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Effect of thiamine supplementation on glycaemic outcomes in adults with type 2 diabetes: a systematic review and meta-analysis

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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 glycaemic outcomes in patients with T2DM.

Methods *Eligibility criteria:* Studies that assessed effect of thiamine supplementation in adults with T2DM which measured glycaemic outcomes—HbA1c, fasting blood glucose (FBG) and/or postprandial 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 standardised 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 glycaemic outcomes with 100–900 mg/day of thiamine or benfotiamine for up to 3 months (HbA1c: MD, −0.02%, 95% CI: −0.35 to 0.31; FBG: MD,−0.20 mmol/L; 95% CI: −0.69 to 0.29; PPG: MD, − 0.20 mmol/L, 95% CI: −2.05 to 1.65 (mean difference, MD)). There was a significant increase in high-density lipoprotein (HDL) (MD, 0.10; 95% CI: 0.10 to 0.20) at 3-month follow-up. Benfotiamine reduced triglyceride level (MD, −1.10; 95% CI: −1.90 to −0.30) in 120 mg/day dose as compared with 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 does not affect glycaemic 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.

PROSPERO registration number CRD42020170520.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Addresses an important topic of control of diabetes with thiamine supplementation including secondary outcomes as well like low-density lipoprotein and triglyceride levels.
⇒ Included only good quality randomised controlled trials, hence the results can be relied on to give direction to future research.
⇒ 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.

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 in 2012 and became the third most common cause of fatal complications.[2] It is a known risk factor for ischaemic heart disease with approximately 20%–30% of patients undergoing coronary artery bypass graft.[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 glycaemic outcomes in patients with T2DM. One vitamin extensively investigated is thiamine (vitamin B1).

Thiamine was identified in 1926 by Jansen and Donath.[5] Thiamine diphosphate 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 and 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 with the water soluble thiamine derivatives. Benfotiamine reduces glucose toxicity caused by hyperglycaemic 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 and activation of protein kinase C. It also works by activating TK 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 T2DM 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 with 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 TK 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 1 month[22] and glycosylated haemoglobin 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 randomised controlled clinical trials (RCTs).

Many studies have investigated the association between fasting blood sugar (FBS), postprandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1c), blood pressure (BP), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (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 hyperglycaemic-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 glycaemic outcomes including fasting blood glucose (FBG), postprandial blood glucose (PPG) 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.

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 31 December 2019 and updated later till 31 December 2021. A final update search was done till 30 June 2022. No additional article was found in the updated search. An initial limited search of PUBMED using the keywords: vitamin B1, thiamine, benfotiamine, DM 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 online supplemental 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.

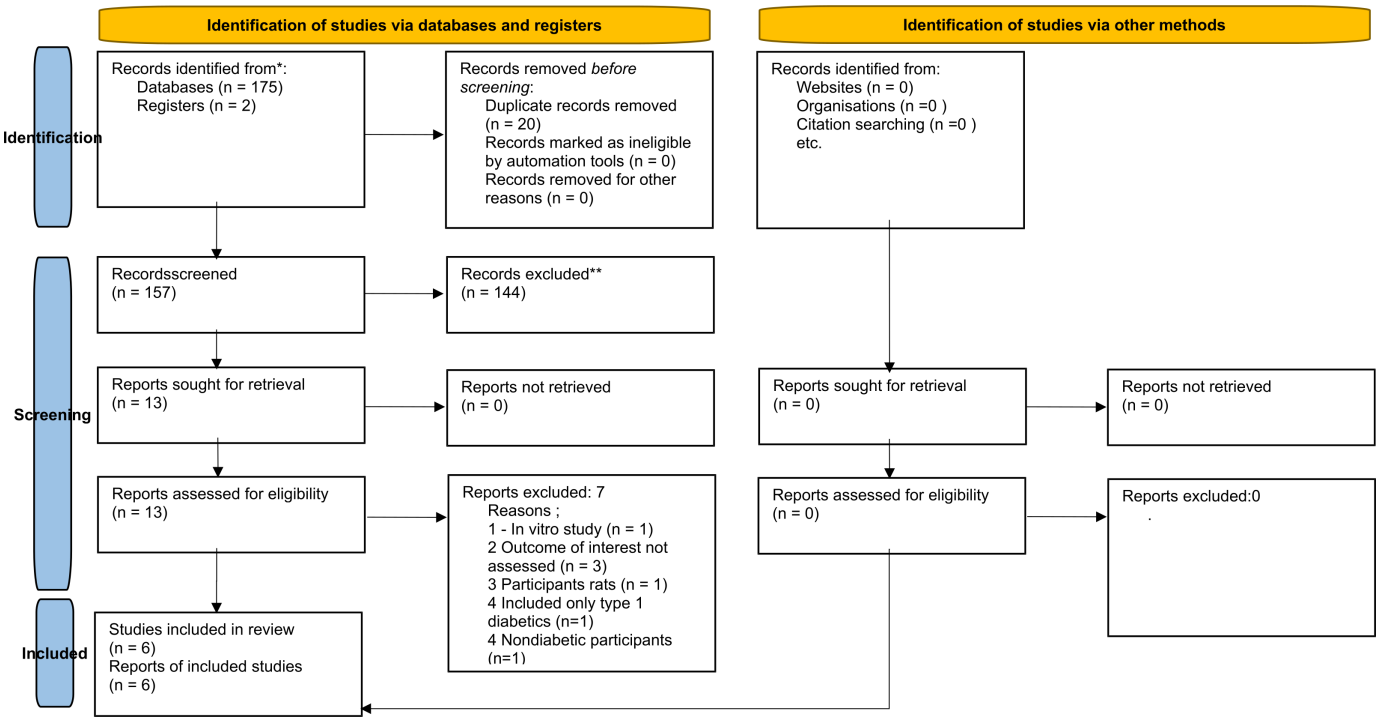

Figure 1 PRISMA 2009 flow diagram for searching. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **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/

Inclusion and exclusion criteria

We searched for RCTs and randomised cross-over trials that investigated the effect of thiamine or benfotiamine administered in any form (eg, tablets, capsules and 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 75 g oral glucose tolerance test 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 ≥200 mg/dL (11.1 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%), (2) FBG level and (3) PPG level 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 body mass index (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 Preferred Reporting Items for Systematic reviews and Meta-Analyses 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 texts of eligible studies were assessed for inclusion and critically appraised independently reviewed by two authors (AM and RF).

Data extraction

Quantitative data were 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 RCTs.[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 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 V.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% CI were calculated. Postintervention mean (SD) was used in meta-analysis. Statistical heterogeneity was assessed in the meta-analysis using the I^2 and χ^2 statistics, and heterogeneity was considered substantial if I^2 >50% and p value of <0.10 in the χ^2 test for heterogeneity.[36] A random-effects model was used in the meta-analysis. Subgroup-analyses 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 (figure 1). 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 online supplemental Appendix II) after examination of the full text against the inclusion criteria. Thus, finally six trials were included (online supplemental Appendix III in the systematic review).

Reasons for exclusion were as follows: 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]

Quality assessment

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

Overall, the quality of the trials was high, with scores ranging from 18/22[16] to 26/26[19] (table 1). While all trials reported that participants were randomised, the precise method of randomisation 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% 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 randomised and that data provided were unbiased. There was a wash-out period of 14 weeks between the interventions.

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] the 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]

Table 1 Assessment of methodological quality

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
Winkler *et al* 1999[16]	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz *et al* 2010[15]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke *et al* 2008[31]	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani *et al* 2009[19]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri *et al* 2013[43]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf *et al* 2010[29]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26

JBI critical appraisal checklist for randomised controlled trials: Q1: Was true randomisation 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 utilised? Q9: Were participants analysed in the groups to which they were randomised? 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 randomisation, parallel groups) accounted for in the conduct and analysis of the trial?
N=0, U=1, Y=2 points.
N, no; NA, not applicable; RCT, randomised controlled trials; U, unclear; Y, yes.

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

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

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 randomised? Q3: Can it be assumed that the trial was not biased from carry-over effects? Q4: Are unbiased data available?
N=0; Y=2; U=1 points.
N, no; NA, not applicable; RCT, randomised controlled trials; U, unclear; Y, yes.

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[43] to 300 mg/day,[19] and the dosage for benfotiamine ranged from 120[16] to 900 mg/day.[29] The follow-up period ranged from 1[15] to 3 months.[19 29]

FBG 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 are summarised in the table of included study characteristics (online supplemental 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.

Glycosylated haemoglobin

Comparison between thiamine supplementation versus placebo

Two trials[15 29] that investigated the effect of thiamine supplementation versus placebo on HbA1c levels demonstrated no statistically significant differences between the groups at less than 3-month follow-up period (mean difference, MD: −0.02%, 95% CI: −0.35 to 0.31) (figure 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 versus 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 with those who received placebo (MD, 0.19; 95% CI: −0.17 to 0.55) (figure 2). Similarly, the third study[31] reported no statistically significant differences in the HbA1c levels among those who received thiamine supplementation compared with those who received placebo.

Comparisons between various dosages of benfotiamine supplementation

One trial[16] that compared 320 and 120 mg/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 to 0.62). Similarly, there were no statistically significant differences in the HbA1c levels among those who received 320 mg/day benfotiamine compared with those who received 150 mg/day benfotiamine (MD, −0.50%; 95% CI: −1.10 to 0.10). There were also no statistically significant differences in the HbA1c levels among those who received 120 mg/day benfotiamine compared with those who received 150 mg/day benfotiamine (MD, −0.30; 95% CI: −1.09 to 0.49).

Fasting blood glucose

Comparison between thiamine supplementation versus placebo

Pooled results from three trials[15 19 43] demonstrated no statistically significant difference in the FBG level between those who received thiamine supplementation

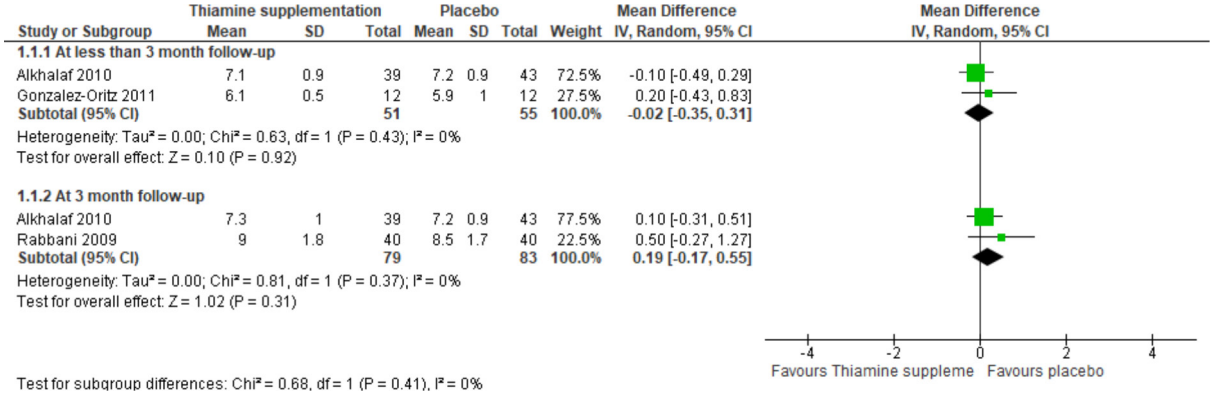

Figure 2 Effect of thiamine supplementation on HbA1c level at less than 3 months and at 3-month follow-up. HbA1c, glycosylated haemoglobin.

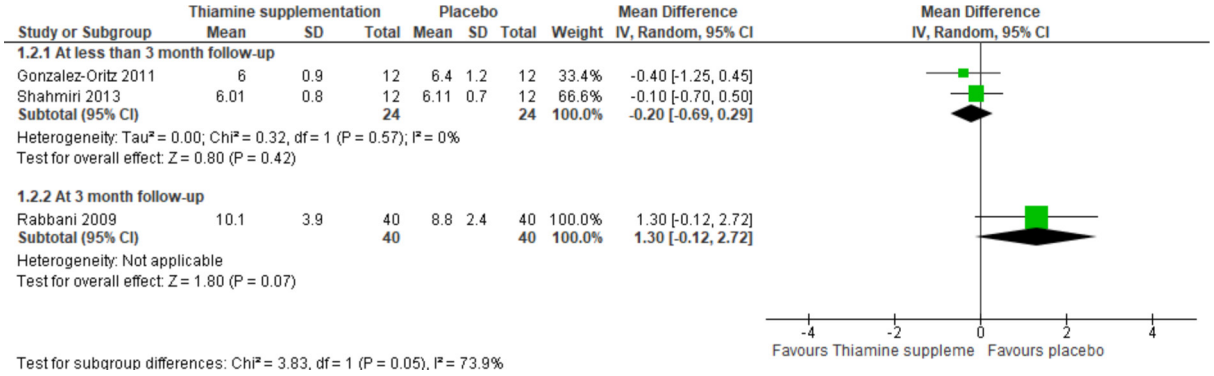

Figure 3 Effect on FBG at less than 3 months and at 3-month follow-up. FBG, fasting blood glucose.

versus placebo after less than 3 months of follow-up (MD, −0.20 mmol/L; CI: −0.69 to 0.29) (figure 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-month follow-up (MD, 1.30 mmol/L; CI: −0.12 to 2.72) (figure 3).

Comparisons between various dosages of benfotiamine supplementation

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

Postprandial blood glucose

Comparison between thiamine supplementation versus placebo

One trial[43] investigated the effect of thiamine supplementation versus 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 versus placebo on PPG levels.

Comparisons between various dosages of benfotiamine supplementation

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

High-density lipoprotein

Comparison between thiamine supplementation versus placebo

Three trials[15 19 29] investigated the effect of thiamine supplementation versus placebo on HDL levels. Pooled results demonstrated no statistically significant difference in the HDL levels between the groups at less than 3 months (MD, 0.10 mmol/L; CI: 0.10 to 0.30) (figure 4), but a statistically significant difference was seen (MD,

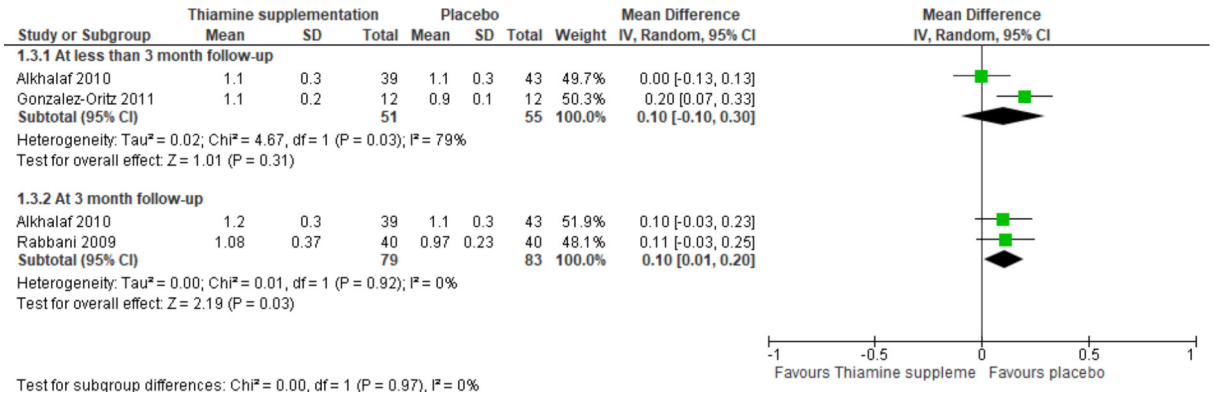

Figure 4 Effect on HDL at less than 3 months and at 3-month follow-up. HDL, high-density lipoprotein.

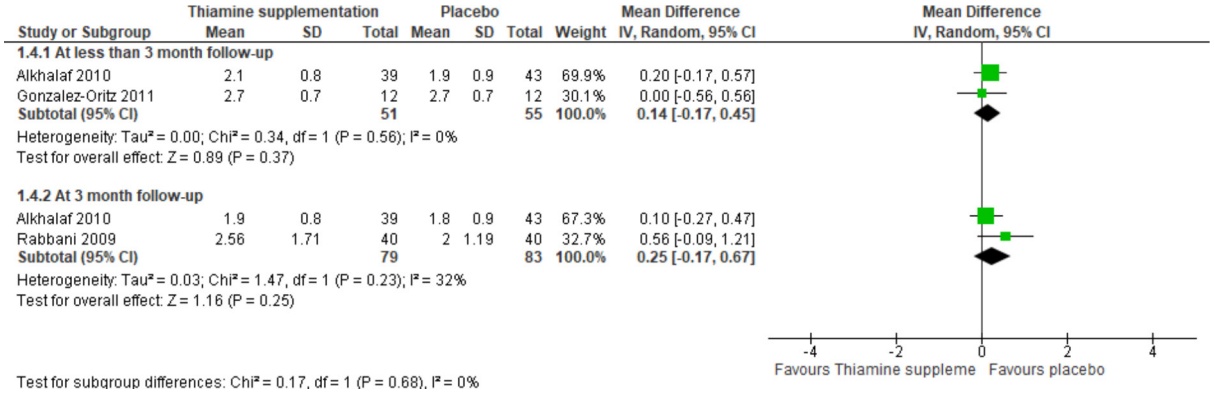

Figure 5 Effect on LDL at less than 3 months and at 3-month follow-up. LDL, low-density lipoprotein.

0.10 mmol/L; 95% CI: 0.01 to 0.20) at 3-month follow-up period (figure 4).

Comparisons between various dosages of benfotiamine supplementation

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

Low-density lipoprotein

Comparison between thiamine supplementation versus placebo

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

Triglycerides

Comparison between thiamine supplementation versus placebo

Three trials[15 19 29] investigated the effect of thiamine supplementation versus 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 to 0.04) (figure 6) as well as the 3-month follow-up period (MD, −0.40 mmol/L; CI: −0.89 to 0.09) (figure 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.

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 with those who received 120 mg/day benfotiamine (MD, 0.30 mmol/L; 95% CI: −0.46 to 1.06). Similarly, there were no statistically significant differences in the HbA1c levels among those who received 320 mg/day benfotiamine compared with those who received 150 mg/day benfotiamine (MD, −0.80 mmol/L; 95% CI: −1.64 to 0.04). HbA1c levels among those who

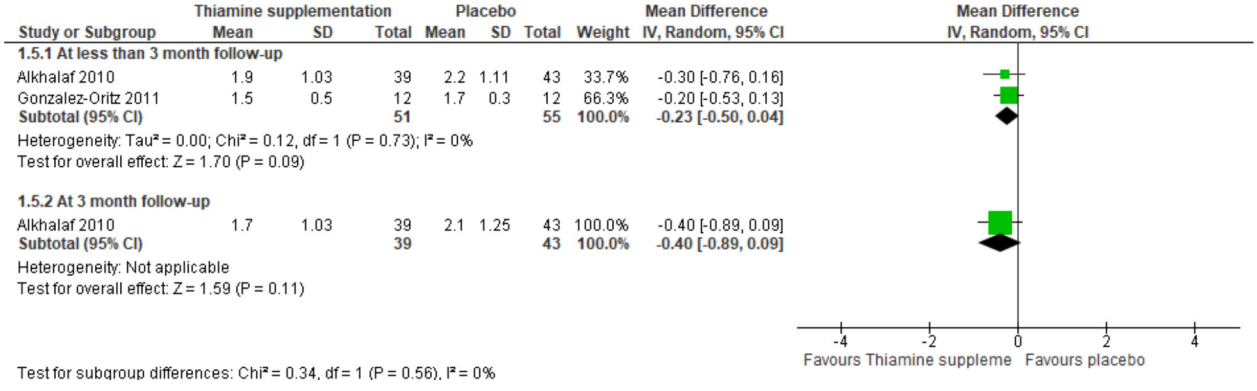

Figure 6 Effect on triglycerides at less than 3 months and at 3-month follow-up.

received 120 mg/day benfotiamine compared was significantly lower compared with those who received 150 mg/day benfotiamine (MD, −1.10 mmol/L; 95% CI: −1.90 to −0.30).

Body mass index

Comparison between thiamine supplementation versus placebo

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

Systolic BP

Comparison between thiamine supplementation versus placebo

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

Diastolic BP

Comparison between thiamine supplementation versus placebo

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

DISCUSSION

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100–900 mg/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 randomisation 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 0.2 mmol/L. Evidence from the literature indicates that a difference of 0.5% HbA1c and 1 mmol/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 T2DM patients receiving 100–900 mg/day thiamine or benfotiamine supplementation compared with those receiving placebo at less than 3 months or at 3-month follow-up. These results could be due the fact that the outcomes were assessed within 3 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 glycaemic outcomes.

A significant reduction in triglyceride level was demonstrated with a 120 mg/day benfotiamine dose compared with 150 mg/day dose. However, when compared with 320 mg/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.

CONCLUSIONS

This review demonstrates that there is no benefit of thiamine supplementation on glycaemic outcomes at doses 100–900 mg/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 glycaemic 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 glycaemic outcomes in T2DM patients.

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Competing interests None declared.

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

Patient consent for publication Not required.

Ethics approval Not applicable.

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double-blind, randomized, placebo-controlled trial. *Diabetes Care* 2012;35:1095–7.
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Appendix I: Search strategy

Search strategy for PubMed

No.	Search terms
1.	Diabetes Mellitus, Adult-Onset□ 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

Muley A, *et al. BMJ Open* 2022; 12:e059834. doi: 10.1136/bmjopen-2021-059834

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, Triglycerides 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, Triglycerides 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)		