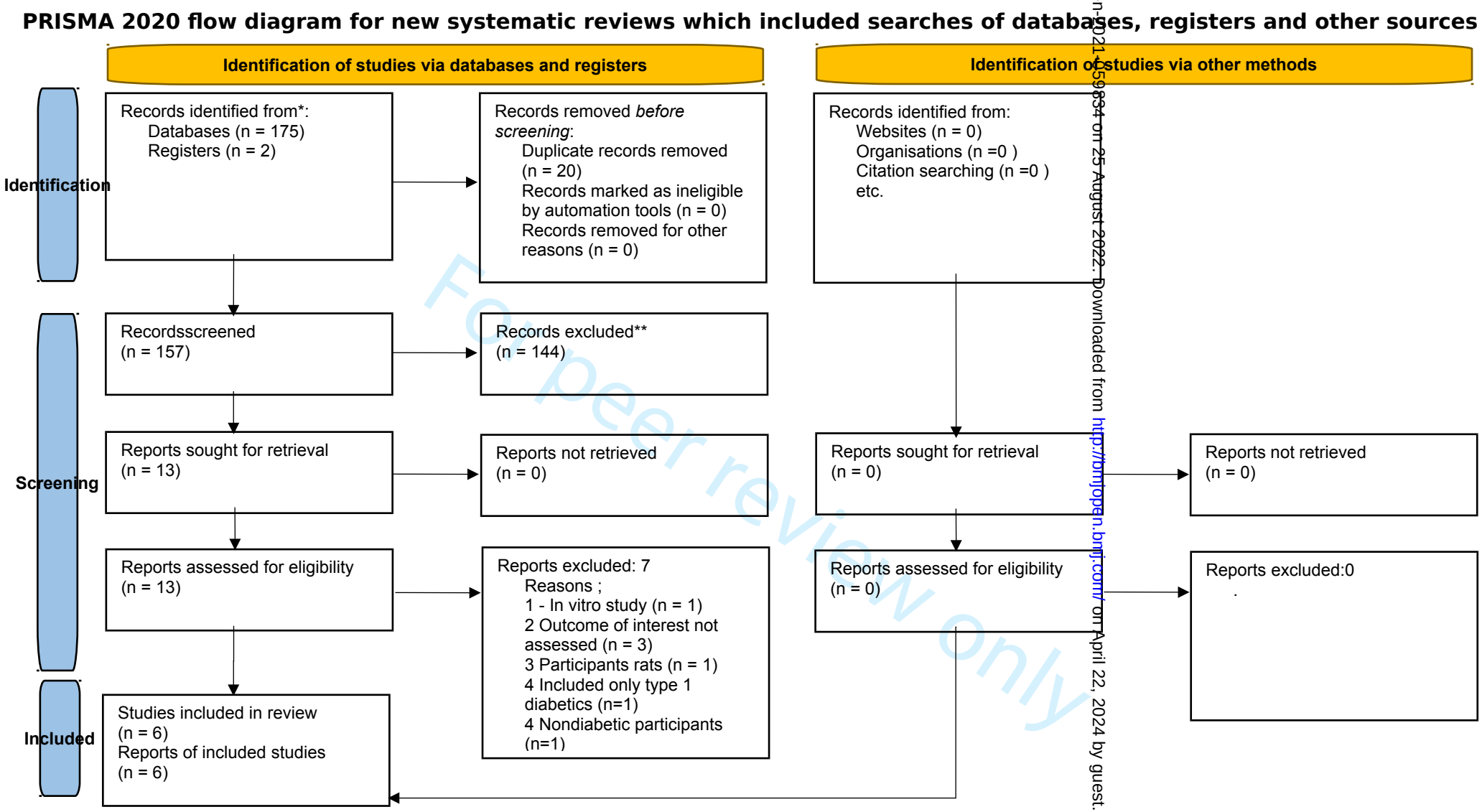


Fig 1: **PRISMA 2020 Flow diagram showing searching results**

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit:http://www.prisma-statement.org/

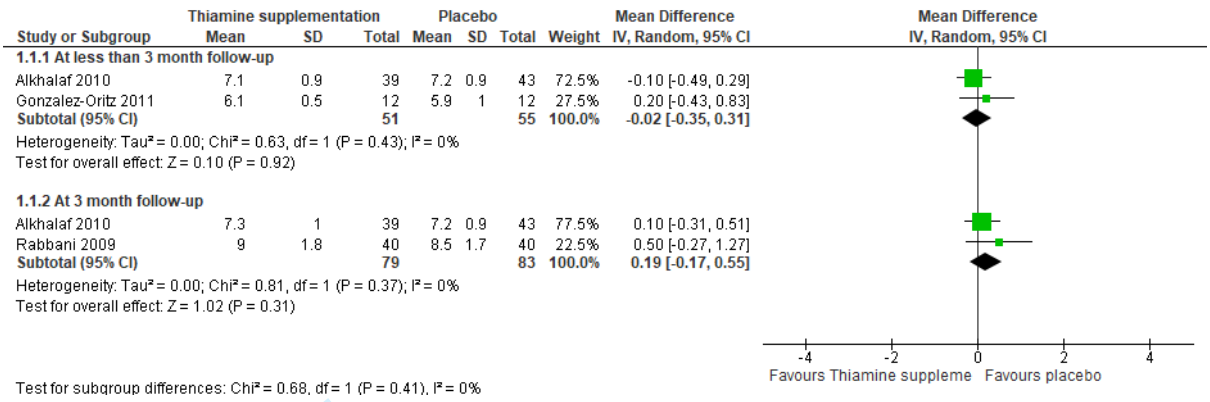


Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.

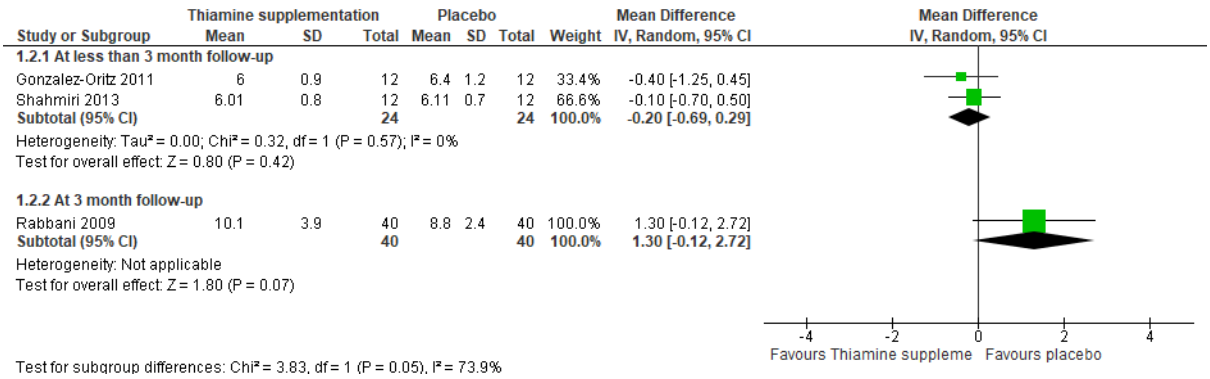


Fig 3: Effect on FBG at less than 3 months and at 3 months follow up

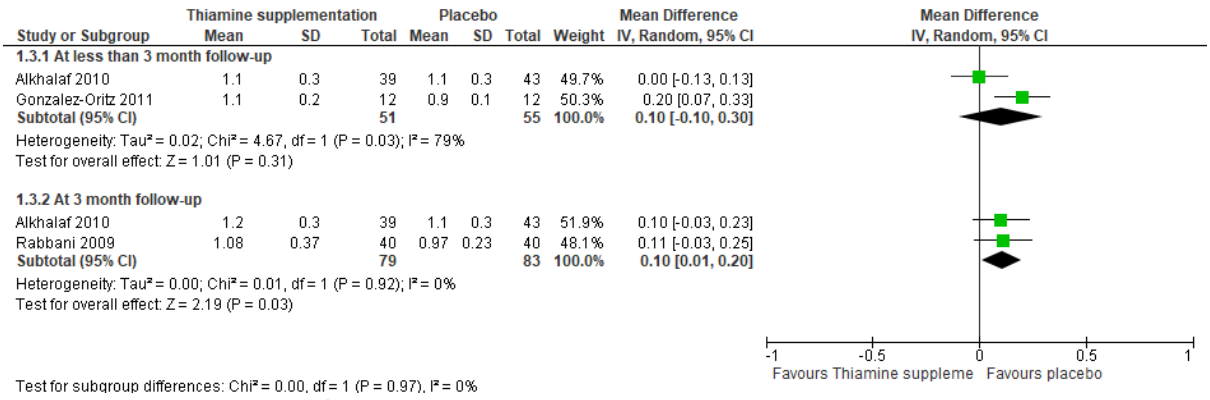


Fig 4: Effect on HDL at less than 3 months and at 3 months follow up

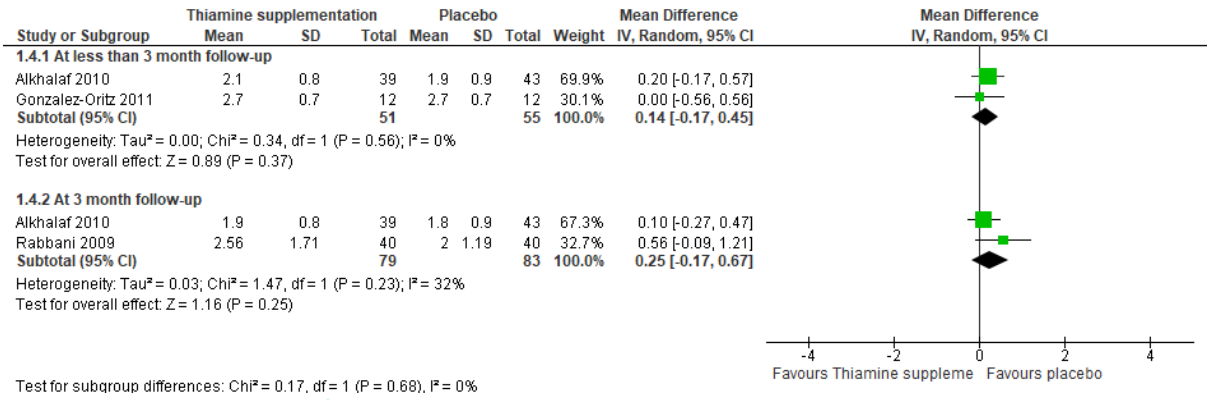


Fig 5: Effect on LDL at less than 3 months and at 3 months follow up

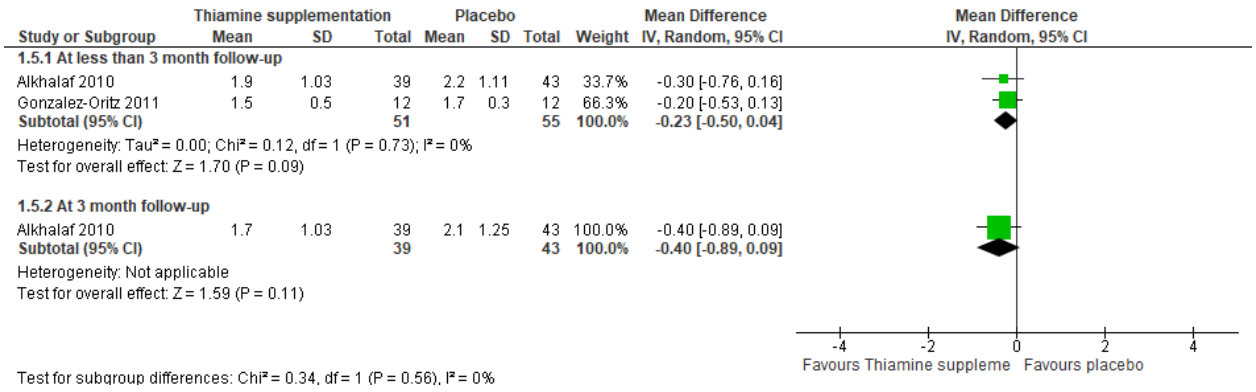


Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up

Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset OR Diabetes Mellitus, Noninsulin-Dependent
2.	Diabetes Mellitus, Ketosis-Resistant
3.	Diabetes Mellitus, Maturity-Onset
4.	Diabetes Mellitus, Non-Insulin Dependent
5.	Non-Insulin-Dependent Diabetes Mellitus
6.	Diabetes Mellitus, Slow-Onset
7.	Diabetes Mellitus, Stable
8.	NIDDM
9.	Diabetes Mellitus, Type II
10.	Thiamin
11.	Vitamin B1
12.	Aneurin
13.	Vitamin B 1
14.	Thiamine Mononitrate
15.	S-benzoylthiamine monophosphate
16.	Benfotiamine
17.	Benphothiamine
18.	Blood sugar
19.	Fasting blood glucose
20.	Post prandial blood glucose
21.	Glycosylated haemoglobin
22.	HbA1C
23.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
24.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
25.	18 OR 19 OR 20 OR 21 OR 22

26.	23 AND 24 AND 25
27.	limit 26 to (english language and humans and (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or RCT))
28.	limit 27 to adults more than 19 years

Search strategy for Cochrane Library

No.	Search terms
1.	Mesh descriptor [Diabetes Mellitus, type 2] explode all trees
2.	Mesh descriptor [vitamin B1] explode all trees
3.	Mesh descriptor [thiamine] explode all trees
4.	Mesh descriptor [Benfotiamine] explode all trees
5.	Mesh descriptor [Glycated haemoglobin] explode all trees
6.	Mesh descriptor [Blood glucose] explode all trees
7.	#2 OR #3 OR #4
8.	#5 OR #6
9.	#1 and #7 and #8

Search strategy for Tripdatabase

No.	Search terms
1.	NIDDM
2.	Type II Diabetes mellitus
3.	Non Insulin Dependent Diabetes Mellitus
4.	Diabetes Mellitus, Type II
5.	Adults
6.	Vitamin B1
7.	Thiamine
8.	Benfotiamine
9.	Benphothiamine
10.	Fasting blood glucose
11.	FBG
12.	Post prandial blood glucose
13.	PPG
14.	HbA1C
15.	Glycosylated hemoglobin
16.	Glycatedhemoglobin
17.	1 OR 2 OR 3 OR 4
18.	6 OR 7 OR 8 OR 9
19.	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
20.	5 AND 17 AND 18 AND 19

Appendix II: List of excluded studies

Excluded articles

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. The Journal of Biochemistry. 2001;129(4):543-9.
Reason for exclusion: In vitro study.

Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. PLoS One. 2012;7(7).
Reason for exclusion: Outcome of interest not assessed.

Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. International journal of clinical pharmacology and therapeutics. 2005;43(2):71-7.
Reason for exclusion: Outcome of interest not assessed.

Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes. 2003;52(8):2110-20.
Reason for exclusion: Participants rats.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metabolic brain disease. 1996;11(1):95-106.
Reason for exclusion: Outcome of interest not assessed.

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care. 2012;35(5):1095-7.
Reason for exclusion: Included only type 1 diabetics.

Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral supplements and longitudinal association with HbA1c levels in the general non-diabetic population—results from the MONICA/KORA S3/F3 study. PloS one. 2015;10(10).
Reason for exclusion: Participants nondiabetic.

Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008[34]	Germany	Double-blind, randomised, placebo-controlled phase-III study was performed in 10 study centres in Germany.	165 patients with type 1 or type 2 diabetes mellitus Mean age 60 years Males 56% vs females 44 % Mean duration of diabetes mellitus 12 years	Group 1: benfotiamine 200mg Group: 2 benfotiamine 100mg Group 3: placebo	HbA1c, FBG, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008[25]	Pakistan	Patients attending the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan	40 patients with type 2 diabetes Age range age 35–65 years Diabetes duration ≥5 years BMI 19–40 kg/m2.	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 3 months	There was no effect of thiamine treatment on glycaemic control, dyslipidaemia or BP.
Alkhalaf. 2010.	Netherlands	Participants attending the Isala Clinics (Zwolle, the Netherlands).	82 patients with type 2 diabetes Age range 40–75 years	Group 1: Benfotiamine (900 mg/day) Group 2: placebo	HbA1c, FBG, BMI, BP, HDL, Triglyceride at 12 weeks	Compared with placebo, benfotiamine treatment did not demonstrate a significant improvement in HbA1c.

Table of included study characteristics

Shahmiri 2013[48]	Australia	Subjects who attended the out-patient clinic, School of Public Health, Curtin University.	17 hyperglycemic subjects (14 IGT, 3 T2DM) Age range 18-75 years BMI 19-40 kg/m2	Group 1: 100 mg thiamine (as thiamine hydrochloride) Group 2: placebo	FBG, and BMI at 3 weeks	Thiamine supplementation resulted in significant decreases in 2-h plasma glucose relative to baseline (8.78±2.20 mmol/l vs. 9.89±2.50, p = 0.004), with no significant change in the placebo arm. Fasting plasma glucose increased significantly from baseline after 6 weeks in the placebo arm (p = 0.003, p = 0.04 and p = 0.02, respectively).
Gonzalez-Oritz 2010[15]	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m^2	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglycerides, BP, BMI at 1 month	Significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, p = 0.024) before and after the intervention, with thiamine administration. There were no changes with the rest of the measurements.
Winkler 1999[24]	Hungary	Unclear	36 patients with T2DM and IDDM Age range 40-70 years.	Group A: 4 x 2 capsules of a complex B-vitamin preparation, (320mg/day benfotiamine) (n=12)	HbA1c, FBG, Triglycerides at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12) Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)		

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg 1, Line 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg6,7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 7, para2, last line
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 8, para 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 8, para 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg 8, para 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 8, para 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 9, para 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 9, para 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 9, para 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 9, para 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg 10, para 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 10, para 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 10, para 2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 10, para 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg 10, para 2
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg 10, para 2
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg 10, para

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			2
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 10, para 1
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg 11, para 1,2, Appendix II
Study characteristics	17	Cite each included study and present its characteristics.	Pg 13, para 1, Appendix III
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig 2-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg 12, para 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg 14 - 19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg 13, para 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 12, para 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg 14-19, Fig 2-6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 19, 20
	23b	Discuss any limitations of the evidence included in the review.	Pg 21
	23c	Discuss any limitations of the review processes used.	Pg 21
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 7, para 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 7, para 3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg 22
Competing interests	26	Declare any competing interests of review authors.	Pg 22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg 22

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/