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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059834
Article Type:	Original research
Date Submitted by the Author:	03-Dec-2021
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Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and metaanalysis  
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8 Running title: Type 2 Diabetes and thiamine  
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31 Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review  
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33 Word count:

34 Abstract: 244

35 Main text: 4868

36 No. of references: 52  
37  
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3 **TITLE:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and metaanalysis  
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7 **ABSTRACT**  
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10 **Objective:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose levels and prevent complications. This systematic review was done to evaluate  
13 effectiveness of thiamine supplementation on glycemc outcomes in patients with T2DM.  
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20 **Methods:** *Design:* RCTs and quasi-experimental studies that assessed effect of thiamine  
21 supplementation in adults with T2DM were considered. Trials which measured the glcemc  
22 outcomes - glycated haemoglobin (HbA1C), fasting blood glucose (FBG), and/or post  
23 prandial blood glucose (PPG) were included. Relevant studies were searched in PUBMED,  
24 Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database  
25 and Google Scholar. Studies obtained were uploaded in to Endnote X8. Two independent  
26 reviewers assessed methodological quality and data extracted. Studies, where possible, were  
27 pooled in a meta-analysis. Results are presented in a narrative format if statistical pooling  
28 was not possible.  
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41 **Results:** Total six trials involving 364 participants were included. No significant beneficial  
42 effects were observed on glycemc outcomes with 100 – 900 mg/day of Thiamine or  
43 benfotiamine for upto 3 months. However, significant increase in HDL was seen (MD 0.10;  
44 CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced triglyceride level (MD -1.10;  
45 95% CI -1.90,-0.30) when given in 120mg/day dose as compared to placebo 150mg/day, but  
46 not in higher doses.  
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56 **Conclusions:** Thiamine supplementation doesn't affect glycemc outcomes but reduces  
57 triglycerides while increasing HDL. Multicentre well designed randomised controlled trial  
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3 with higher doses of thiamine and 1-2 years follow up will give better idea regarding effect of  
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5 thiamine on glycaemic outcomes in T2DM.  
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8 **Strengths:** This systematic review addresses an important topic of control of diabetes with  
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10 thiamine supplementation and includes a few important secondary outcomes as well like LDL  
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12 and triglyceride levels. This is a systematic review of good quality RCTs, hence the results  
13  
14 can be relied upon to give direction to future research.  
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18 **Limitations:** This review includes single-centre trials published only in the English language.  
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20 Sample sizes of the included studies were small although some had addressed this issue using  
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22 statistical power. Furthermore, there was a lack of trials investigating the outcomes for some  
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24 comparisons. The follow-up period also varied and was short lasting that is, only for upto  
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26 three months.  
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30 **Summary:**  
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- 34 • Thiamine supplementation does not have any beneficial effect on sugar levels in  
35 patients of Type 2 DM.  
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  - 38 • Significant increase in HDL level is seen at three months follow-up.  
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  - 41 • Triglyceride levels also reduce significantly with 120 mg/day compared to 150  
42 mg/day benfotiamine.  
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48 **Key words:** Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review  
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## 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.<sup>1</sup> Type 2 diabetes mellitus was the cause of 4.2 million fatalities in 2019 globally.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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

1  
2  
3 reported that benfotiamine reduces glucose toxicity caused by hyperglycemia in diabetes  
4 mellitus (DM) by activating glucose metabolism and insulin synthesis.<sup>9</sup>It also has a role in  
5 blocking pathways responsible for hyperglycaemia induced damage, such as the hexosamine  
6 pathway, formation of Advanced Glycation End Products (AGEs) and activation of protein  
7 kinase C. Benfotiamine also works by activating transketolase which is the rate limiting  
8 enzyme of the non-oxidative branch of the pentose phosphate pathway.<sup>10</sup>  
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### 18 *How the intervention might work*

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21 Many studies have reported about 75% lower blood thiamine levels, low erythrocyte TK  
22 activity and high erythrocyte thiamine pyrophosphate (TPP) activity in type 2 DM  
23 patients<sup>11,14,122</sup> due to reduction in absorption of thiamine from the intestine and decreased  
24 membrane transport of thiamine<sup>15,16</sup> with an increased renal clearance and fractional excretion  
25 of thiamine<sup>133</sup>. In another study 18% of the participants showed lower thiamine concentration  
26 compared to the lower limit of the normal range.<sup>17</sup>  
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36 Although relatively low doses of thiamine saturate the thiamine transporter in the intestine,  
37 there is continuous slow passive diffusion at high concentration.<sup>18</sup> Based on this observation  
38 it has been suggested that high dose thiamine supplementation (20-50-fold the normal daily  
39 requirement) leads to the maximum TPP-saturated transketolase activity<sup>19</sup> and prevents  
40 hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial  
41 cells in vitro.<sup>20</sup> In women, thiamine intake has been shown to have a strong association with  
42 glucose tolerance.<sup>21</sup> Other studies have reported that thiamine decreased blood glucose  
43 concentration in one month<sup>22</sup> and glycosylated hemoglobin decreased significantly with  
44 benfotiamine therapy within 45 days.<sup>23</sup>  
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57 Many studies have investigated the association between fasting blood sugar (FBS), post  
58 prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C) and various vitamins  
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3 (including thiamine) and minerals<sup>13,15,17-25</sup> but with inconsistent results. Some studies  
4 reported significant inverse association for thiamine supplementation<sup>19-21,23</sup> while other  
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6 intervention studies did not find any significant association with thiamine.<sup>13,15,17,18,20,26</sup>  
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10 As dietary supplementation can be an easily feasible and an economic strategy to control  
11 sugar levels and prevent hyperglycemia related complications, we aim to conduct a  
12 systematic review and meta-analysis to find out the relationship of supplementation of  
13 thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A  
14 preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic  
15 Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was  
16 conducted and no systematic reviews were identified. Therefore, the question for the review  
17 is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including  
18 fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults  
19 with T2DM?  
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### 34 **Methods**

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36 The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI)  
37 methodology for systematic reviews of effectiveness evidence<sup>30</sup> by two independent reviewers  
38 using the Joanna Briggs Institute System for the Unified Management, Assessment and  
39 Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.<sup>31</sup> The  
40 proposed systematic review was registered in PROSPERO (Registration no.  
41 CRD42020170520).  
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#### 50 *Literature search strategy*

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53 The search strategy aimed to find both published and unpublished studies which included a  
54 three-step search strategy that was carried out in December 2019. An initial limited search of  
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3 blood glucose was undertaken. Text words contained in the title, abstract and index terms of  
4 the studies identified were used to inform the development of a search strategy for the second  
5 step which was tailored for each information source. Published studies were searched for  
6 including the databases: PUBMED, Tripdatabase and the Cochrane Central Register of  
7 Controlled Trials (CENTRAL) (The Cochrane Library). A full search strategy for the  
8 databases is detailed in Appendix I. The following databases were searched to find any  
9 unpublished studies: the National Institute of Health Clinical Database  
10 (<http://ClinicalTrials.gov>) and Google Scholar. The final step of the search strategy included  
11 a review of the reference list of all trials selected for critical appraisal. The search was  
12 restricted to papers published in the English language.  
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### 27 *Inclusion and exclusion criteria*

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30 We searched for randomised controlled trials and randomised cross-over trials that  
31 investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets,  
32 capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined as  
33 either: plasma glucose  $\geq 200$  mg/dl ( $\geq 11.1$  mmol/l) during a 75g oral glucose tolerance test  
34 (OGTT) or fasting plasma glucose  $\geq 126$  mg/dl ( $\geq 7.0$  mmol/dl) or HbA1c  $\geq 6.5\%$  (48  
35 mmol/mol) or in a person with typical symptoms of hyperglycaemia with a random plasma  
36 glucose of  $\geq 200$ mg/dL (11.1 mmol/L).Trials that included the following primary outcomes  
37 (1) HbA1c (%) (2) Fasting blood glucose level (FBG) (3) Postprandial blood glucose level  
38 (PPG) were included in the review. The following secondary outcomes were also included in  
39 the review: serum triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials  
40 in which the outcomes were measured in different units were included and results were  
41 converted to desired units for meta-analysis. Reviews, retrospective studies, observational  
42 studies, letters to the editors, and conference abstracts were excluded. Any discrepancies  
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2  
3 were resolved by discussion with a third author (HL). The results of the search is presented in  
4  
5 a PRISMA flow diagram (Figure 1).  
6  
7

### 8 9 *Screening*

10  
11 The titles and abstracts of all the identified citations were independently screened by two  
12  
13 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
14  
15 studies were assessed for inclusion and critically appraised independently reviewed by two  
16  
17 authors (AM and RF).  
18  
19

### 20 21 22 *Data extraction*

23  
24  
25 Quantitative data was extracted from all trials included in the review by two independent  
26  
27 reviewers (RF and HL) using the data extraction tool outlined in JBI SUMARI. The data  
28  
29 extracted included specific details about the type of intervention, populations, context, study  
30  
31 design and duration, study methods and other outcomes of significance to the review question  
32  
33 and specific objectives.  
34  
35

### 36 37 38 *Quality assessment*

39  
40  
41 Methodological quality was assessed using the standardized critical appraisal instruments  
42  
43 from the Joanna Briggs Institute for RCTs.<sup>30</sup> An additional risk of bias exists in cross-over  
44  
45 RCTs, therefore a further four questions were used to assess the methodological quality of  
46  
47 these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of  
48  
49 Interventions.  
50  
51

### 52 53 54 *Data synthesis and analysis*

55  
56  
57 Data from included studies were pooled in a statistical meta-analysis model using Review  
58  
59 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>32</sup> The continuous data  
60

1  
2  
3 extracted from the cross-over RCTs were treated as if from a parallel trial<sup>33</sup>. All pooled  
4  
5 statistics were subject to double data entry with two independent reviewers. For continuous  
6  
7 data, effect sizes are expressed as weighted mean differences and corresponding 95%  
8  
9 confidence intervals (CI) were calculated. Statistical heterogeneity was assessed in the meta-  
10  
11 analysis using the  $I^2$  and chi-squared statistics, and heterogeneity was considered substantial  
12  
13 if  $I^2 > 50\%$  and P value  $< 0.10$  in the chi-square test for heterogeneity.<sup>34</sup> A random effects  
14  
15 model was used in the meta-analysis. Subgroup-analysis according to type of intervention  
16  
17 and length of intervention period were performed. For results which were not possible to  
18  
19 present in a meta-analysis, the findings have been presented in a narrative form.  
20  
21  
22

#### 23 24 25 *Patient and public involvement:*

26  
27  
28 No patient involved.  
29

#### 30 31 **Results**

32  
33  
34 The search results identified 145 potential trials, with 127 potential trials remaining after  
35  
36 duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials  
37  
38 were identified for potential inclusion in the review. (Appendix II) The reference lists of the  
39  
40 11 trials were examined and full texts of a further two trials were obtained. From a total of 13  
41  
42 trials, seven trials were excluded after examination of the full text against the inclusion  
43  
44 criteria (see Appendix III). Thus, finally six trials were included in the systematic review.  
45  
46  
47 (Figure1)  
48

49  
50  
51 Reasons for exclusion were: participants type 1 diabetic<sup>35</sup> or non-diabetic<sup>36</sup>, in vitro study<sup>37</sup>,  
52  
53 did not assess the outcome of interest<sup>28,38,39</sup> and study done on rats.<sup>40</sup>  
54

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55  
56 Insert Figure1 here  
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### 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 <sup>24</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>34</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>25</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>48</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>32</sup>	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<sup>16</sup> to 26/26<sup>19</sup>

(Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>41</sup> 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 <sup>48</sup>	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<sup>15,16,19,27,29</sup> and one was cross-over RCT.<sup>41</sup> The six trials were conducted in six different countries – Germany<sup>29</sup>, Pakistan<sup>19</sup>, Netherlands<sup>27</sup>, Australia<sup>41</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>41</sup> to 165<sup>29</sup> 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.<sup>16,27</sup> One trial<sup>27</sup> had male predominance (77% vs 33%) while the other<sup>16</sup> had female predominance (61% vs 39%). The mean age of the patients ranged from 52 ± 8 years<sup>16</sup> to 65.3 ± 5.9 years.<sup>27</sup>

Five of the six trials compared the intervention to placebo and one trial<sup>16</sup> compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from

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2  
3 100 mg/day<sup>41</sup> to 300mg/day<sup>19</sup> and the dosage for benfotiamine ranged from 120mg/ day<sup>16</sup> to  
4  
5 900mg/day.<sup>27</sup>. The follow-up period ranged from 1 month<sup>15</sup> to 3 months.<sup>19,27</sup>  
6  
7

8 Fasting blood glucose was reported in four trials,<sup>15,16,19,41</sup> PPG in two trials,<sup>16,41</sup> HbA1c in five  
9 trials,<sup>15,16,19,27,29</sup> HDL in four trials,<sup>15,16,19,27</sup> LDL in three trials,<sup>15,19,27</sup> triglycerides in four  
10 trials,<sup>15,16,19,27</sup>, systolic and diastolic BP in three trials<sup>15,19,27</sup> and BMI in two trials.<sup>15,41</sup> Data  
11  
12 extracted from all trials is summarized in the table of included study characteristics  
13  
14 (Appendix III).  
15  
16  
17

## 18 **HbA1C**

### 19 *Comparison between Thiamine supplementation vs Placebo*

20  
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23  
24 Two trials<sup>15,27</sup> that investigated the effect of thiamine supplementation vs placebo on HbA1C  
25  
26 levels demonstrated no statistically significant differences between the groups at less than 3-  
27  
28 month follow-up period. (MD-0.02, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with  
29  
30 placebo was 5.9% and with thiamine was 5.88%.  
31  
32  
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34

35  
36 Three trials<sup>19,27,29</sup> investigated the effect of thiamine supplementation vs placebo on HbA1C  
37  
38 levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis.  
39  
40 Pooled data demonstrated no statistically significant differences in the HbA1C levels among  
41  
42 those who received thiamine supplementation compared to those who received placebo (MD  
43  
44 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study<sup>29</sup> reported no statistically  
45  
46 significant differences in the HbA1C levels among those who received thiamine  
47  
48 supplementation compared to those who received placebo.  
49  
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53 Insert Figure 2

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### 54 55 56 57 58 59 *Comparisons between various dosages of Benfotiamine supplementation*

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2  
3 One trial<sup>16</sup> that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level  
4 demonstrated no statistically significant differences in the HbA1C levels between the two  
5 groups (MD -0.20; 95% CI -1.02, 0.62). Similarly, there were no statistically significant  
6 differences in the HbA1C levels among those who received 320 mg/day benfotiamine  
7 compared to those who received 150 mg/day benfotiamine (MD -0.50; 95% CI -1.10, 0.10).  
8 There were also no statistically significant differences in the HbA1C levels among those who  
9 received 120 mg/day benfotiamine compared to those who received 150 mg/day  
10 benfotiamine (MD -0.30; 95% CI -1.09, 0.49).  
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## 22 **FBG**

### 23 *Comparison between Thiamine supplementation vs Placebo*

24  
25 Pooled results from three trials <sup>15,19,41</sup> demonstrated no statistically significant difference in  
26 the FBG level between those who received thiamine supplementation vs placebo after less  
27 than 3 months of follow-up (MD -0.20; CI -0.69, 0.29) (Fig 3). The absolute effect with  
28 placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no  
29 statistically significant difference in the FBG level between the groups after 3 months follow-  
30 up (MD 1.30; CI -0.12, 2.72) (Fig 3).  
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46 **Insert Fig 3 here**

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### 47 *Comparisons between various dosages of Benfotiamine supplementation*

48  
49 One trial<sup>16</sup> that compared 320mg/day and 120mg/day of benfotiamine on FBG levels  
50 demonstrated no statistically significant differences in the FBG levels among those who  
51 received 320 mg/day benfotiamine compared to those who received 120 mg/day  
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1  
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3 benfotiamine (MD 0.60; CI -0.93, 2.13). Similarly, there were no statistically significant  
4 differences in the FBG levels among those who received 320 mg/day benfotiamine compared  
5  
6 to those who received 150 mg/day benfotiamine (MD -0.20; CI -1.60, 1.20). There were also  
7  
8 no statistically significant differences in the FBG levels among those who received 120  
9  
10 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.80,  
11  
12  
13  
14  
15 CI -2.36, 0.76).

## 16 17 18 **PPG**

### 19 20 21 *Comparison between Thiamine supplementation vs Placebo*

22  
23 One trial<sup>41</sup> investigated the effect of thiamine supplementation vs placebo on PPG levels.  
24  
25 However, due to the paucity of the reported data, the authors were contacted to obtain further  
26  
27 information. No response was received from the authors hence we were unable to conclude  
28  
29 the effect of thiamine supplementation vs placebo on PPG levels.  
30  
31

### 32 33 34 *Comparisons between various dosages of benfotiamine supplementation*

35  
36 One trial<sup>16</sup> compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results  
37  
38 demonstrated no statistically significant differences in the PPG levels among those who  
39  
40 received 320 mg/day benfotiamine compared to those who received 120 mg/day  
41  
42 benfotiamine (MD - 0.20, CI -2.05, 1.65). Similarly, there were no statistically significant  
43  
44 differences in the PPG levels among those who received 320 mg/day benfotiamine compared  
45  
46 to those who received 150 mg/day benfotiamine (MD -0.20; CI -1.63, 1.23). There were also  
47  
48 no statistically significant differences in the PPG levels among those who received 120  
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50 mg/day benfotiamine compared to those who received 150 mg/day benfotiamine (MD 0.00;  
51  
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54  
55 CI -1.62, 1.62).

## HDL

### *Comparison between Thiamine supplementation vs Placebo*

Three trials <sup>15,19,27</sup> 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).

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**Insert Fig 4 here**

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial <sup>16</sup> 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 <sup>15,19,27</sup> 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).

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**Insert Fig 5**

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**Triglycerides***Comparison between Thiamine supplementation vs Placebo*

Three trials<sup>15,19,27</sup> 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.

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**Insert Fig 6**

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*Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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<sup>15,19,27</sup> 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.<sup>14</sup> 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<sup>42,43</sup> 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<sup>44</sup>.

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3 The results of the review also demonstrated no significant differences in FBG, , LDL, and  
4 BMI in T2DMpatients receiving 100 to 900 mg/day thiamine or benfotiamine  
5 supplementation compared to those receiving placebo at less than three months or at three  
6 months follow-up. These results could be due the fact that the outcomes were assessed within  
7 three months of administration of thiamine. It has been established that plasma thiamine level  
8 is associated with increased fractional excretion of thiamine resulting in decreased thiamine  
9 concentration by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore trials with longer term  
10 follow-up are required to assess the effect of thiamine on glycemc outcomes.  
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24 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
25 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
26 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
27 as the dose was escalated. This result should be interpreted with caution as these results are  
28 based on a single study with a sample size of 36 participants.  
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38 Various other factors could have influenced the results of the review including different  
39 populations and the presence of underlying health conditions which can cause high blood  
40 glucose despite thiamine supplementation. It has been shown that people with poorly  
41 controlled diabetes often experience micronutrient deficiencies <sup>45</sup>.Hence there is substantial  
42 interest globally to find easily accessible and inexpensive treatments such as thiamine  
43 supplementation for T2DM.  
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#### 54 *Limitations of this review*

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57 Despite summarising the evidence, several limitations of this review should be noted. Firstly,  
58 the review includes single-centre trials published only in the English language which limits  
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60

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3 the generalizability of the results. Sample sizes of the included studies were small although  
4  
5 some had addressed this issue using statistical power. Furthermore, there was a lack of trials  
6  
7 investigating the outcomes for some comparisons. The follow-up period also varied and was  
8  
9 short lasting that is, only for upto three months.  
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## 16 **Conclusions**

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19 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
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21 outcomes at doses 100mg/day to 900mg/day for up to 3 months. Until further research is  
22  
23 available practices will be dictated by existing policies and available resources. However,  
24  
25 some important points are identified like - the studies published this far have all been single  
26  
27 centric studies, with small sample size, using varying doses and follow-up for only 3 months.  
28  
29 Therefore, more robust multicentre well designed randomised controlled trial with higher  
30  
31 doses of thiamine for long enough follow-up of 1-2 years using sample size based on power  
32  
33 calculation should be undertaken to address the confusion regarding benefit of thiamine  
34  
35 supplementation on glyceic outcomes in T2DM. One such study if undertaken would be  
36  
37 able to give specific recommendations on whether or not to consider thiamine  
38  
39 supplementation for improving glyceic outcomes in T2DM patients.  
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48 *Ethics statement:* This study does not involve any human or animal participant.  
49

50  
51 *Funding:* No additional sources of funding.  
52

53  
54 *Disclosure of Interest:* The authors declare that they have no competing interests.  
55

56  
57 *Contribution:* All authors contributed to the study  
58  
59  
60

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3 AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data  
4  
5 acquisition and analysis; PM: Data collection, manuscript preparation.  
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8 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
9

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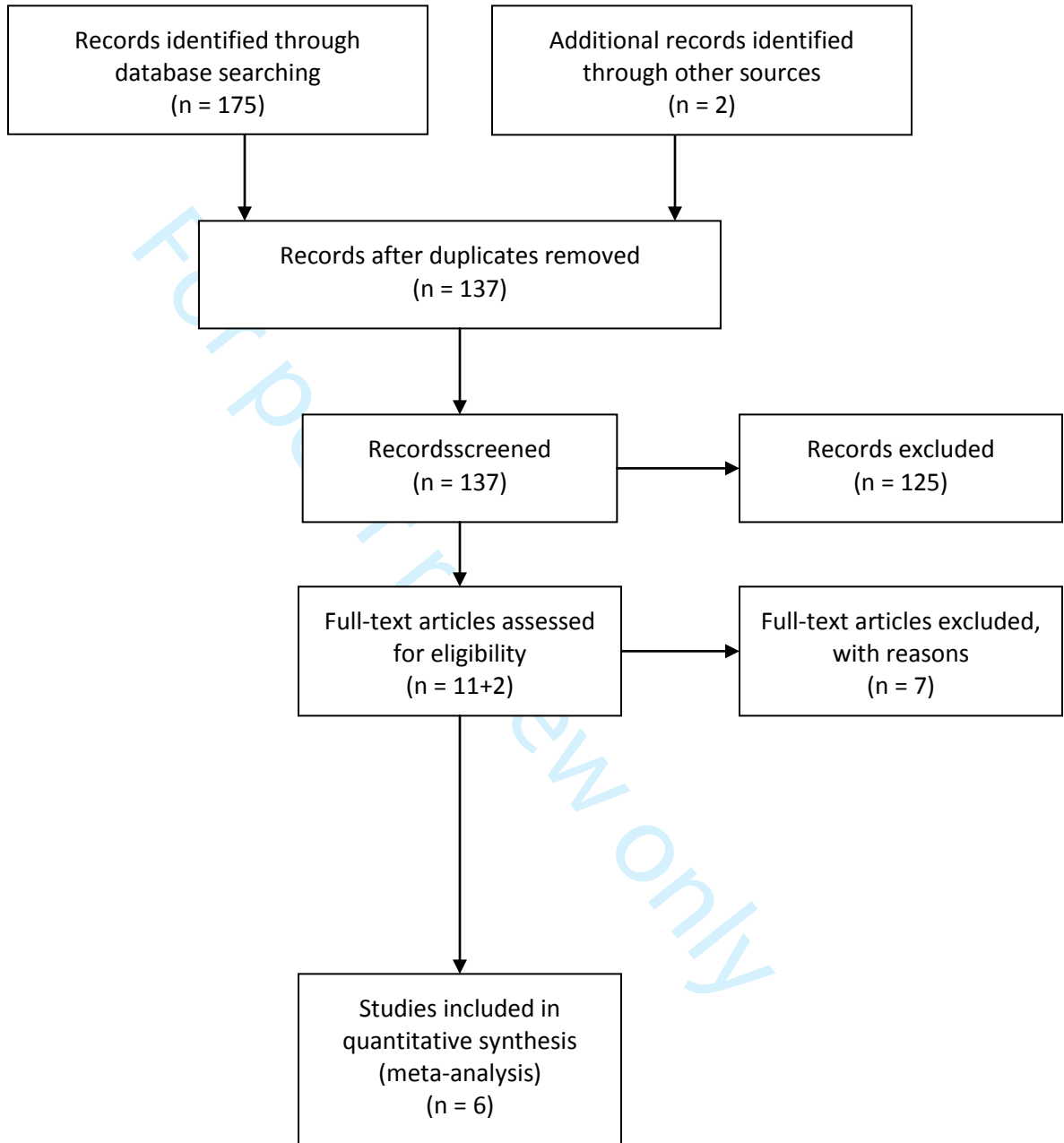
# PRISMA 2009 Flow Diagram<sup>57</sup>

Identification

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Eligibility

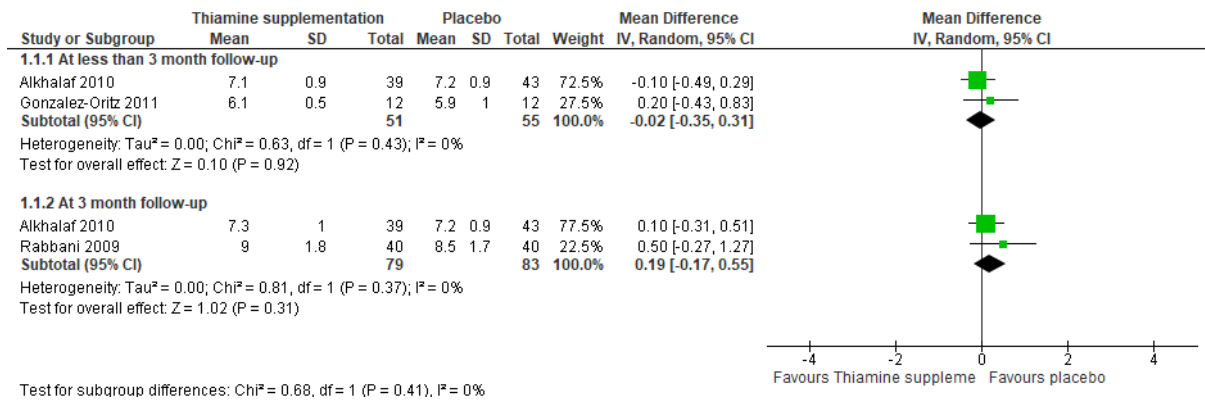
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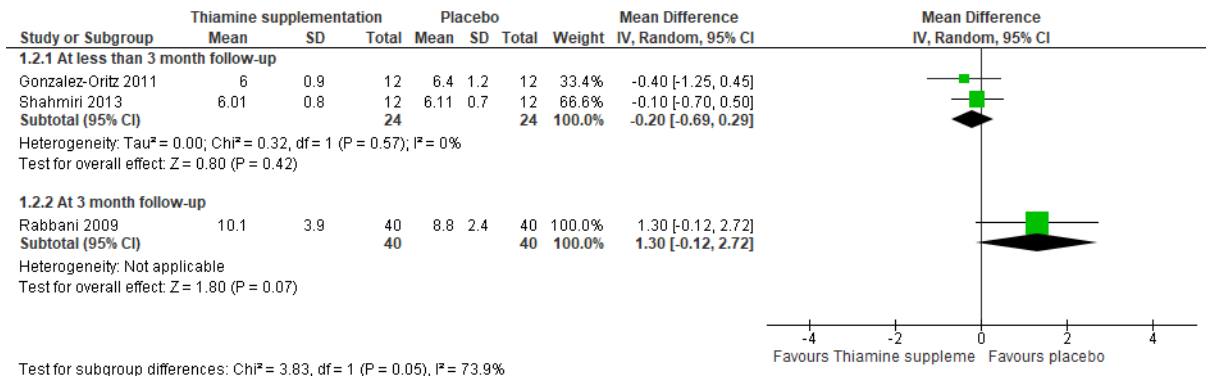
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

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

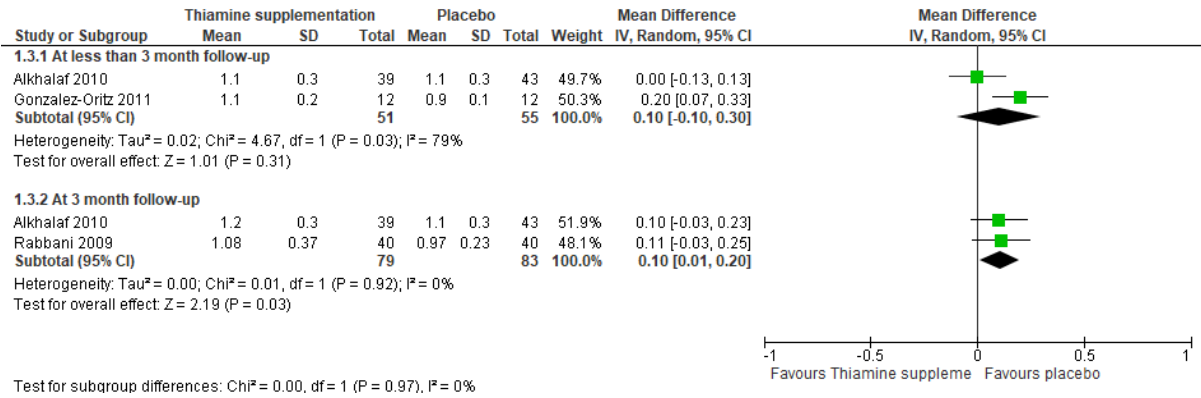


**Fig 3: Effect on FBG at less than 3 months and at 3 months follow up**

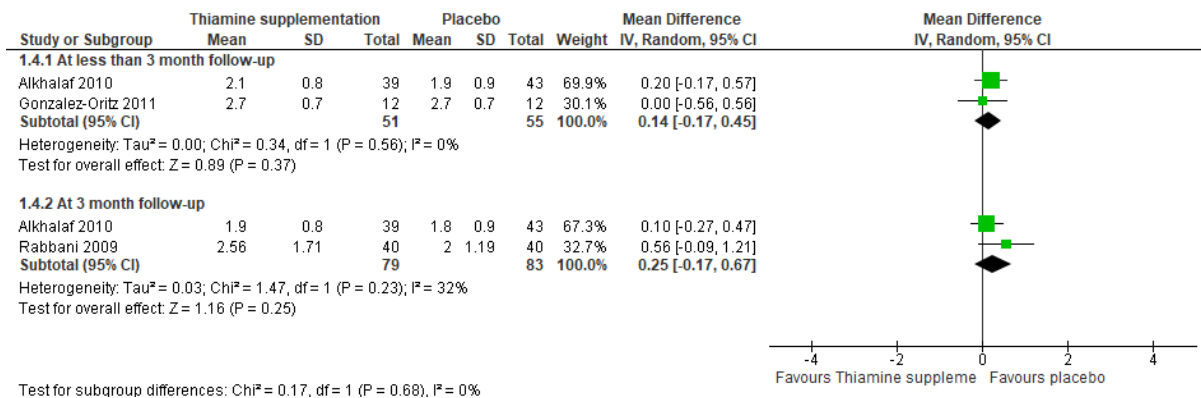


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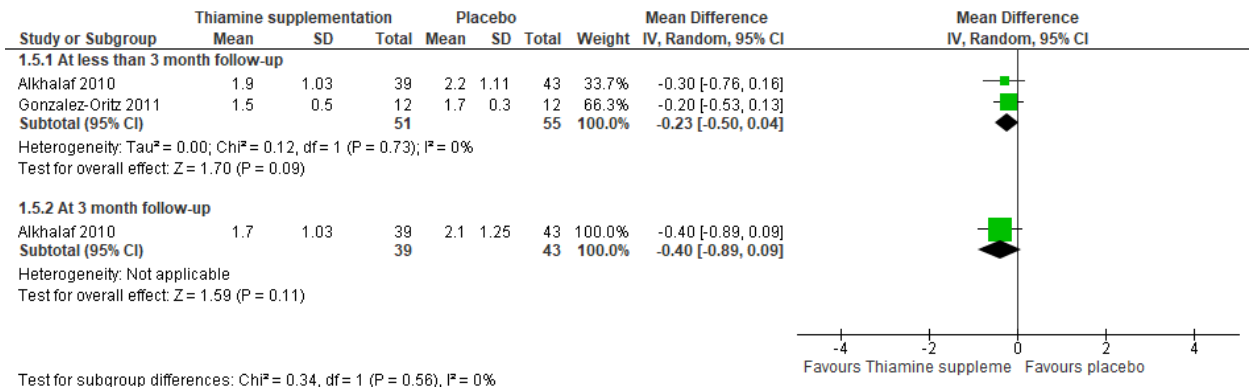
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**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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 <input type="checkbox"/> 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

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**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



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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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16 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
17 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
18 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

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

24 **Reason for exclusion: Outcome of interest not assessed.**  
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27 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
28 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

29 **Reason for exclusion: Participants rats.**  
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33 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
34 *Metabolic brain disease*. 1996;11(1):95-106.

35 **Reason for exclusion: Outcome of interest not assessed.**  
36

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

42 **Reason for exclusion: Included only type 1 diabetics.**  
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46 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
47 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
48 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

49 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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 $\geq 5$ years BMI 19–40 kg/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC, 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, FBC, 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

				<p>Group B: daily doses of only 3 x 1 capsules of the complex B-vitamin preparation (120mg/day benfotiamine)(n=12)</p> <p>Group C: pure benfotiamine (150mg/day benfotiamine)(n=12)</p>	
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## 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.<sup>1</sup> 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.<sup>1</sup> In the adult population, its prevalence has almost doubled from 4.7% to 8.5% in the last four decades.<sup>1</sup> In 1980, 108 million adults were reported to have diabetes. The figure increased to about 422 million in 2014<sup>1</sup> which is expected to be more than 592 million by 2035.<sup>2</sup>

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.<sup>5-7</sup> In 2012, it led to 59,258,034 disability adjusted life years (DALYs) and became the third most common cause of fatal complications.<sup>3</sup> From 1990 to 2013, the mortalities due to T2DM increased by 89.7% to make it the seventh leading cause of death.<sup>4</sup> Hence it is vital that prevention and/or optimal management strategies are implemented to reduce the effect of this global epidemic.

Thiamine (vitamin B1) was identified in 1926 by Jansen et al.<sup>8</sup> 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).<sup>9</sup> The pancreas also has high concentration of thiamine.<sup>10</sup> Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>11</sup> As a result, vitamin B1 deficiency leads to a marked decrease in synthesis and secretion of insulin.<sup>12-13</sup> In addition, high thiamine level is found in high fiber foods which have been reported to decrease postprandial glycemia in diabetic patients.<sup>14</sup>

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3 Benfotiamine is a type of allithiamine, a lipid soluble thiamine derivative which more efficiently raises  
4 thiamine level in blood as compared to the water soluble thiamine derivatives. It has been proved that it  
5 reduces glucose toxicity caused by hyperglycemia in DM by activating glucose metabolism and insulin  
6 synthesis.<sup>15</sup> It also has a role in blocking many pathways responsible for hyperglycaemia induced  
7 damage, e.g; the hexosamine pathway, formation of AGEs and activation of protein kinase C. It also  
8 works by activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
9 pentose phosphate pathway.<sup>16</sup>

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

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

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

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3 As dietary supplementation can be an easily feasible and economic strategy to control sugar levels and  
4 prevent hyperglycemia related complications, we aim to do a systematic review and metaanalysis to find  
5 out the relationship of supplementation of vitamin B1 or Benfotiamine with FBS, PP2BS and HbA1c  
6 concentrations in adults. During the initial search, about 10 RCTs which addressed the study question  
7 were identified. However, no systematic review has addressed this question as yet. Considering the  
8 relevance of this topic, this systematic review will provide updated evidence for the effect of thiamine  
9 supplementation on glycaemic outcomes.  
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## 14 **Keywords**

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17 Type 2 diabetes mellitus, vitamin B1, benfotiamine, glycaemic control, HbA1C.  
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## 20 **Inclusion criteria**

### 21 **Participants**

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23 The review will consider studies in which participants aged more than 18 years received thiamine or  
24 benfotiamine supplementation and effect of this supplementation on FBS or PP2BS or HbA1C was  
25 assessed as an outcome. Studies will be included irrespective of the prediabetic or diabetic status of their  
26 population.  
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### 30 **Intervention(s)**

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32 This review will consider studies that evaluate the effect of thiamine supplementation on levels of blood  
33 glucose in adults.  
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### 36 **Comparator(s)**

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38 This review will compare the studies that compare the intervention to any other treatments, placebo or  
39 control products such as other dietary supplements.  
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### 42 **Outcomes**

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44 Studies that have reported outcome in terms of fasting blood sugar (FBS), postprandial blood sugar  
45 (PP2BS) and/or glycated hemoglobin (HbA1C) will be included.  
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### 48 **Types of studies**

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50 This review will include only experimental studies that are randomized controlled trials. Studies complying  
51 with the inclusion criteria, published in English, and published as far back as possible will be included.  
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## 54 **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 and vitamin 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 independent reviewers will then screen 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.<sup>45</sup> 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<sup>46</sup> to find good quality studies to be include in the review. The three reviewers will discuss the points of disagreements to reach a consensus. 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<sup>46</sup> will be used to decide whether random or fixed effects model will be used for meta-analysis.<sup>7</sup> 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.<sup>47</sup>

## Assessing certainty in the findings

A 'summary of findings' table will be created using GRADEPro GDT software.<sup>48</sup> 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

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3 None  
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## 6 **Conflicts of interest**

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8 None  
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## PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Title, Pg 1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction 2 <sup>nd</sup> 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
<b>METHODS</b>			
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)). For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	Methods data synthesis and analysis, Pg 7-8



PRISMA 2020 Checklist

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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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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.	
<b>OTHER INFORMATION</b>			
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.	Disclosure 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

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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2  
3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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8 Running title: Type 2 Diabetes and thiamine  
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10 Authors:

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28  
29  
30

31 Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review  
32

33 Word count:

34 Abstract: 244

35 Main text: 4868

36 No. of references: 52  
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3 **TITLE:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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7 **ABSTRACT**  
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10 **Objective:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose levels and prevent complications. The aim of this systematic review was to evaluate  
13 effectiveness of thiamine supplementation on glycemc outcomes in patients with T2DM.  
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20 **Methods:** A three-step search strategy to locate RCTs was conducted in PUBMED,  
21 Tripdatabase, the Cochrane Central Register, National Institute of Health Clinical Database  
22 and Google Scholar from database inception until December 2019. Studies that assessed  
23 effect of thiamine supplementation in adults with T2DM were considered for inclusion.  
24 Studies that measured glycemc outcomes - glycated haemoglobin (HbA1C), fasting blood  
25 glucose (FBG), and/or post prandial blood glucose (PPG) were included. Two independent  
26 reviewers assessed methodological quality and data extracted. Where possible, studies were  
27 pooled in a meta-analysis. Results were presented in a narrative format if statistical pooling  
28 was not possible.  
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41 **Results:** Six trials involving 364 participants were included. No significant beneficial effects  
42 were observed on glycemc outcomes with 100 – 900 mg/day of Thiamine or benfotiamine  
43 for up to 3 months (HbA1C: MD -0.02 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -  
44 0.69, 0.29; PPG : MD – 0.20 mmol/l, CI -2.05, 1.65). However, there was a significant  
45 increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months follow-up. Benfotiamine reduced  
46 triglyceride level (MD -1.10; 95% CI -1.90,-0.30) when given in 120mg/day dose as  
47 compared to placebo 150mg/day, however this was not demonstrated in higher doses.  
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3 **Conclusions:** Thiamine supplementation was found to not affect glycaemic outcomes,  
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5 however reduces triglycerides while increasing HDL. Multicentre well designed randomised  
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7 controlled trial with higher doses of thiamine and with a follow-up period of 1-2 will provide  
8  
9 further evidence regarding the effect of thiamine on glycaemic outcomes in T2DM.  
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13 **Strengths:** This systematic review addresses an important topic on the control of diabetes  
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15 with thiamine supplementation, including important secondary outcomes such as LDL and  
16  
17 triglyceride levels. The inclusion of good quality RCTs ensures the results are robust and  
18  
19 provide evidence for diabetes management and direction of future research.  
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23 **Limitations:** This review includes single-centre trials published only in the English language.  
24  
25 Sample sizes of the included studies were small although some had addressed this issue with  
26  
27 statistical power. Furthermore, there was a lack of trials investigating the outcomes for some  
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29 comparisons. The follow-up periods also varied among trials with some trials having a  
30  
31 limited follow-up period of only up to three months.  
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35 **Summary:**  
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38 • Thiamine supplementation does not have any beneficial effect on sugar levels in  
39  
40 patients of Type 2 DM.  
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44 • Significant increase in HDL level is seen at three months follow-up.  
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- 47  
48 • Triglyceride levels also reduce significantly with 120 mg/day compared to 150  
49  
50 mg/day benfotiamine.  
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52  
53 Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review  
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## 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.<sup>1</sup>

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.<sup>2</sup> It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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.<sup>9</sup> It also has a role in blocking pathways responsible for

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3 hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced  
4 Glycation End Products (AGEs) and activation of protein kinase C. It also works by  
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6 activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
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8 pentose phosphate pathway.<sup>10</sup>  
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### 12 13 *How the intervention might work*

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

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Although relatively low doses of thiamine saturate the thiamine transporter in the intestine,  
there is continuous slow passive diffusion at high concentration.<sup>18</sup> 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<sup>19</sup> and prevents  
hyperglycaemia - induced delayed replication of human umbilical and retinal endothelial  
cells in vitro.<sup>20</sup> In women, thiamine intake has been shown to have a strong association with  
glucose tolerance.<sup>21</sup> Other studies have reported that thiamine decreased blood glucose  
concentration in one month<sup>22</sup> and glycosylated hemoglobin decreased significantly with  
benfotiamine therapy within 45 days.<sup>23</sup>

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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<sup>13,15,17-25</sup> but with  
inconsistent results. Some studies reported significant inverse association for thiamine

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3 supplementation<sup>19-21,23</sup> while other intervention studies did not find any significant association  
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5 with thiamine.<sup>13,15,17,18,20,26</sup>  
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8 As dietary supplementation can be an easily feasible and an economic strategy to control  
9  
10 sugar levels and prevent hyperglycemia related complications, we aim to conduct a  
11  
12 systematic review and meta-analysis to find out the relationship of supplementation of  
13  
14 thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A  
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16 preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic  
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18 Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was  
19  
20 conducted and no systematic reviews were identified. Therefore, the question for the review  
21  
22 is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including  
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24 fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults  
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26 with T2DM?  
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### 31 **Methods**

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34 The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI)  
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36 methodology for systematic reviews of effectiveness evidence<sup>30</sup> by two independent reviewers  
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38 using the Joanna Briggs Institute System for the Unified Management, Assessment and  
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40 Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.<sup>31</sup> The  
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42 proposed systematic review was registered in PROSPERO (Registration no.  
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44 CRD42020170520).  
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#### 48 *Literature search strategy*

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51 The search strategy aimed to find both published and unpublished studies which included a  
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53 three-step search strategy to include all relevant articles published till 31<sup>st</sup> December 2019..  
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55 An initial limited search of PUBMED using the keywords: vitamin B1, thiamine,  
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57 benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in  
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3 the title, abstract and index terms of the studies identified were used to inform the  
4 development of a search strategy for the second step which was tailored for each information  
5 source. Published studies were searched for including the databases: PUBMED, Tripdatabase  
6 and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library).  
7  
8 A full search strategy for the databases is detailed in Appendix I. The following databases  
9 were searched to find any unpublished studies: the National Institute of Health Clinical  
10 Database (<http://ClinicalTrials.gov>) and Google Scholar. The final step of the search strategy  
11 included a review of the reference list of all trials selected for critical appraisal. The search  
12 was restricted to papers published in the English language.  
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### 25 *Inclusion and exclusion criteria*

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27 We searched for randomised controlled trials and randomised cross-over trials that  
28 investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets,  
29 capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined  
30 based on ADA (American Diabetes Association) guidelines as either: plasma glucose  $\geq 200$   
31 mg/dl ( $\geq 11.1$  mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma  
32 glucose  $\geq 126$  mg/dl ( $\geq 7.0$  mmol/dl) or HbA1c  $\geq 6.5\%$  (48 mmol/mol) or in a person with  
33 typical symptoms of hyperglycaemia with a random plasma glucose of  $\geq 200$ mg/dL (11.1  
34 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting  
35 blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the  
36 review. The following secondary outcomes were also included in the review: serum  
37 triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the  
38 outcomes were measured in different units were included and results were converted to  
39 desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters  
40 to the editors, and conference abstracts were excluded. Any discrepancies were resolved by  
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3 discussion with a third author (HG). The results of the search is presented in a PRISMA flow  
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5 diagram (Figure 1).  
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### 8 9 *Screening*

10  
11 The titles and abstracts of all the identified citations were independently screened by two  
12  
13 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
14  
15 studies were assessed for inclusion and critically appraised independently reviewed by two  
16  
17 authors (AM and RF).  
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### 20 21 22 *Data extraction*

23  
24 Quantitative data was extracted from all trials included in the review by two independent  
25  
26 reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data  
27  
28 extracted included specific details about the type of intervention, populations, context, study  
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30 design and duration, study methods and other outcomes of significance to the review question  
31  
32 and specific objectives.  
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### 36 37 38 *Quality assessment*

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40 Methodological quality was assessed using the standardized critical appraisal instruments  
41  
42 from the Joanna Briggs Institute for RCTs.<sup>30</sup> An additional risk of bias exists in cross-over  
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44 RCTs, therefore a further four questions were used to assess the methodological quality of  
45  
46 these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of  
47  
48 Interventions.  
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### 51 52 53 *Data synthesis and analysis*

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55 Data from included studies were pooled in a statistical meta-analysis model using Review  
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57 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>32</sup> The continuous data  
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3 extracted from the cross-over RCTs were treated as if from a parallel trial<sup>33</sup>. All pooled  
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5 statistics were subject to double data entry with two independent reviewers. For continuous  
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7 data, effect sizes are expressed as mean differences and corresponding 95% confidence  
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9 intervals (CI) were calculated. Statistical heterogeneity was assessed in the meta-analysis  
10  
11 using the  $I^2$  and chi-squared statistics, and heterogeneity was considered substantial if  $I^2 > 50\%$   
12  
13 and P value  $< 0.10$  in the chi-square test for heterogeneity.<sup>34</sup> A random effects model was used  
14  
15 in the meta-analysis. Subgroup-analysis according to type of intervention and length of  
16  
17 intervention period were performed. For results which were not possible to present in a meta-  
18  
19 analysis, the findings have been presented in a narrative form.  
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#### 23 24 25 *Patient and public involvement:*

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28 No patient involved.  
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#### 30 31 **Results**

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34 The search results identified 145 potential trials, with 127 potential trials remaining after  
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36 duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials  
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38 were identified for potential inclusion in the review. (Appendix II) The reference lists of the  
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40 11 trials were examined and full texts of a further two trials were obtained. From a total of 13  
41  
42 trials, seven trials were excluded after examination of the full text against the inclusion  
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44 criteria (see Appendix III). Thus, finally six trials were included in the systematic review.  
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46  
47 (Figure1)

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50 Reasons for exclusion were: participants type 1 diabetic<sup>35</sup> or non-diabetic<sup>36</sup>, in vitro study<sup>37</sup>,  
51  
52 did not assess the outcome of interest<sup>28,38,39</sup> and study done on rats.<sup>40</sup>  
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55  
56 Insert Figure1 here  
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### 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 <sup>24</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>34</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>25</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>48</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>32</sup>	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<sup>16</sup> to 26/26<sup>19</sup>

(Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>41</sup> 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 <sup>48</sup>	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<sup>15,16,19,27,29</sup> and one was cross-over RCT.<sup>41</sup> The six trials were conducted in six different countries – Germany<sup>29</sup>, Pakistan<sup>19</sup>, Netherlands<sup>27</sup>, Australia<sup>41</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>41</sup> to 165<sup>29</sup> 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.<sup>16,27</sup> One trial<sup>27</sup> had male predominance (77% vs 33%) while the other<sup>16</sup> had female predominance (61% vs 39%). The mean age of the patients ranged from 52 ± 8 years<sup>16</sup> to 65.3 ± 5.9 years.<sup>27</sup>

Five of the six trials compared the intervention to placebo and one trial<sup>16</sup> compared various dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from



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3 100 mg/day<sup>41</sup> to 300mg/day<sup>19</sup> and the dosage for benfotiamine ranged from 120mg/ day<sup>16</sup> to  
4  
5 900mg/day.<sup>27</sup>. The follow-up period ranged from 1 month<sup>15</sup> to 3 months.<sup>19,27</sup>  
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8 Fasting blood glucose was reported in four trials,<sup>15,16,19,41</sup> PPG in two trials,<sup>16,41</sup> HbA1c in five  
9 trials,<sup>15,16,19,27,29</sup> HDL in four trials,<sup>15,16,19,27</sup> LDL in three trials,<sup>15,19,27</sup> triglycerides in four  
10 trials,<sup>15,16,19,27</sup>, systolic and diastolic BP in three trials<sup>15,19,27</sup> and BMI in two trials.<sup>15,41</sup> Data  
11  
12 extracted from all trials is summarized in the table of included study characteristics  
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14 (Appendix III).  
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### 18 *Heterogeneity among studies*

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24 *Heterogeneity measured was insignificant ( $I^2 < 50\%$ ) for all parameters except FBG which*  
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26 *was accounted for by using random effects model for meta-analysis.*  
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## 29 **HbA1C**

### 30 *Comparison between Thiamine supplementation vs Placebo*

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35 Two trials<sup>15,27</sup> that investigated the effect of thiamine supplementation vs placebo on HbA1C  
36 levels demonstrated no statistically significant differences between the groups at less than 3-  
37 month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with  
38 placebo was 5.9% and with thiamine was 5.88%.  
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45 Three trials<sup>19,27,29</sup> investigated the effect of thiamine supplementation vs placebo on HbA1C  
46 levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis.  
47 Pooled data demonstrated no statistically significant differences in the HbA1C levels among  
48 those who received thiamine supplementation compared to those who received placebo (MD  
49 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study<sup>29</sup> reported no statistically  
50 significant differences in the HbA1C levels among those who received thiamine  
51 supplementation compared to those who received placebo.  
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Insert Figure 2

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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; 95% CI -1.09, 0.49).

### **FBG**

#### *Comparison between Thiamine supplementation vs Placebo*

Pooled results from three trials<sup>15,19,41</sup> 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).

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**Insert Fig 3 here**

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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 mmol/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<sup>41</sup> 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<sup>16</sup> 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

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3 who received 120 mg/day benfotiamine compared to those who received 150 mg/day  
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5 benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).  
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## 10 11 **HDL**

### 12 13 14 *Comparison between Thiamine supplementation vs Placebo*

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

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### 31 32 33 *Comparisons between various dosages of Benfotiamine supplementation*

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36 One trial <sup>16</sup> compared two dosages of Benfotiamine demonstrated no statistically significant  
37 differences in the HDL levels among those who received 320 mg/day benfotiamine compared  
38 to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36 ).  
39  
40 Similarly, there were no statistically significant differences in the HDL levels among those  
41 who received 320 mg/day benfotiamine compared to those who received 150 mg/day  
42 benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant  
43 differences in the HDL levels among those who received 120 mg/day benfotiamine compared  
44 to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).  
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## 54 55 **LDL**

### 56 57 58 *Comparison between Thiamine supplementation vs Placebo*

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

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**Triglycerides***Comparison between Thiamine supplementation vs Placebo*

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25 Three trials <sup>15,19,27</sup> investigated the effect of thiamine supplementation vs placebo on  
26 triglyceride levels. The results demonstrated no statistically significant differences in the  
27 triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04)  
28 (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) .  
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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.

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**Insert Fig 6**

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*Comparisons between various dosages of Benfotiamine supplementation*

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One trial<sup>16</sup> 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

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3 HbA1C levels among those who received 320 mg/day benfotiamine compared to those who  
4 received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels  
5  
6 among those who received 120 mg/day benfotiamine compared was significantly lower  
7  
8 compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -  
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10 1.90,-0.30)  
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## 14 15 **BMI**

### 16 17 18 *Comparison between Thiamine supplementation vs Placebo*

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21 Three trials <sup>15,19,27</sup> investigated the effect of thiamine supplementation vs placebo on BMI  
22  
23 levels. Pooled results demonstrated no statistically significant differences in the BMI levels  
24  
25 between the groups at less than 3 month (MD -0.22 kg/m<sup>2</sup>; 95% CI -2.23, 1.79).  
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## 29 **Systolic BP**

### 30 31 32 *Comparison between Thiamine supplementation vs Placebo*

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35 Three trials <sup>15,25,32</sup> investigated the effect of thiamine supplementation vs placebo on systolic  
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37 BP levels. Pooled results demonstrated no statistically significant differences in the systolic  
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39 BP levels between the groups at less than 3 month (MD 2.08 mmHg; 95% CI -3.34, 7.50) as  
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41 well as the 3 month follow up period (MD 0.82 mmHg; 95% CI -4.67, 6.30).  
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## 45 **Diastolic BP**

### 46 47 48 *Comparison between Thiamine supplementation vs Placebo*

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

Plasma thiamine levels have been reported to be 75% lower in patients with T2DM.<sup>14</sup> 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<sup>42,43</sup> 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<sup>44</sup>.

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

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3 is associated with increased fractional excretion of thiamine resulting in decreased thiamine  
4 concentration by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore, trials with longer term  
5 follow-up are required to assess the effect of thiamine on glycaemic outcomes.  
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12 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
13 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
14 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
15 as the dose was escalated. This result should be interpreted with caution as these results are  
16 based on a single study with a sample size of 36 participants.  
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26 Various other factors could have influenced the results of the review including different  
27 populations in different studies (with different diabetes risk) and the presence of underlying  
28 health conditions (like presence of autoimmune diseases) which can cause high blood glucose  
29 despite thiamine supplementation. It has been shown that people with poorly controlled  
30 diabetes often experience micronutrient deficiencies <sup>45</sup>. Hence there is substantial interest  
31 globally to find easily accessible and inexpensive treatments such as thiamine  
32 supplementation for T2DM.  
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#### 45 *Limitations of this review*

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47 Despite summarising the evidence, several limitations of this review should be noted. Firstly,  
48 the review includes single-centre trials published only in the English language which limits  
49 the generalizability of the results. Sample sizes of the included studies were small although  
50 some had addressed this issue using statistical power. Furthermore, there was a lack of trials  
51 investigating the outcomes for a variety of comparisons, further trials are needed to  
52 investigate multiple comparisons. Additionally, the follow-up period varied among trials  
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3 with some having a short period of only up to three months, which may limit the effect of the  
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5 intervention and results.  
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## 11 **Conclusions**

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14 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
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16 outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to  
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18 change practices. Therefore, existing practices will be dictated by current policies. However,  
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20 some important points have been identified such as, the studies published to date have been  
21  
22 single centric studies, with small sample size, varying doses and follow-up for only 3 months.  
23  
24 Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer  
25  
26 follow-up of 1-2 years using sample size based on power calculation should be undertaken to  
27  
28 address the confusion regarding benefit of thiamine supplementation on glycemic outcomes  
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30 in T2DM. One such study if undertaken would be able to give specific recommendations on  
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32 whether or not to consider thiamine supplementation for improving glycemic outcomes in  
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34 T2DM patients.  
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43 *Ethics statement:* This study does not involve any human or animal participant.  
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45  
46 *Funding:* No additional sources of funding.  
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48  
49 *Data availability:* No additional data available.  
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52 *Disclosure of Interest:* The authors declare that they have no competing interests.  
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55 *Contribution:* All authors contributed to the study  
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3 AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data  
4 acquisition and analysis; PM: Data collection, manuscript preparation.  
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8 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
9

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4 supplementation on peripheral nerve function and inflammatory markers in patients with type  
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13 longitudinal association with HbA1c levels in the general non-diabetic population—results  
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20 Figure Legends:  
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23 Fig 1: PRISMA 2009 Flow Diagram for searching  
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26 Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3  
27 months follow up.  
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30 Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.  
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33 Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.  
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36 Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.  
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39 Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up  
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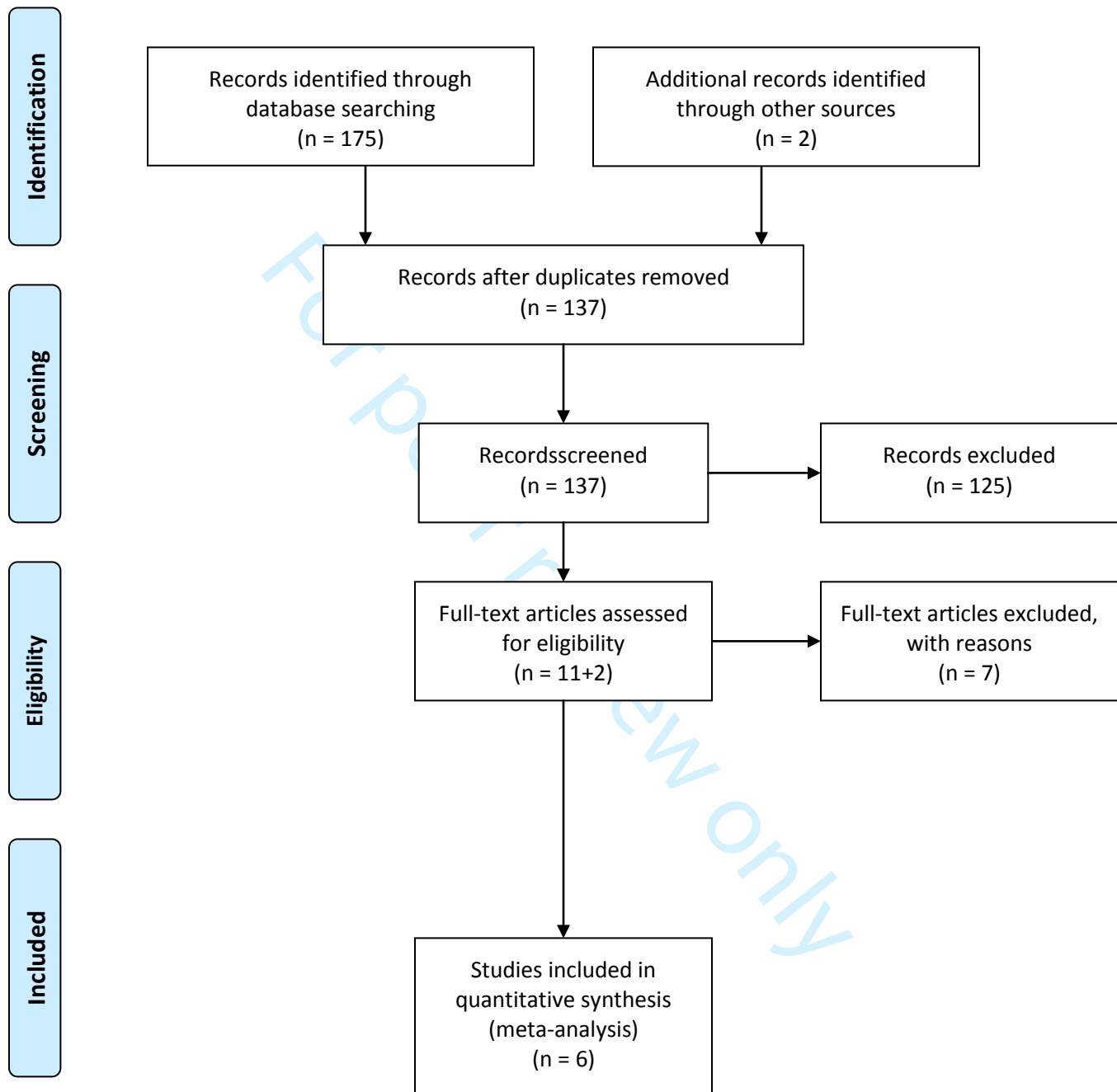


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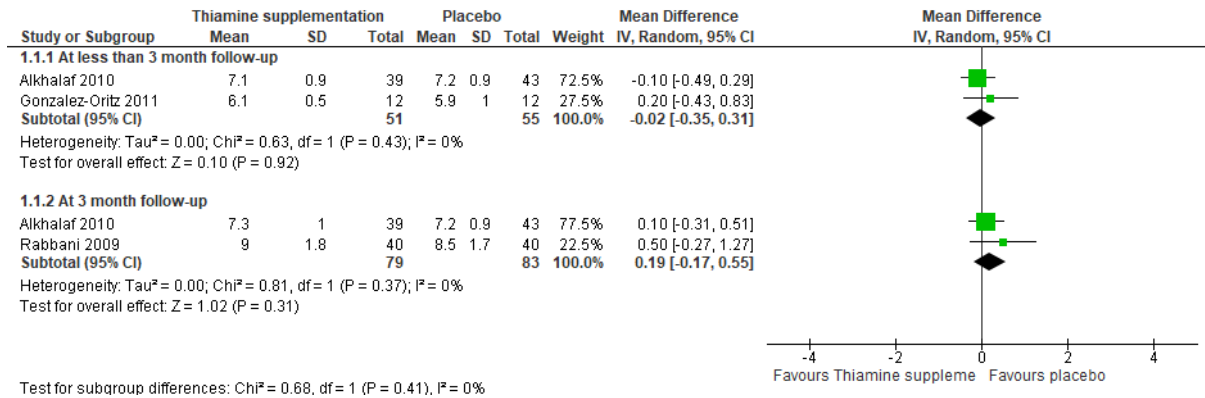
## PRISMA 2009 Flow Diagram<sup>57</sup>



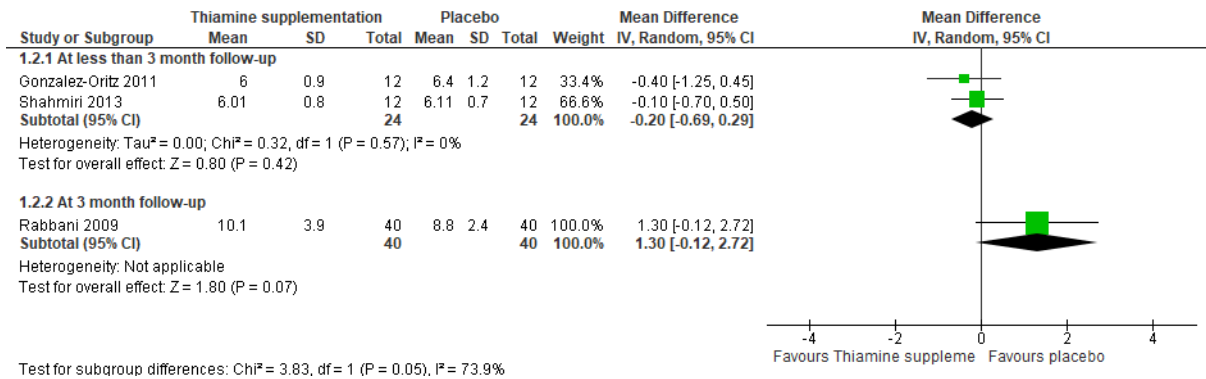
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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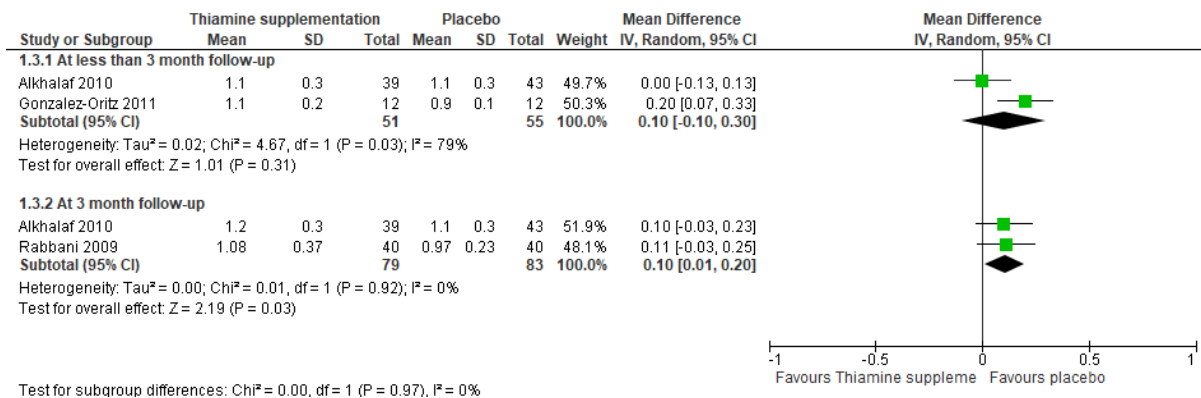
**Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.**



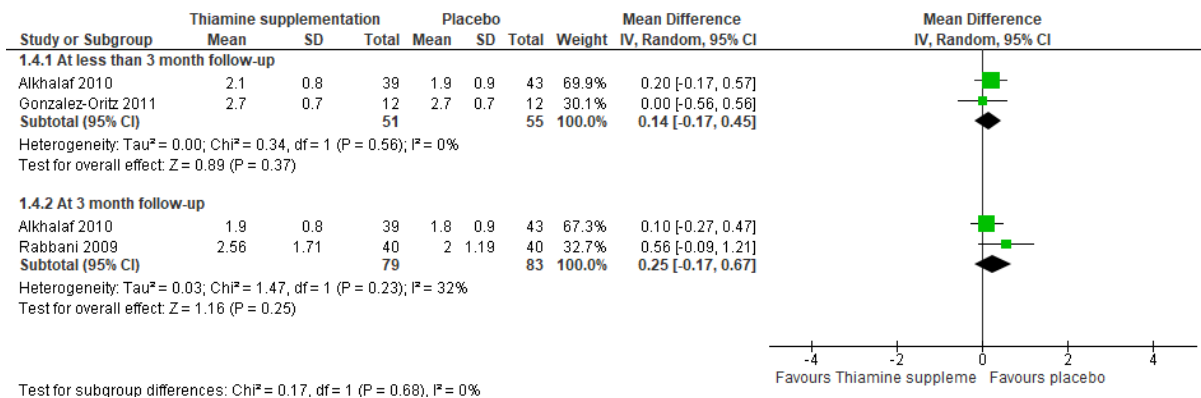
**Fig 3: Effect on FBG at less than 3 months and at 3 months follow up**

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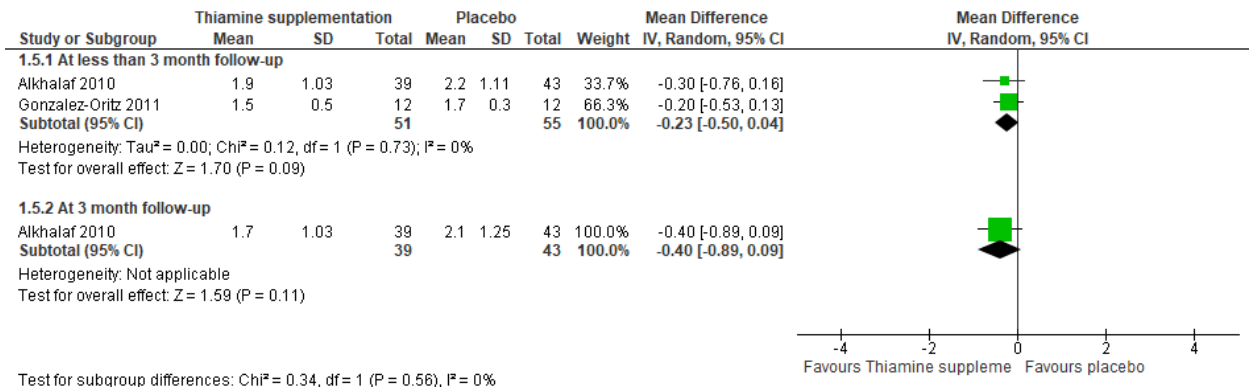
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**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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**



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4 *Appendix I: Search strategy*  
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7 **Search strategy for PubMed**

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No.	Search terms
1.	Diabetes Mellitus, Adult-Onset <input type="checkbox"/> 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

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**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
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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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15 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
16 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
17 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

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

23 **Reason for exclusion: Outcome of interest not assessed.**  
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26 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
27 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

28 **Reason for exclusion: Participants rats.**  
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31 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
32 *Metabolic brain disease*. 1996;11(1):95-106.

33 **Reason for exclusion: Outcome of interest not assessed.**  
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35  
36 Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-  
37 term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers  
38 in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial.  
39 *Diabetes Care*. 2012;35(5):1095-7.

40 **Reason for exclusion: Included only type 1 diabetics.**  
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43 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
44 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
45 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

46 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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 $\geq 5$ years BMI 19–40 kg/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC, 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, FBC, 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride at 6 weeks.	No differences in metabolic outcomes between the three groups.



Table of included study characteristics

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				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)		
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# PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Title, Pg 1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction 2 <sup>nd</sup> 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
<b>METHODS</b>			
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)). For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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.	
<b>OTHER INFORMATION</b>			
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

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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2  
3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
5  
6  
7

8 Running title: Type 2 Diabetes and thiamine  
9

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28  
29  
30

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

32 Word count:

33 Abstract: 244

34 Main text: 4868

35 No. of references: 52  
36  
37  
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3 **TITLE:** Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
5  
6

7 **ABSTRACT**  
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10 **Background:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic  
13 outcomes in patients with T2DM.  
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19 **Methods:**  
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23 *Eligibility criteria:* Studies that assessed effect of thiamine supplementation in adults with  
24 T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or  
25 post prandial blood glucose (PPG) were included.  
26  
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30 *Information sources:* PUBMED, Tripdatabase, the Cochrane Central Register, National  
31 Institute of Health Clinical Database and Google Scholar were searched until December 2021  
32 for RCTs.  
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37

38 *Risk of bias:* It was assessed using standardized critical appraisal instruments from the Joanna  
39 Briggs Institute for RCTs.  
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42

43 *Synthesis of results:* Where possible, studies were pooled in a meta-analysis. Results were  
44 presented in a narrative format if statistical pooling was not possible.  
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49 **Results:**  
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52 *Included studies:* Six trials involving 364 participants.  
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55 *Synthesis of results:* No significant beneficial effects were observed on glycemic outcomes  
56 with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02  
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3 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD - 0.20 mmol/l, CI  
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5 -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months  
6  
7 follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in  
8  
9 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in  
10  
11 higher doses.  
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## 14 15 **Discussion:**

16  
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18 *Limitations of evidence:* Inclusion of single-centre trials published only in English, small  
19  
20 sample sizes of included studies, lack of trials investigating outcomes for some comparisons  
21  
22 and varying follow-up periods.  
23  
24

25  
26 *Interpretation:* Thiamine supplementation doesn't affect glycaemic outcomes, however  
27  
28 reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher  
29  
30 doses of thiamine and a follow-up period of 1-2 years will provide better evidence.  
31  
32

## 33 34 **Strengths:**

- 35  
36 • Addresses an important topic of control of diabetes with thiamine supplementation  
37  
38 including secondary outcomes as well like LDL and triglyceride levels.  
39  
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- 41  
42 • Included only good quality RCTs, hence the results can be relied upon to give  
43  
44 direction to future research.  
45  
46
- 47  
48 • **Limitations:** The review includes single-centre trials published only in the English  
49  
50 language.  
51  
52
- 53  
54 • Sample sizes of the included studies were small although some had addressed this  
55  
56 issue using statistical power.  
57  
58
- 59  
60 • 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

For peer review only

## 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.<sup>1</sup>

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.<sup>2</sup> It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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.<sup>9</sup>It also has a role in blocking pathways responsible for

1  
2  
3 hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced  
4 Glycation End Products (AGEs) and activation of protein kinase C. It also works by  
5  
6 activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
7  
8 pentose phosphate pathway.<sup>10</sup>  
9  
10  
11

### 12 13 *How the intervention might work*

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

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

1  
2  
3 Many studies have investigated the association between fasting blood sugar (FBS), post  
4 prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL,  
5 HDL, triglycerides and various vitamins (including thiamine) and minerals<sup>13,15,17-28</sup> but with  
6 inconsistent results. Some studies reported significant inverse association for thiamine  
7 supplementation<sup>19-21,23</sup> while other intervention studies did not find any significant association  
8 with thiamine.<sup>13,15,17,18,20,29-31</sup>

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

## 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **Methods**

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43  
44 The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI)  
45 methodology for systematic reviews of effectiveness evidence<sup>32</sup> by two independent  
46 reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment  
47 and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.<sup>33</sup> The  
48 proposed systematic review was registered in PROSPERO (Registration no.  
49 CRD42020170520).

### 50 51 52 53 54 55 56 57 *Literature search strategy*

1  
2  
3 The search strategy aimed to find both published and unpublished studies which included a  
4 three-step search strategy to include all relevant articles published till 31<sup>st</sup> December 2021.  
5  
6 An initial limited search of PUBMED using the keywords: vitamin B1, thiamine,  
7  
8 benfotiamine, diabetes mellitus and blood glucose was undertaken. Text words contained in  
9  
10 the title, abstract and index terms of the studies identified were used to inform the  
11  
12 development of a search strategy for the second step which was tailored for each information  
13  
14 source. Published studies were searched for including the databases: PUBMED, Tripdatabase  
15  
16 and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library).  
17  
18 A full search strategy for the databases is detailed in Appendix I. The following databases  
19  
20 were searched to find any unpublished studies: the National Institute of Health Clinical  
21  
22 Database (<http://ClinicalTrials.gov>) and Google Scholar. The final step of the search strategy  
23  
24 included a review of the reference list of all trials selected for critical appraisal. The search  
25  
26 was restricted to papers published in the English language.  
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### 34 *Inclusion and exclusion criteria*

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37 We searched for randomised controlled trials and randomised cross-over trials that  
38  
39 investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets,  
40  
41 capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined  
42  
43 based on ADA (American Diabetes Association) guidelines as either: plasma glucose  $\geq$  200  
44  
45 mg/dl ( $\geq$  11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma  
46  
47 glucose  $\geq$  126 mg/dl ( $\geq$  7.0 mmol/dl) or HbA1c  $\geq$  6.5% (48 mmol/mol) or in a person with  
48  
49 typical symptoms of hyperglycaemia with a random plasma glucose of  $\geq$  200mg/dL (11.1  
50  
51 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting  
52  
53 blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the  
54  
55 review. The following secondary outcomes were also included in the review: serum  
56  
57 triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the  
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1  
2  
3 outcomes were measured in different units were included and results were converted to  
4 desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters  
5 to the editors, and conference abstracts were excluded. Any discrepancies were resolved by  
6 discussion with a third author (HG). The results of the search is presented in a PRISMA flow  
7 diagram (Figure 1).  
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9  
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### 14 15 *Screening*

16  
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18 The titles and abstracts of all the identified citations were independently screened by two  
19 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
20 studies were assessed for inclusion and critically appraised independently reviewed by two  
21 authors (AM and RF).  
22  
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### 28 29 *Data extraction*

30  
31  
32 Quantitative data was extracted from all trials included in the review by two independent  
33 reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data  
34 extracted included specific details about the type of intervention, populations, context, study  
35 design and duration, study methods and other outcomes of significance to the review question  
36 and specific objectives.  
37  
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### 43 44 *Quality assessment*

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46  
47 Methodological quality was assessed using the standardized critical appraisal instruments  
48 from the Joanna Briggs Institute for RCTs.<sup>32</sup> An additional risk of bias exists in cross-over  
49 RCTs, therefore a further four questions were used to assess the methodological quality of  
50 these RCTs as recommended in the Cochrane Handbook for Systematic Reviews of  
51 Interventions.  
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### 58 59 *Data synthesis and analysis*

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3 Data from included studies were pooled in a statistical meta-analysis model using Review  
4 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>34</sup> The continuous data  
5  
6 extracted from the cross-over RCTs were treated as if from a parallel trial.<sup>35</sup> All pooled  
7  
8 statistics were subject to double data entry with two independent reviewers. For continuous  
9  
10 data, effect sizes are expressed as mean differences and corresponding 95% confidence  
11  
12 intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis.  
13  
14 Statistical heterogeneity was assessed in the meta-analysis using the  $I^2$  and chi-squared  
15  
16 statistics, and heterogeneity was considered substantial if  $I^2 > 50\%$  and P value  $< 0.10$  in the  
17  
18 chi-square test for heterogeneity.<sup>36</sup> A random effects model was used in the meta-analysis.  
19  
20 Subgroup-analysis according to type of intervention and length of intervention period were  
21  
22 performed. For results which were not possible to present in a meta-analysis, the findings  
23  
24 have been presented in a narrative form.  
25  
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### 30 31 *Patient and public involvement:*

32  
33  
34 No patient involved.  
35  
36

## 37 38 **Results**

39  
40 The search results identified 145 potential trials, with 127 potential trials remaining after  
41  
42 duplicates were removed. After a review of the title and abstract of all 127 trials, 11 trials  
43  
44 were identified for potential inclusion in the review. (Appendix II) The reference lists of the  
45  
46 11 trials were examined and full texts of a further two trials were obtained. From a total of 13  
47  
48 trials, seven trials were excluded after examination of the full text against the inclusion  
49  
50 criteria (see Appendix III). Thus, finally six trials were included in the systematic review.  
51  
52 (Figure1)  
53  
54

55  
56  
57 Reasons for exclusion were: participants type 1 diabetic<sup>37</sup> or non-diabetic<sup>38</sup>, in vitro study<sup>39</sup>,  
58  
59 did not assess the outcome of interest<sup>30,40,41</sup> and study done on rats.<sup>42</sup>  
60



---

Insert Figure 1 here

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### 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	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
Winkler 1999 <sup>16</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>31</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>19</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>43</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>29</sup>	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<sup>16</sup> to 26/26<sup>19</sup> (Table 1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>43</sup> 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)

	<b>Citation</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Score</b>
1	Shahmiri 2013 <sup>43</sup>	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<sup>15,16,19,29,31</sup> and one was cross-over RCT.<sup>43</sup> The six trials were conducted in six different countries – Germany<sup>31</sup>, Pakistan<sup>19</sup>, Netherlands<sup>29</sup>, Australia<sup>43</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>43</sup> to 165<sup>31</sup> 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.<sup>16,29</sup> One trial<sup>29</sup> had male

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3 predominance (77% vs 33%) while the other <sup>16</sup> had female predominance (61% vs 39%).The  
4  
5 mean age of the patients ranged from 52 ± 8 years <sup>16</sup> to 65.3 ± 5.9 years.<sup>29</sup>  
6  
7

8  
9 Five of the six trials compared the intervention to placebo and one trial <sup>16</sup> compared various  
10  
11 dosages of thiamine supplementation. The dosage for thiamine supplementation ranged from  
12  
13 100 mg/day<sup>43</sup> to 300mg/day <sup>19</sup> and the dosage for benfotiamine ranged from 120 mg/ day <sup>16</sup> to  
14  
15 900mg/day.<sup>29</sup> The follow-up period ranged from 1 month<sup>15</sup> to 3 months.<sup>19,29</sup>  
16  
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18  
19 Fasting blood glucose was reported in four trials,<sup>15,16,19,43</sup> PPG in two trials,<sup>16,43</sup> HbA1c in five  
20  
21 trials,<sup>15,16,19,29,31</sup> HDL in four trials,<sup>15,16,19,29</sup> LDL in three trials,<sup>15,19,29</sup> triglycerides in four  
22  
23 trials,<sup>15,16,19,29</sup>, systolic and diastolic BP in three trials <sup>15,19,29</sup> and BMI in two trials. <sup>15,43</sup> Data  
24  
25 extracted from all trials is summarized in the table of included study characteristics  
26  
27 (Appendix III).  
28

### 29 30 *Heterogeneity among studies:*

31  
32  
33 There was no heterogeneity among studies for HbA1C ( $I^2 = 0\%$ ,  $p=0.41$ ), HDL ( $I^2 = 0\%$ ,  
34  
35  $p=0.97$ ), LDL ( $I^2 = 0\%$ ,  $p=0.88$ ) and triglycerides ( $I^2 = 0\%$ ,  $p=0.56$ ). Heterogeneity measured  
36  
37 for FBG was significant ( $I^2 = 79\%$ ;  $p=0.05$ ), which was accounted for by using random  
38  
39 effects model for meta-analysis.  
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41

## 42 43 **HbA1C**

### 44 45 46 *Comparison between Thiamine supplementation vs Placebo*

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48  
49 Two trials <sup>15,29</sup> that investigated the effect of thiamine supplementation vs placebo on HbA1C  
50  
51 levels demonstrated no statistically significant differences between the groups at less than 3-  
52  
53 month follow-up period. (MD -0.02 %, 95% CI -0.35, 0.31) (Fig 2) The absolute effect with  
54  
55 placebo was 5.9% and with thiamine was 5.88%.  
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3 Three trials <sup>19,29,31</sup> investigated the effect of thiamine supplementation vs placebo on HbA1C  
4 levels at 3 month follow-up, however only two trials could be pooled in the meta-analysis.  
5  
6 Pooled data demonstrated no statistically significant differences in the HbA1C levels among  
7  
8 those who received thiamine supplementation compared to those who received placebo (MD  
9  
10 0.19, 95% CI -0.17, 0.55) (Fig 2). Similarly, the third study<sup>31</sup> reported no statistically  
11  
12 significant differences in the HbA1C levels among those who received thiamine  
13  
14 supplementation compared to those who received placebo.  
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20 Insert Figure 2

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### 21 22 23 24 25 26 *Comparisons between various dosages of Benfotiamine supplementation*

27  
28  
29 One trial<sup>16</sup> that compared 320mg/day and 120mg/day of Benfotiamine on HbA1C level  
30 demonstrated no statistically significant differences in the HbA1C levels between the two  
31 groups (MD -0.20 %; 95% CI -1.02, 0.62). Similarly, there were no statistically significant  
32 differences in the HbA1C levels among those who received 320 mg/day benfotiamine  
33 compared to those who received 150 mg/day benfotiamine (MD -0.50 %; 95% CI -1.10,  
34 0.10). There were also no statistically significant differences in the HbA1C levels among  
35 those who received 120 mg/day benfotiamine compared to those who received 150 mg/day  
36 benfotiamine (MD -0.30; 955 CI -1.09, 0.49).  
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### 48 **FBG**

#### 49 50 51 *Comparison between Thiamine supplementation vs Placebo*

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53  
54 Pooled results from three trials <sup>15,19,43</sup> demonstrated no statistically significant difference in  
55 the FBG level between those who received thiamine supplementation vs placebo after less  
56 than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3).The absolute effect  
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3 with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no  
4 statistically significant difference in the FBG level between the groups after 3 months follow-  
5 up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).  
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14 **Insert Fig 3 here**  
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#### 17 18 19 *Comparisons between various dosages of Benfotiamine supplementation*

20  
21  
22 One trial<sup>16</sup> that compared 320mg/day and 120mg/day of benfotiamine on FBG levels  
23 demonstrated no statistically significant differences in the FBG levels among those who  
24 received 320 mg/day benfotiamine compared to those who received 120 mg/day  
25 benfotiamine (MD 0.60 mmmol/l; CI -0.93, 2.13). Similarly, there were no statistically  
26 significant differences in the FBG levels among those who received 320 mg/day  
27 benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l;  
28 CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels  
29 among those who received 120 mg/day benfotiamine compared to those who received 150  
30 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).  
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#### 44 **PPG**

##### 45 46 47 *Comparison between Thiamine supplementation vs Placebo*

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49  
50 One trial<sup>43</sup> investigated the effect of thiamine supplementation vs placebo on PPG levels.  
51 However, due to the paucity of the reported data, the authors were contacted to obtain further  
52 information. No response was received from the authors hence we were unable to conclude  
53 the effect of thiamine supplementation vs placebo on PPG levels.  
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##### 60 *Comparisons between various dosages of benfotiamine supplementation*

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3 One trial<sup>16</sup> compared 320mg/day and 120mg/day of Benfotiamine on PPG levels. The results  
4 demonstrated no statistically significant differences in the PPG levels among those who  
5 received 320 mg/day benfotiamine compared to those who received 120 mg/day  
6 benfotiamine (MD – 0.20 mmol/l, CI -2.05, 1.65). Similarly, there were no statistically  
7 significant differences in the PPG levels among those who received 320 mg/day benfotiamine  
8 compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l; CI -1.63,  
9 1.23). There were also no statistically significant differences in the PPG levels among those  
10 who received 120 mg/day benfotiamine compared to those who received 150 mg/day  
11 benfotiamine (MD 0.00 mmol/l; CI -1.62, 1.62).  
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## 28 HDL

### 29 *Comparison between Thiamine supplementation vs Placebo*

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

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### 47 *Comparisons between various dosages of Benfotiamine supplementation*

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51 One trial<sup>16</sup> compared two dosages of Benfotiamine demonstrated no statistically significant  
52 differences in the HDL levels among those who received 320 mg/day benfotiamine compared  
53 to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36 ).  
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58 Similarly, there were no statistically significant differences in the HDL levels among those  
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3 who received 320 mg/day benfotiamine compared to those who received 150 mg/day  
4 benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant  
5 differences in the HDL levels among those who received 120 mg/day benfotiamine compared  
6 to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).  
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### 13 **LDL**

#### 14 *Comparison between Thiamine supplementation vs Placebo*

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

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### 32 **Triglycerides**

#### 33 *Comparison between Thiamine supplementation vs Placebo*

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

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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<sup>15,19,29</sup> 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<sup>2</sup>; 95% CI -2.23, 1.79).

### **Systolic BP**

#### *Comparison between Thiamine supplementation vs Placebo*

Three trials<sup>15,27,34</sup> 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<sup>15,27,34</sup> 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<sup>44,45</sup> 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<sup>46</sup>.

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6 The results of the review also demonstrated no significant differences in FBG, LDL, and BMI  
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8 in T2DM patients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation  
9  
10 compared to those receiving placebo at less than three months or at three months follow-up.  
11  
12 These results could be due the fact that the outcomes were assessed within three months of  
13  
14 administration of thiamine. It has been established that plasma thiamine level is associated  
15  
16 with increased fractional excretion of thiamine resulting in decreased thiamine concentration  
17  
18 by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore, trials with longer term follow-up are  
19  
20 required to assess the effect of thiamine on glycemic outcomes.  
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26 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
27  
28 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
29  
30 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
31  
32 as the dose was escalated. This result should be interpreted with caution as these results are  
33  
34 based on a single study with a sample size of 36 participants.  
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40 Various other factors could have influenced the results of the review including different  
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42 populations in different studies (with different diabetes risk) and the presence of underlying  
43  
44 health conditions (like presence of autoimmune diseases) which can cause high blood glucose  
45  
46 despite thiamine supplementation. It has been shown that people with poorly controlled  
47  
48 diabetes often experience micronutrient deficiencies <sup>47</sup>. Hence there is substantial interest  
49  
50 globally to find easily accessible and inexpensive treatments such as thiamine  
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52 supplementation for T2DM.  
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58 *Limitations of this review*  
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- 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.

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2  
3 *Disclosure of Interest:* The authors declare that they have no competing interests.  
4  
5

6 *Contribution:* All authors contributed to the study  
7  
8

9 AM, RF: Study concept and design, data analysis, manuscript preparation; HL: Data  
10 acquisition and analysis; PM: Data collection, manuscript preparation.  
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14 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
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4 improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-  
5 over trial. *Eur J Nutr.* 2013;52(7):1821-4.  
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30 management of adults with diabetes. *Diabetes Care.* 2014;37(Supplement 1):S120-S43.  
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34 Figure Legends:

35  
36 Fig 1: PRISMA 2009 Flow Diagram for searching

37  
38  
39 Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3  
40 months follow up.  
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42  
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44 Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.  
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47 Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.  
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50 Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.  
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53 Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up  
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

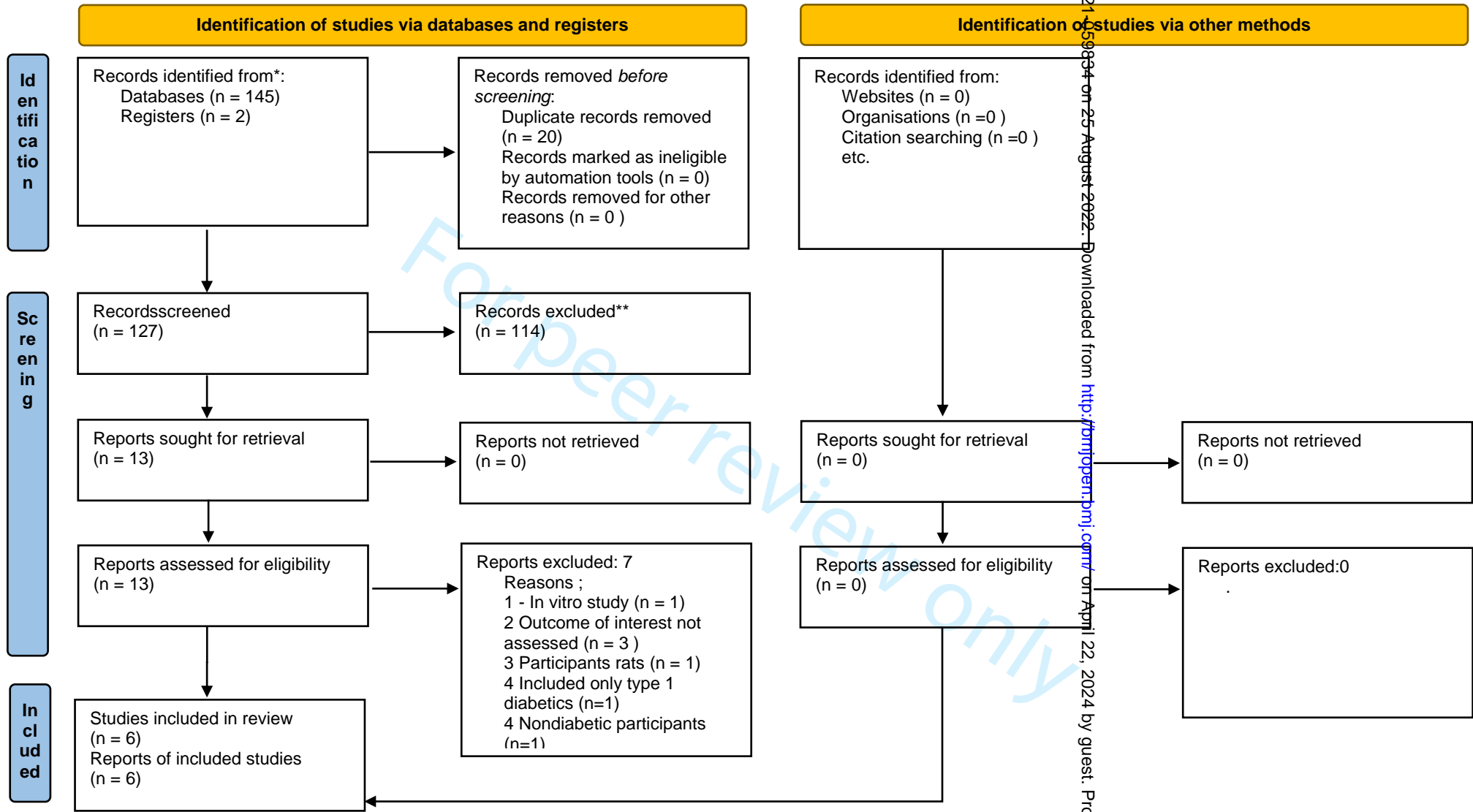


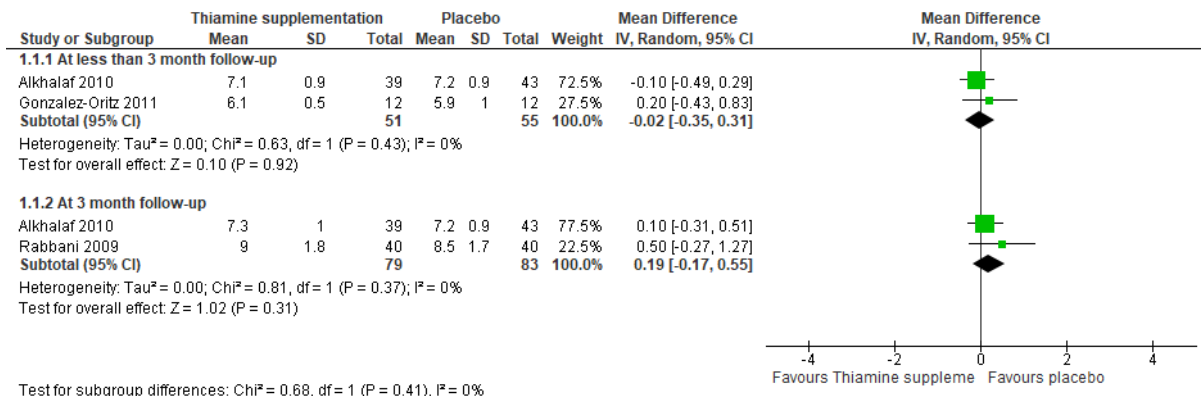
Fig 1: PRISMA 2020 Flow diagram showing searching results

\*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).

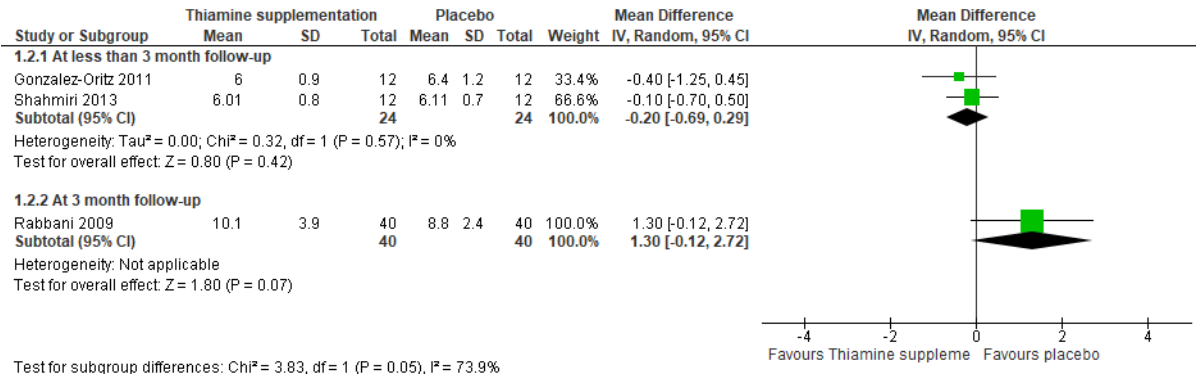
\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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/>

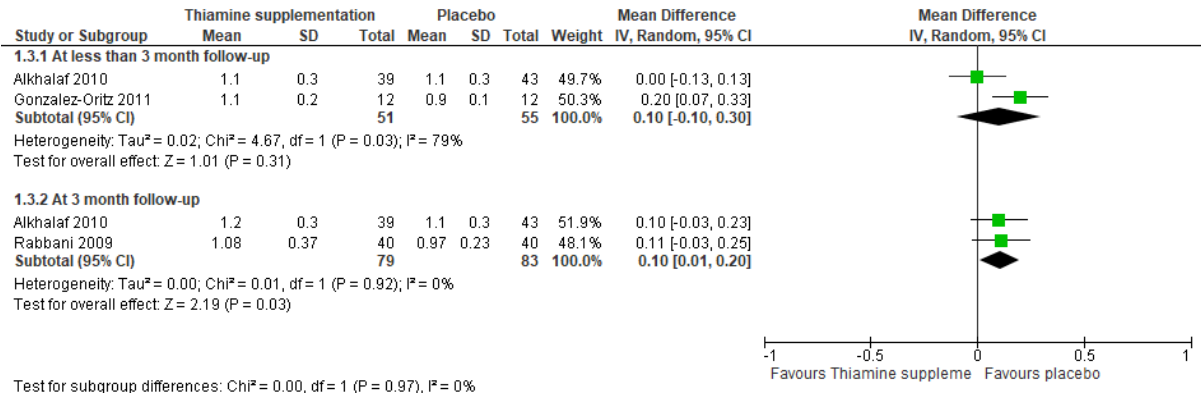
bmjopen-2021-059894 on 25 August 2022. Downloaded from <http://bmjopen.bmj.com/> on April 22, 2024 by guest. Protected by copyright.



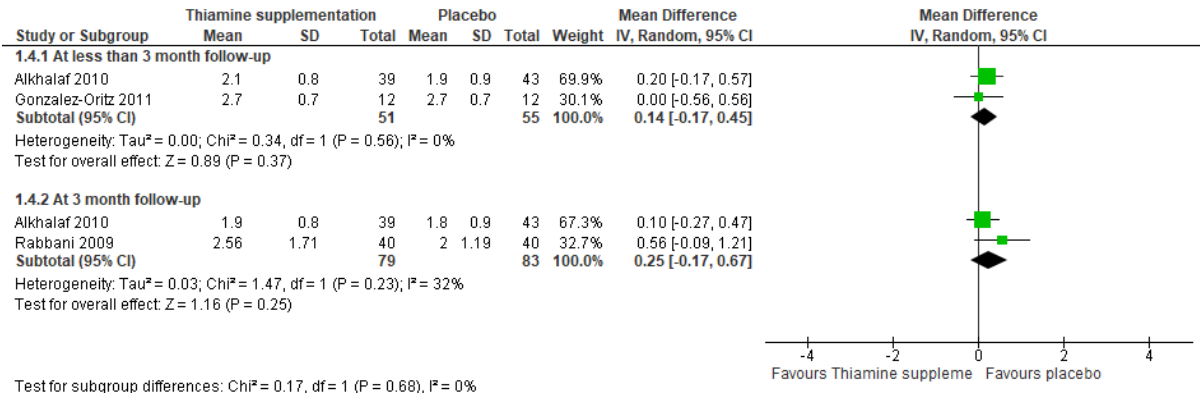
**Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.**



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

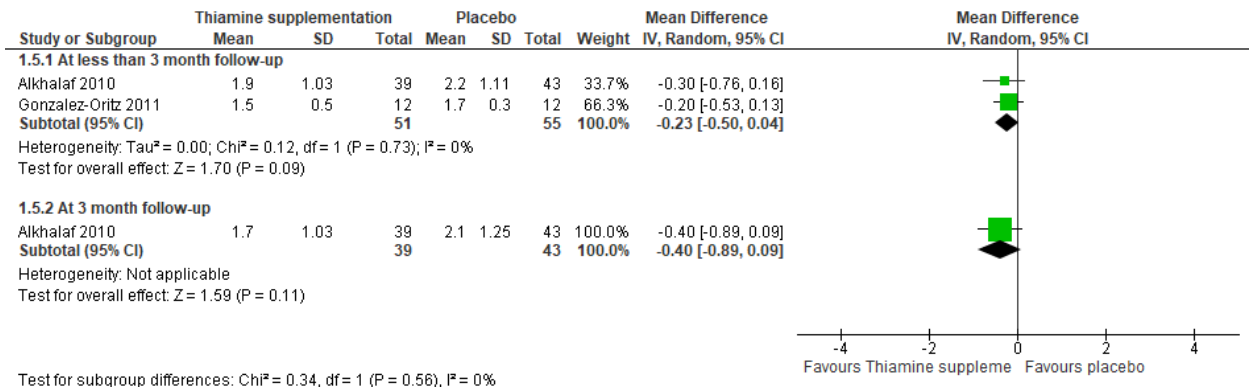


**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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 <input type="checkbox"/> 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

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**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

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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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16 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
17 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
18 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

19 **Reason for exclusion: Outcome of interest not assessed.**  
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21  
22 Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *International*  
23 *journal of clinical pharmacology and therapeutics*. 2005;43(2):71-7.

24 **Reason for exclusion: Outcome of interest not assessed.**  
25

26  
27 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
28 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

29 **Reason for exclusion: Participants rats.**  
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33 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
34 *Metabolic brain disease*. 1996;11(1):95-106.

35 **Reason for exclusion: Outcome of interest not assessed.**  
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38 Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-  
39 term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers  
40 in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial.  
41 *Diabetes Care*. 2012;35(5):1095-7.

42 **Reason for exclusion: Included only type 1 diabetics.**  
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46 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
47 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
48 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

49 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC, 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, FBC, 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

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

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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8 Running title: Type 2 Diabetes and thiamine  
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10 Authors:

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

32 Word count:

33 Abstract: 244

34 Main text: 4868

35 No. of references: 52  
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3 **TITLE:** Effect of Thiamine supplementation on glycemic outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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7 **ABSTRACT**  
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10 **Background:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemic  
13 outcomes in patients with T2DM.  
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19 **Methods:**  
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23 *Eligibility criteria:* Studies that assessed effect of thiamine supplementation in adults with  
24 T2DM which measured glycemic outcomes - HbA1C, fasting blood glucose (FBG), and/or  
25 post prandial blood glucose (PPG) were included.  
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30 *Information sources:* PUBMED, Tripdatabase, the Cochrane Central Register, National  
31 Institute of Health Clinical Database and Google Scholar were searched until December 2021  
32 for RCTs.  
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38 *Risk of bias:* It was assessed using standardized critical appraisal instruments from the Joanna  
39 Briggs Institute for RCTs.  
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43 *Synthesis of results:* Where possible, studies were pooled in a meta-analysis. Results were  
44 presented in a narrative format if statistical pooling was not possible.  
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49 **Results:**  
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52 *Included studies:* Six trials involving 364 participants.  
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55 *Synthesis of results:* No significant beneficial effects were observed on glycemic outcomes  
56 with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02  
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3 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD - 0.20 mmol/l, CI  
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5 -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months  
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7 follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in  
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9 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in  
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11 higher doses.  
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### 14 15 **Discussion:**

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18 *Limitations of evidence:* Inclusion of single-centre trials published only in English, small  
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20 sample sizes of included studies, lack of trials investigating outcomes for some comparisons  
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22 and varying follow-up periods.  
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25  
26 *Interpretation:* Thiamine supplementation doesn't affect glycaemic outcomes, however  
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28 reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher  
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30 doses of thiamine and a follow-up period of 1-2 years will provide better evidence.  
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32

### 33 34 **Strengths:**

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36 • Addresses an important topic of control of diabetes with thiamine supplementation  
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38 including secondary outcomes as well like LDL and triglyceride levels.  
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- 41  
42 • Included only good quality RCTs, hence the results can be relied upon to give  
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44 direction to future research.  
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### 47 48 **Limitations:**

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50 • The review includes single-centre trials published only in the English language.  
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- 53  
54 • Sample sizes of the included studies were small although some had addressed this  
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56 issue using statistical power.  
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- 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

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## 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.<sup>1</sup>

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.<sup>2</sup> It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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.<sup>9</sup> It also has a role in blocking pathways responsible for

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2  
3 hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced  
4 Glycation End Products (AGEs) and activation of protein kinase C. It also works by  
5  
6 activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
7  
8 pentose phosphate pathway.<sup>10</sup>  
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### 11 12 13 *How the intervention might work* 14

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

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

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2  
3 Many studies have investigated the association between fasting blood sugar (FBS), post  
4 prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL,  
5 HDL, triglycerides and various vitamins (including thiamine) and minerals<sup>13,15,17-28</sup> but with  
6 inconsistent results. Some studies reported significant inverse association for thiamine  
7 supplementation<sup>19-21,23</sup> while other intervention studies did not find any significant association  
8 with thiamine.<sup>13,15,17,18,20,29-31</sup>

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

## 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **Methods**

42  
43 The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI)  
44 methodology for systematic reviews of effectiveness evidence<sup>32</sup> by two independent  
45 reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment  
46 and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.<sup>33</sup> The  
47 proposed systematic review was registered in PROSPERO (Registration no.  
48 CRD42020170520).

### 49 50 51 52 53 54 55 56 57 *Literature search strategy*

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3 The search strategy aimed to find both published and unpublished studies which included a  
4 three-step search strategy to include all relevant articles published till 31<sup>st</sup> December 2019  
5 and updated later till 31<sup>st</sup> December 2021. A final update search was done till 30<sup>th</sup> June 2022.  
6  
7 No additional article was found in the updated search. An initial limited search of PUBMED  
8 using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose  
9 was undertaken. Text words contained in the title, abstract and index terms of the studies  
10 identified were used to inform the development of a search strategy for the second step which  
11 was tailored for each information source. Published studies were searched for including the  
12 databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials  
13 (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in  
14 Appendix I. The following databases were searched to find any unpublished studies: the  
15 National Institute of Health Clinical Database (<http://ClinicalTrials.gov>) and Google Scholar.  
16 The final step of the search strategy included a review of the reference list of all trials  
17 selected for critical appraisal. The search was restricted to papers published in the English  
18 language.

### 19 *Inclusion and exclusion criteria*

20 We searched for randomised controlled trials and randomised cross-over trials that  
21 investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets,  
22 capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined  
23 based on ADA (American Diabetes Association) guidelines as either: plasma glucose  $\geq 200$   
24 mg/dl ( $\geq 11.1$  mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma  
25 glucose  $\geq 126$  mg/dl ( $\geq 7.0$  mmol/dl) or HbA1c  $\geq 6.5\%$  (48 mmol/mol) or in a person with  
26 typical symptoms of hyperglycaemia with a random plasma glucose of  $\geq 200$ mg/dL (11.1  
27 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting  
28 blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the  
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3 review. The following secondary outcomes were also included in the review: serum  
4 triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the  
5 outcomes were measured in different units were included and results were converted to  
6 desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters  
7 to the editors, and conference abstracts were excluded. Any discrepancies were resolved by  
8 discussion with a third author (HG). The results of the search is presented in a PRISMA flow  
9 diagram (Figure 1).  
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### 20 *Screening*

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23 The titles and abstracts of all the identified citations were independently screened by two  
24 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
25 studies were assessed for inclusion and critically appraised independently reviewed by two  
26 authors (AM and RF).  
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### 33 *Data extraction*

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

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51 Methodological quality of parallel group RCTs was assessed using the widely used critical  
52 JBI checklist for randomised controlled trials.<sup>32</sup> This checklist comprises of 13 items that  
53 assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored  
54 as '2' when the criteria were found adequately reported for the study, '1' when the  
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3 information was unclear and '0' when there was no reporting based on the criteria. The  
4 minimal obtainable score was 0 and the maximum 26. For unclear information, authors were  
5 contacted for more information and a decision made accordingly. An additional risk of bias  
6 exists in cross-over RCTs, therefore a further four questions were used to assess the  
7 additional risk of bias exists in cross-over RCTs, therefore a further four questions were used  
8 to assess the methodological quality of these RCTs as recommended in the Cochrane  
9 Handbook for Systematic Reviews of Interventions.  
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### 20 *Data synthesis and analysis*

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23 Data from included studies were pooled in a statistical meta-analysis model using Review  
24 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>34</sup> The continuous data  
25 extracted from the cross-over RCTs were treated as if from a parallel trial.<sup>35</sup> All pooled  
26 statistics were subject to double data entry with two independent reviewers. For continuous  
27 data, effect sizes are expressed as mean differences and corresponding 95% confidence  
28 intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis.  
29  
30 Statistical heterogeneity was assessed in the meta-analysis using the  $I^2$  and chi-squared  
31 statistics, and heterogeneity was considered substantial if  $I^2 > 50\%$  and P value  $< 0.10$  in the  
32 chi-square test for heterogeneity.<sup>36</sup> A random effects model was used in the meta-analysis.  
33  
34 Subgroup-analysis according to type of intervention and length of intervention period were  
35 performed. For results which were not possible to present in a meta-analysis, the findings  
36 have been presented in a narrative form.  
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### 50 *Patient and public involvement:*

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52 No patient involved.  
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## 58 **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<sup>37</sup> or non-diabetic<sup>38</sup>, in vitro study<sup>39</sup>, did not assess the outcome of interest<sup>30,40,41</sup> and study done on rats.<sup>42</sup>

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Insert Figure1 here

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### *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 <sup>16</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>31</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>19</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>43</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>29</sup>	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

JBIC 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<sup>16</sup> to 26/26<sup>19</sup> (Table

1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>43</sup> 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)

	<b>Citation</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Score</b>
1	Shahmiri 2013 <sup>43</sup>	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<sup>15,16,19,29,31</sup> and one was cross-over RCT.<sup>43</sup> The six trials were conducted in six different countries – Germany<sup>31</sup>, Pakistan<sup>19</sup>, Netherlands<sup>29</sup>, Australia<sup>43</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>43</sup> to 165<sup>31</sup> 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.<sup>16,29</sup> One trial<sup>29</sup> had male predominance (77% vs 33%) while the other<sup>16</sup> had female predominance (61% vs 39%). The mean age of the patients ranged from 52 ± 8 years<sup>16</sup> to 65.3 ± 5.9 years.<sup>29</sup>

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

Fasting blood glucose was reported in four trials,<sup>15,16,19,43</sup> PPG in two trials,<sup>16,43</sup> HbA1c in five trials,<sup>15,16,19,29,31</sup> HDL in four trials,<sup>15,16,19,29</sup> LDL in three trials,<sup>15,19,29</sup> triglycerides in four trials,<sup>15,16,19,29</sup>, systolic and diastolic BP in three trials<sup>15,19,29</sup> and BMI in two trials.<sup>15,43</sup> 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<sup>15,29</sup> 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<sup>19,29,31</sup> 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<sup>31</sup> reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

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Insert Figure 2

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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

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2  
3 those who received 120 mg/day benfotiamine compared to those who received 150 mg/day  
4  
5 benfotiamine (MD -0.30; 95% CI -1.09, 0.49).  
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## 8 **FBG**

### 9 10 11 *Comparison between Thiamine supplementation vs Placebo*

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14 Pooled results from three trials<sup>15,19,43</sup> demonstrated no statistically significant difference in  
15  
16 the FBG level between those who received thiamine supplementation vs placebo after less  
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18 than 3 months of follow-up (MD -0.20 mmol/l; CI -0.69, 0.29) (Fig 3). The absolute effect  
19  
20 with placebo was 6.11 mmol/L and with thiamine was 5.91 mmol/L. Similarly there was no  
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22 statistically significant difference in the FBG level between the groups after 3 months follow-  
23  
24 up (MD 1.30 mmol/l; CI -0.12, 2.72) (Fig 3).  
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32 **Insert Fig 3 here**

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### 33 34 35 36 37 38 *Comparisons between various dosages of Benfotiamine supplementation*

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40  
41 One trial<sup>16</sup> that compared 320mg/day and 120mg/day of benfotiamine on FBG levels  
42  
43 demonstrated no statistically significant differences in the FBG levels among those who  
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45 received 320 mg/day benfotiamine compared to those who received 120 mg/day  
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47 benfotiamine (MD 0.60 mmol/l; CI -0.93, 2.13). Similarly, there were no statistically  
48  
49 significant differences in the FBG levels among those who received 320 mg/day  
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51 benfotiamine compared to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l;  
52  
53 CI -1.60, 1.20). There were also no statistically significant differences in the FBG levels  
54  
55 among those who received 120 mg/day benfotiamine compared to those who received 150  
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57 mg/day benfotiamine (MD -0.80 mmol/l, CI -2.36, 0.76).  
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## PPG

### *Comparison between Thiamine supplementation vs Placebo*

One trial<sup>43</sup> 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<sup>16</sup> 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<sup>15,19,29</sup> 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

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

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#### 9 10 11 *Comparisons between various dosages of Benfotiamine supplementation*

12  
13  
14 One trial <sup>16</sup> compared two dosages of Benfotiamine demonstrated no statistically significant  
15 differences in the HDL levels among those who received 320 mg/day benfotiamine compared  
16 to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36 ).  
17  
18 Similarly, there were no statistically significant differences in the HDL levels among those  
19 who received 320 mg/day benfotiamine compared to those who received 150 mg/day  
20 benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant  
21 differences in the HDL levels among those who received 120 mg/day benfotiamine compared  
22 to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).  
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#### 33 **LDL**

##### 34 35 36 *Comparison between Thiamine supplementation vs Placebo*

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

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#### 50 51 52 53 54 55 **Triglycerides**

##### 56 57 58 *Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on  
4 triglyceride levels. The results demonstrated no statistically significant differences in the  
5 triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04)  
6 (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) .  
7  
8 The study by Rabbani provided Median and minimum and maximum scores and hence could  
9 not be included in the meta-analysis. The results however demonstrated no statistically  
10 significant differences in the triglyceride levels between the groups at the 3 month follow-up.  
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**Insert Fig 6**

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*Comparisons between various dosages of Benfotiamine supplementation*

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26 One trial<sup>16</sup> that compared various dosages of Benfotiamine demonstrated no statistically  
27 significant differences in the triglyceride levels among those who received 320 mg/day  
28 benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l;  
29 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the  
30 HbA1C levels among those who received 320 mg/day benfotiamine compared to those who  
31 received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels  
32 among those who received 120 mg/day benfotiamine compared was significantly lower  
33 compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -  
34 1.90,-0.30)  
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**BMI***Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on BMI  
4 levels. Pooled results demonstrated no statistically significant differences in the BMI levels  
5  
6 between the groups at less than 3 month (MD -0.22 kg/m<sup>2</sup>; 95% CI -2.23, 1.79).  
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### 10 **Systolic BP**

#### 11 *Comparison between Thiamine supplementation vs Placebo*

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

#### 27 *Comparison between Thiamine supplementation vs Placebo*

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29  
30 Three trials <sup>15,27,34</sup> investigated the effect of thiamine supplementation vs placebo on diastolic  
31 BP levels. Pooled results demonstrated no statistically significant differences in the diastolic  
32 BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as  
33 well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).  
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### 45 **Discussion**

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48 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
49 outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides  
50 while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid  
51 soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and  
52 HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and  
53 diastolic BP and BMI. Since this review only included trials that were undertaken in people  
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3 with T2DM, only six trials were eligible for inclusion of which one was a cross over trial.  
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5 The overall methodological quality of the trials was variable as the assessment criteria  
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7 regarding the method of randomization and allocation concealment was not reported in four  
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9 trials.  
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13 For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment  
14  
15 effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the  
16  
17 literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG <sup>44,45</sup> is considered  
18  
19 as clinically significant. In our review, the treatment effect sizes did not reach the point of  
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21 clinical significance for both HbA1C and FBG which could be due to the small sample sizes  
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23 in the included studies. Nevertheless, the small reductions identified in HbA1C and blood  
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25 glucose levels can reduce the health impacts associated with T2DM <sup>46</sup>.  
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32 The results of the review also demonstrated no significant differences in FBG, LDL, and BMI  
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34 in T2DM patients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation  
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36 compared to those receiving placebo at less than three months or at three months follow-up.  
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38 These results could be due the fact that the outcomes were assessed within three months of  
39  
40 administration of thiamine. It has been established that plasma thiamine level is associated  
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42 with increased fractional excretion of thiamine resulting in decreased thiamine concentration  
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44 by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore, trials with longer term follow-up are  
45  
46 required to assess the effect of thiamine on glycemic outcomes.  
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52 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
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54 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
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56 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
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3 as the dose was escalated. This result should be interpreted with caution as these results are  
4  
5 based on a single study with a sample size of 36 participants.  
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10 Various other factors could have influenced the results of the review including different  
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12 populations in different studies (with different diabetes risk) and the presence of underlying  
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14 health conditions (like presence of autoimmune diseases) which can cause high blood glucose  
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16 despite thiamine supplementation. It has been shown that people with poorly controlled  
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18 diabetes often experience micronutrient deficiencies <sup>47</sup>. Hence there is substantial interest  
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20 globally to find easily accessible and inexpensive treatments such as thiamine  
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22 supplementation for T2DM.  
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### 26 27 28 *Limitations of this review*

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

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52 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
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54 outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to  
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56 change practices. Therefore, existing practices will be dictated by current policies. However,  
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58 some important points have been identified such as, the studies published to date have been  
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3 single centric studies, with small sample size, varying doses and follow-up for only 3 months.  
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5 Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer  
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7 follow-up of 1-2 years using sample size based on power calculation should be undertaken to  
8  
9 address the confusion regarding benefit of thiamine supplementation on glycemc outcomes  
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11 in T2DM. One such study if undertaken would be able to give specific recommendations on  
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13 whether or not to consider thiamine supplementation for improving glycemc outcomes in  
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15 T2DM patients.  
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23 *Ethics statement:* This study does not involve any human or animal participant.  
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26 *Funding:* No additional sources of funding.  
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28

29 *Data availability:* No additional data available.  
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32 *Disclosure of Interest:* The authors declare that they have no competing interests.  
33  
34

35 *Contribution:* AM, RF: Study concept and design, data analysis, manuscript preparation; HL:  
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37 Data acquisition, manuscript preparation and analysis; PM: Data collection, manuscript  
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39 preparation and analysis.  
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42 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
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#### Figure Legends:

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59 Fig 1: PRISMA 2009 Flow Diagram for searching  
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3 Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3  
4 months follow up.  
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8 Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.  
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11 Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.  
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14 Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.  
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17 Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up  
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### PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

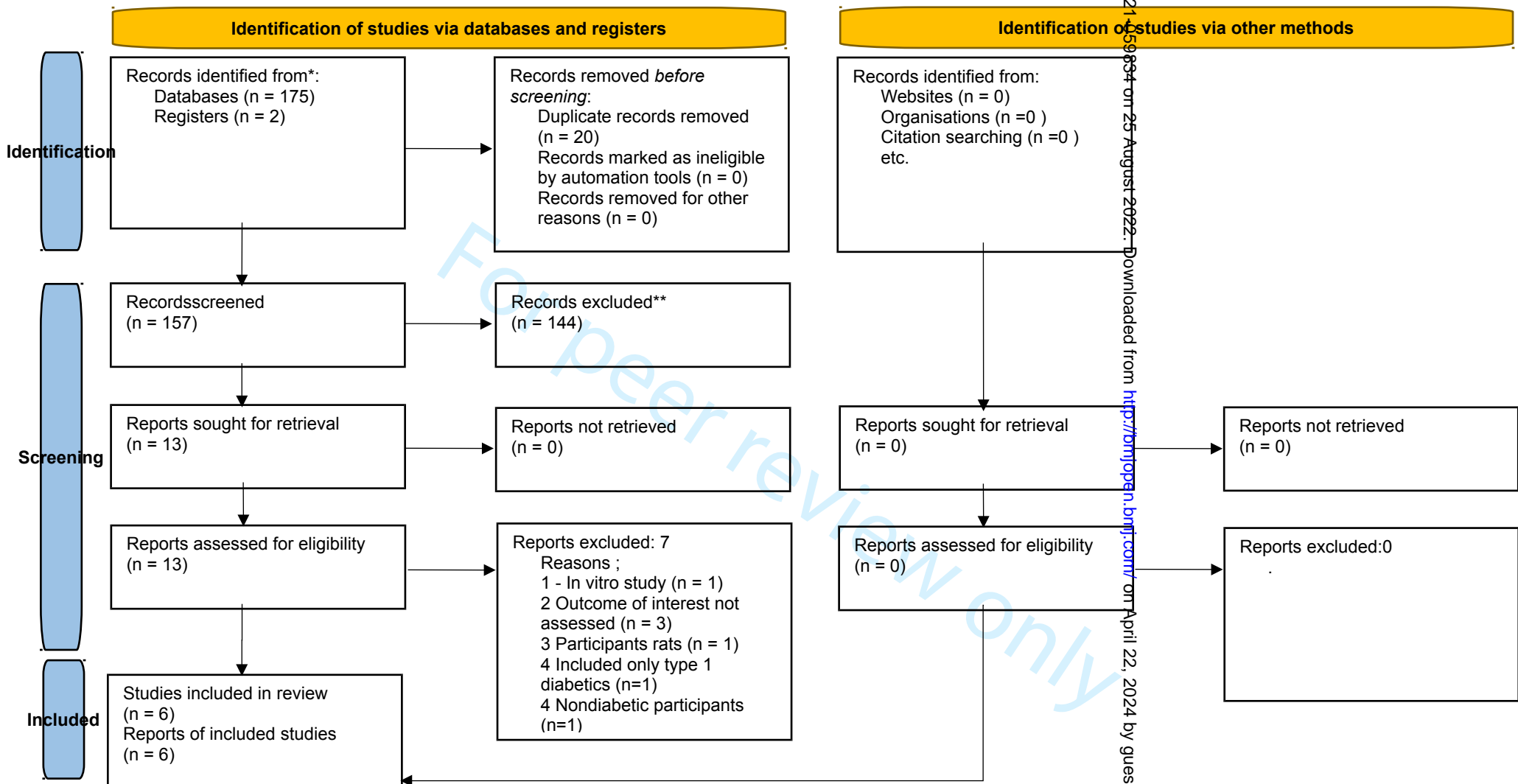


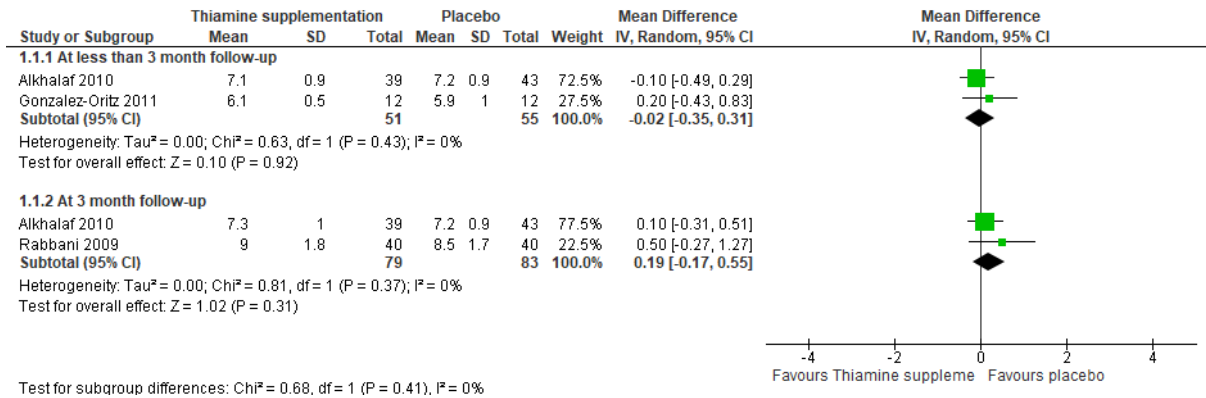
Fig 1: PRISMA 2020 Flow diagram showing searching results

\*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).

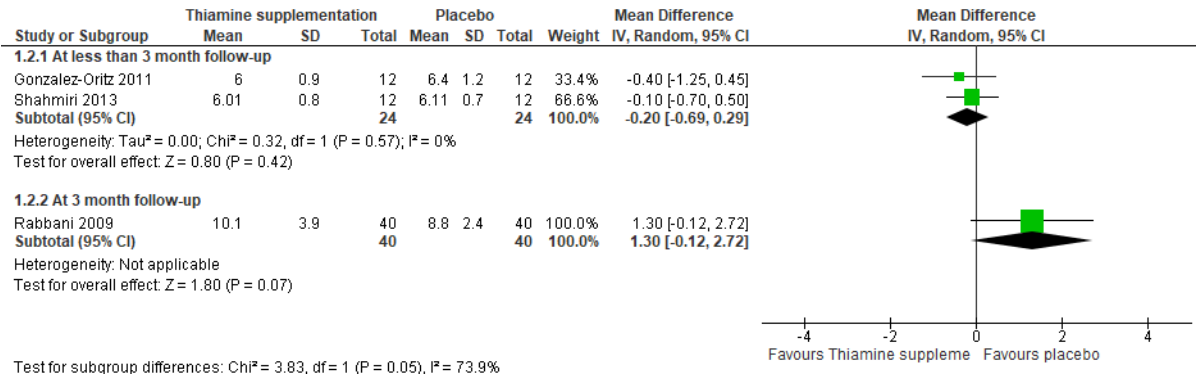
\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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/>

bmjopen-2021-015984 on 25 August 2022. Downloaded from <http://bmjopen.bmj.com/> on April 22, 2024 by guest. Protected by copyright.

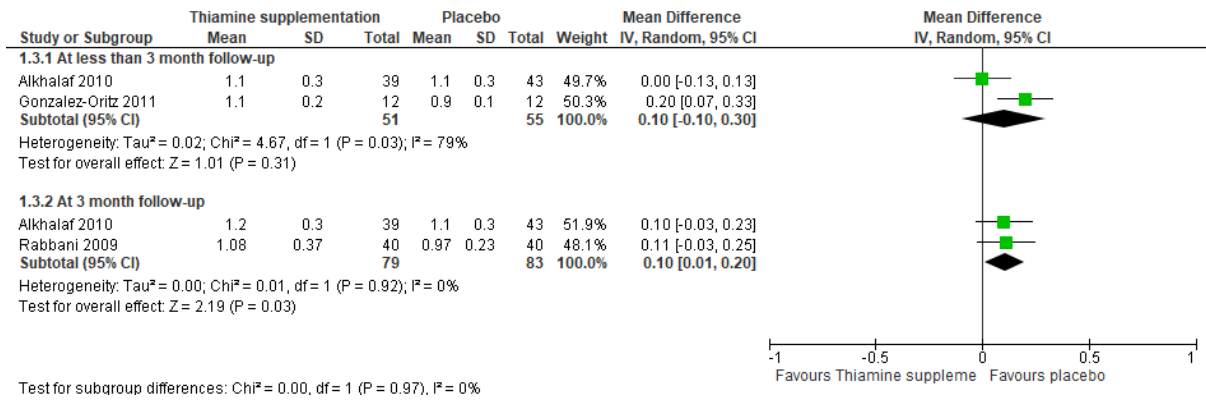


**Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.**

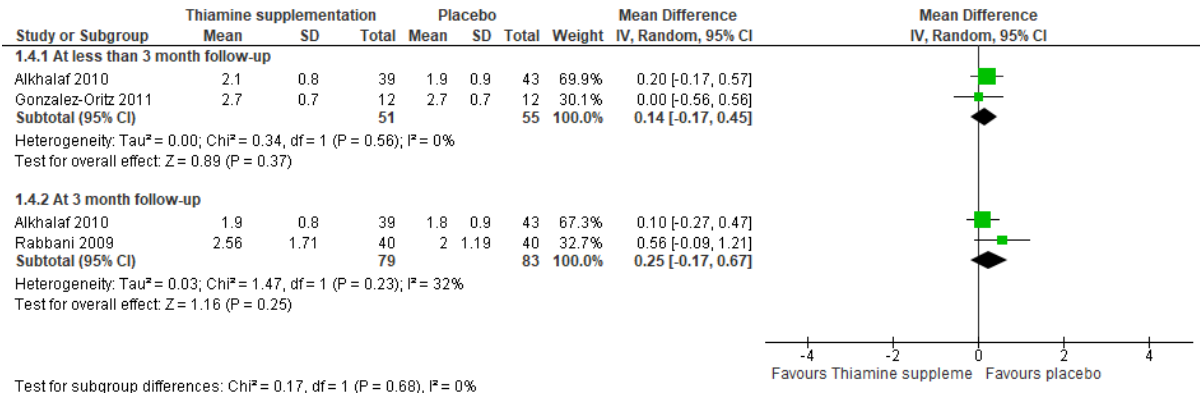


**Fig 3: Effect on FBG at less than 3 months and at 3 months follow up**

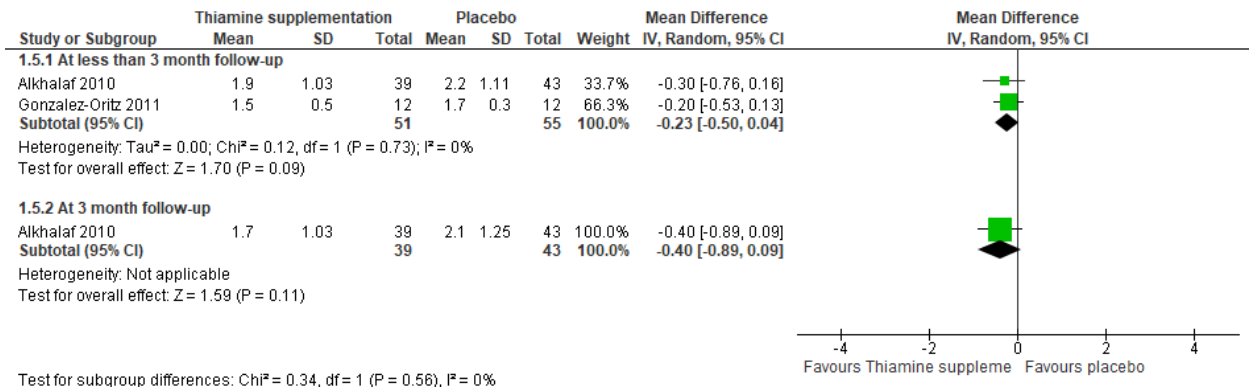
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**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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 <input type="checkbox"/> 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

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**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

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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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15  
16 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
17 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
18 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

19 **Reason for exclusion: Outcome of interest not assessed.**  
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21  
22 Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *International*  
23 *journal of clinical pharmacology and therapeutics*. 2005;43(2):71-7.

24 **Reason for exclusion: Outcome of interest not assessed.**  
25

26  
27 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
28 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

29 **Reason for exclusion: Participants rats.**  
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32  
33 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
34 *Metabolic brain disease*. 1996;11(1):95-106.

35 **Reason for exclusion: Outcome of interest not assessed.**  
36

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

42 **Reason for exclusion: Included only type 1 diabetics.**  
43

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45  
46 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
47 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
48 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

49 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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 $\geq 5$ years BMI 19–40 kg/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC, 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, FBC, 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

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

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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8 Running title: Type 2 Diabetes and thiamine  
9

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

32 Word count:

33 Abstract: 244

34 Main text: 4868

35 No. of references: 52  
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3 **TITLE:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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7 **ABSTRACT**  
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10 **Background:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemc  
13 outcomes in patients with T2DM.  
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20 **Methods:**  
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23 *Eligibility criteria:* Studies that assessed effect of thiamine supplementation in adults with  
24 T2DM which measured glycemc outcomes - HbA1C, fasting blood glucose (FBG), and/or  
25 post prandial blood glucose (PPG) were included.  
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31 *Information sources:* PUBMED, Tripdatabase, the Cochrane Central Register, National  
32 Institute of Health Clinical Database and Google Scholar were searched until December 2021  
33 for RCTs.  
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39 *Risk of bias:* It was assessed using standardized critical appraisal instruments from the Joanna  
40 Briggs Institute for RCTs.  
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44 *Synthesis of results:* Where possible, studies were pooled in a meta-analysis. Results were  
45 presented in a narrative format if statistical pooling was not possible.  
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49 **Results:**  
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52 *Included studies:* Six trials involving 364 participants.  
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56 *Synthesis of results:* No significant beneficial effects were observed on glycemc outcomes  
57 with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02  
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3 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD – 0.20 mmol/l, CI  
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5 -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months  
6  
7 follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in  
8  
9 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in  
10  
11 higher doses.  
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### 14 15 **Discussion:**

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18 *Limitations of evidence:* Inclusion of single-centre trials published only in English, small  
19  
20 sample sizes of included studies, lack of trials investigating outcomes for some comparisons  
21  
22 and varying follow-up periods.  
23  
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25  
26 *Interpretation:* Thiamine supplementation doesn't affect glycaemic outcomes, however  
27  
28 reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher  
29  
30 doses of thiamine and a follow-up period of 1-2 years will provide better evidence.  
31  
32

### 33 34 **Strengths:**

- 35  
36 • Addresses an important topic of control of diabetes with thiamine supplementation  
37  
38 including secondary outcomes as well like LDL and triglyceride levels.  
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- 41  
42 • Included only good quality RCTs, hence the results can be relied upon to give  
43  
44 direction to future research.  
45  
46

### 47 48 **Limitations:**

- 49  
50 • The review includes single-centre trials published only in the English language.  
51  
52
- 53  
54 • Sample sizes of the included studies were small although some had addressed this  
55  
56 issue using statistical power.  
57  
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- 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

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## 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.<sup>1</sup>

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.<sup>2</sup> It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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.<sup>9</sup>It also has a role in blocking pathways responsible for

1  
2  
3 hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced  
4 Glycation End Products (AGEs) and activation of protein kinase C. It also works by  
5  
6 activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
7  
8 pentose phosphate pathway.<sup>10</sup>  
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### 11 12 13 *How the intervention might work* 14

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

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



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3 Many studies have investigated the association between fasting blood sugar (FBS), post  
4 prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL,  
5 HDL, triglycerides and various vitamins (including thiamine) and minerals<sup>13,15,17-28</sup> but with  
6 inconsistent results. Some studies reported significant inverse association for thiamine  
7 supplementation<sup>19-21,23</sup> while other intervention studies did not find any significant association  
8 with thiamine.<sup>13,15,17,18,20,29-31</sup>  
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10  
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12 As dietary supplementation can be an easily feasible and an economic strategy to control  
13 sugar levels and prevent hyperglycemia related complications, we aim to conduct a  
14 systematic review and meta-analysis to find out the relationship of supplementation of  
15 thiamine or benfotiamine with FBS, PP2BS and HbA1c concentrations in adults. A  
16 preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic  
17 Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was  
18 conducted and no systematic reviews were identified. Therefore, the question for the review  
19 is: What is the effectiveness of vitamin B1 supplementation on glycemic outcomes including  
20 fasting blood glucose, post prandial blood glucose and or glycated haemoglobin in adults  
21 with T2DM?  
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## 40 **Methods**

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43 The systematic review was conducted in accordance with the Joanna Briggs Institute (JBI)  
44 methodology for systematic reviews of effectiveness evidence<sup>32</sup> by two independent  
45 reviewers using the Joanna Briggs Institute System for the Unified Management, Assessment  
46 and Review of Information and the 2017 Joanna Briggs Institute Reviewer's Manual.<sup>33</sup> The  
47 proposed systematic review was registered in PROSPERO (Registration no.  
48 CRD42020170520).  
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### 57 *Literature search strategy*

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3 The search strategy aimed to find both published and unpublished studies which included a  
4 three-step search strategy to include all relevant articles published till 31<sup>st</sup> December 2019  
5 and updated later till 31<sup>st</sup> December 2021. A final update search was done till 30<sup>th</sup> June 2022.  
6  
7 No additional article was found in the updated search. An initial limited search of PUBMED  
8 using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose  
9 was undertaken. Text words contained in the title, abstract and index terms of the studies  
10 identified were used to inform the development of a search strategy for the second step which  
11 was tailored for each information source. Published studies were searched for including the  
12 databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials  
13 (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in  
14 Appendix I. The following databases were searched to find any unpublished studies: the  
15 National Institute of Health Clinical Database (<http://ClinicalTrials.gov>) and Google Scholar.  
16 The final step of the search strategy included a review of the reference list of all trials  
17 selected for critical appraisal. The search was restricted to papers published in the English  
18 language.

### 19 *Inclusion and exclusion criteria*

20 We searched for randomised controlled trials and randomised cross-over trials that  
21 investigated the effect of thiamine or benfotiamine administered in any form (e.g. tablets,  
22 capsules, liquid) on adults with T2DM. For the purpose of this review, T2DM was defined  
23 based on ADA (American Diabetes Association) guidelines as either: plasma glucose  $\geq$  200  
24 mg/dl ( $\geq$  11.1 mmol/l) during a 75g oral glucose tolerance test (OGTT) or fasting plasma  
25 glucose  $\geq$  126 mg/dl ( $\geq$  7.0 mmol/dl) or HbA1c  $\geq$  6.5% (48 mmol/mol) or in a person with  
26 typical symptoms of hyperglycaemia with a random plasma glucose of  $\geq$  200mg/dL (11.1  
27 mmol/L). Trials that included the following primary outcomes (1) HbA1c (%) (2) Fasting  
28 blood glucose level (FBG) (3) Postprandial blood glucose level (PPG) were included in the  
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3 review. The following secondary outcomes were also included in the review: serum  
4 triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the  
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6 outcomes were measured in different units were included and results were converted to  
7  
8 desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters  
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10 to the editors, and conference abstracts were excluded. Any discrepancies were resolved by  
11  
12 discussion with a third author (HG). The results of the search is presented in a PRISMA flow  
13  
14 diagram (Figure 1).  
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### 20 *Screening*

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23 The titles and abstracts of all the identified citations were independently screened by two  
24  
25 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
26  
27 studies were assessed for inclusion and critically appraised independently reviewed by two  
28  
29 authors (AM and RF).  
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### 33 *Data extraction*

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36 Quantitative data was extracted from all trials included in the review by two independent  
37  
38 reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data  
39  
40 extracted included specific details about the type of intervention, populations, context, study  
41  
42 design and duration, study methods and other outcomes of significance to the review question  
43  
44 and specific objectives.  
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### 48 *Quality assessment*

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51 Methodological quality of parallel group RCTs was assessed using the widely used critical  
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53 JBI checklist for randomised controlled trials.<sup>32</sup> This checklist comprises of 13 items that  
54  
55 assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored  
56  
57 as '2' when the criteria were found adequately reported for the study, '1' when the  
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3 information was unclear and '0' when there was no reporting based on the criteria. The  
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5 minimal obtainable score was 0 and the maximum 26. For unclear information, authors were  
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7 contacted for more information and a decision made accordingly. An additional risk of bias  
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9 exists in cross-over RCTs, therefore a further four questions were used to assess the  
10  
11 additional risk of bias exists in cross-over RCTs, therefore a further four questions were used  
12  
13 to assess the methodological quality of these RCTs as recommended in the Cochrane  
14  
15 Handbook for Systematic Reviews of Interventions.  
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### 20 *Data synthesis and analysis*

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23 Data from included studies were pooled in a statistical meta-analysis model using Review  
24  
25 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>34</sup> The continuous data  
26  
27 extracted from the cross-over RCTs were treated as if from a parallel trial.<sup>35</sup> All pooled  
28  
29 statistics were subject to double data entry with two independent reviewers. For continuous  
30  
31 data, effect sizes are expressed as mean differences and corresponding 95% confidence  
32  
33 intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis.  
34  
35 Statistical heterogeneity was assessed in the meta-analysis using the  $I^2$  and chi-squared  
36  
37 statistics, and heterogeneity was considered substantial if  $I^2 > 50\%$  and P value  $< 0.10$  in the  
38  
39 chi-square test for heterogeneity.<sup>36</sup> A random effects model was used in the meta-analysis.  
40  
41 Subgroup-analysis according to type of intervention and length of intervention period were  
42  
43 performed. For results which were not possible to present in a meta-analysis, the findings  
44  
45 have been presented in a narrative form.  
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### 50 *Patient and public involvement:*

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52 No patient involved.  
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## 56 **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<sup>37</sup> or non-diabetic<sup>38</sup>, in vitro study<sup>39</sup>, did not assess the outcome of interest<sup>30,40,41</sup> and study done on rats.<sup>42</sup>

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Insert Figure1 here

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### *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 <sup>16</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>31</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>19</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>43</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>29</sup>	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

JBIC 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<sup>16</sup> to 26/26<sup>19</sup> (Table

1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>43</sup> 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)

	<b>Citation</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Score</b>
1	Shahmiri 2013 <sup>43</sup>	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<sup>15,16,19,29,31</sup> and one was cross-over RCT.<sup>43</sup> The six trials were conducted in six different countries – Germany<sup>31</sup>, Pakistan<sup>19</sup>, Netherlands<sup>29</sup>, Australia<sup>43</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>43</sup> to 165<sup>31</sup> 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.<sup>16,29</sup> One trial<sup>29</sup> had male predominance (77% vs 33%) while the other<sup>16</sup> had female predominance (61% vs 39%). The mean age of the patients ranged from 52 ± 8 years<sup>16</sup> to 65.3 ± 5.9 years.<sup>29</sup>

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

Fasting blood glucose was reported in four trials,<sup>15,16,19,43</sup> PPG in two trials,<sup>16,43</sup> HbA1c in five trials,<sup>15,16,19,29,31</sup> HDL in four trials,<sup>15,16,19,29</sup> LDL in three trials,<sup>15,19,29</sup> triglycerides in four trials,<sup>15,16,19,29</sup>, systolic and diastolic BP in three trials<sup>15,19,29</sup> and BMI in two trials.<sup>15,43</sup> 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<sup>15,29</sup> 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<sup>19,29,31</sup> 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<sup>31</sup> reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

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Insert Figure 2

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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; 95% CI -1.09, 0.49).

## FBG

### *Comparison between Thiamine supplementation vs Placebo*

Pooled results from three trials<sup>15,19,43</sup> 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).

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**Insert Fig 3 here**

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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 mmol/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<sup>43</sup> 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<sup>16</sup> 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<sup>15,19,29</sup> 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

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

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#### 9 10 11 *Comparisons between various dosages of Benfotiamine supplementation*

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14 One trial <sup>16</sup> compared two dosages of Benfotiamine demonstrated no statistically significant  
15 differences in the HDL levels among those who received 320 mg/day benfotiamine compared  
16 to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36 ).  
17 Similarly, there were no statistically significant differences in the HDL levels among those  
18 who received 320 mg/day benfotiamine compared to those who received 150 mg/day  
19 benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant  
20 differences in the HDL levels among those who received 120 mg/day benfotiamine compared  
21 to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).  
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#### 33 **LDL**

##### 34 35 36 *Comparison between Thiamine supplementation vs Placebo*

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

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#### 50 51 52 53 54 55 **Triglycerides**

##### 56 57 58 *Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on  
4 triglyceride levels. The results demonstrated no statistically significant differences in the  
5 triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04)  
6 (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) .  
7  
8 The study by Rabbani provided Median and minimum and maximum scores and hence could  
9 not be included in the meta-analysis. The results however demonstrated no statistically  
10 significant differences in the triglyceride levels between the groups at the 3 month follow-up.  
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**Insert Fig 6**

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### *Comparisons between various dosages of Benfotiamine supplementation*

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26 One trial<sup>16</sup> that compared various dosages of Benfotiamine demonstrated no statistically  
27 significant differences in the triglyceride levels among those who received 320 mg/day  
28 benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l;  
29 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the  
30 HbA1C levels among those who received 320 mg/day benfotiamine compared to those who  
31 received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels  
32 among those who received 120 mg/day benfotiamine compared was significantly lower  
33 compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -  
34 1.90,-0.30)  
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### **BMI**

#### *Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on BMI  
4 levels. Pooled results demonstrated no statistically significant differences in the BMI levels  
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6 between the groups at less than 3 month (MD -0.22 kg/m<sup>2</sup>; 95% CI -2.23, 1.79).  
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### 10 **Systolic BP**

#### 11 *Comparison between Thiamine supplementation vs Placebo*

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

#### 27 *Comparison between Thiamine supplementation vs Placebo*

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30 Three trials <sup>15,27,34</sup> investigated the effect of thiamine supplementation vs placebo on diastolic  
31 BP levels. Pooled results demonstrated no statistically significant differences in the diastolic  
32 BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as  
33 well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).  
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### 45 **Discussion**

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48 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
49 outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides  
50 while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid  
51 soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and  
52 HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and  
53 diastolic BP and BMI. Since this review only included trials that were undertaken in people  
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3 with T2DM, only six trials were eligible for inclusion of which one was a cross over trial.  
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5 The overall methodological quality of the trials was variable as the assessment criteria  
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7 regarding the method of randomization and allocation concealment was not reported in four  
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9 trials.  
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13 For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment  
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15 effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the  
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17 literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG <sup>44,45</sup> is considered  
18  
19 as clinically significant. In our review, the treatment effect sizes did not reach the point of  
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21 clinical significance for both HbA1C and FBG which could be due to the small sample sizes  
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23 in the included studies. Nevertheless, the small reductions identified in HbA1C and blood  
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25 glucose levels can reduce the health impacts associated with T2DM <sup>46</sup>.  
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32 The results of the review also demonstrated no significant differences in FBG, LDL, and BMI  
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34 in T2DM patients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation  
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36 compared to those receiving placebo at less than three months or at three months follow-up.  
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38 These results could be due the fact that the outcomes were assessed within three months of  
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40 administration of thiamine. It has been established that plasma thiamine level is associated  
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42 with increased fractional excretion of thiamine resulting in decreased thiamine concentration  
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44 by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore, trials with longer term follow-up are  
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46 required to assess the effect of thiamine on glycemic outcomes.  
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52 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
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54 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
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56 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
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3 as the dose was escalated. This result should be interpreted with caution as these results are  
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5 based on a single study with a sample size of 36 participants.  
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10 Various other factors could have influenced the results of the review including different  
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12 populations in different studies (with different diabetes risk) and the presence of underlying  
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14 health conditions (like presence of autoimmune diseases) which can cause high blood glucose  
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16 despite thiamine supplementation. It has been shown that people with poorly controlled  
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18 diabetes often experience micronutrient deficiencies <sup>47</sup>. Hence there is substantial interest  
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20 globally to find easily accessible and inexpensive treatments such as thiamine  
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22 supplementation for T2DM.  
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### 28 *Limitations of this review*

- 31 • The review includes single-centre trials published only in the English language.
- 32  
33 • Sample sizes of the included studies were small although some had addressed this  
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35 issue using statistical power.  
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- 38 • There was a lack of trials investigating the outcomes for a variety of comparisons,  
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- 41 • The follow-up period varied among trials.  
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### 49 **Conclusions**

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51 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
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53 outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to  
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55 change practices. Therefore, existing practices will be dictated by current policies. However,  
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57 some important points have been identified such as, the studies published to date have been  
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3 single centric studies, with small sample size, varying doses and follow-up for only 3 months.  
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5 Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer  
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7 follow-up of 1-2 years using sample size based on power calculation should be undertaken to  
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9 address the confusion regarding benefit of thiamine supplementation on glycemic outcomes  
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11 in T2DM. One such study if undertaken would be able to give specific recommendations on  
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13 whether or not to consider thiamine supplementation for improving glycemic outcomes in  
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15 T2DM patients.  
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23 *Ethics statement:* This study does not involve any human or animal participant.  
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26 *Funding:* No additional sources of funding.  
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29 *Data availability:* No additional data available.  
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32 *Disclosure of Interest:* The authors declare that they have no competing interests.  
33  
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35 *Contribution:* AM, RF: Study concept and design, data analysis, manuscript preparation; HL:  
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37 Data acquisition, manuscript preparation and analysis; PM: Data collection, manuscript  
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39 preparation and analysis.  
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42 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
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4 controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy.  
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from the MONICA/KORA S3/F3 study. *PLoS One*. 2015;10(10).

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4 and increased formation of methylglyoxal in human red blood cells during hyperglycaemia  
5 by thiamine in vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.  
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11 glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic  
12 nephropathy. *PLoS One*. 2012;7(7).  
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21 nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.  
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25 improves glucose tolerance in hyperglycemic individuals: a randomized, double-blind cross-  
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35 monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the  
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44 management of adults with diabetes. *Diabetes Care*. 2014;37(Supplement 1):S120-S43.  
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#### Figure Legends:

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59 Fig 1: PRISMA 2009 Flow Diagram for searching  
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3 Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3  
4 months follow up.  
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8 Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.  
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11 Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.  
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14 Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.  
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17 Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up  
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### PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

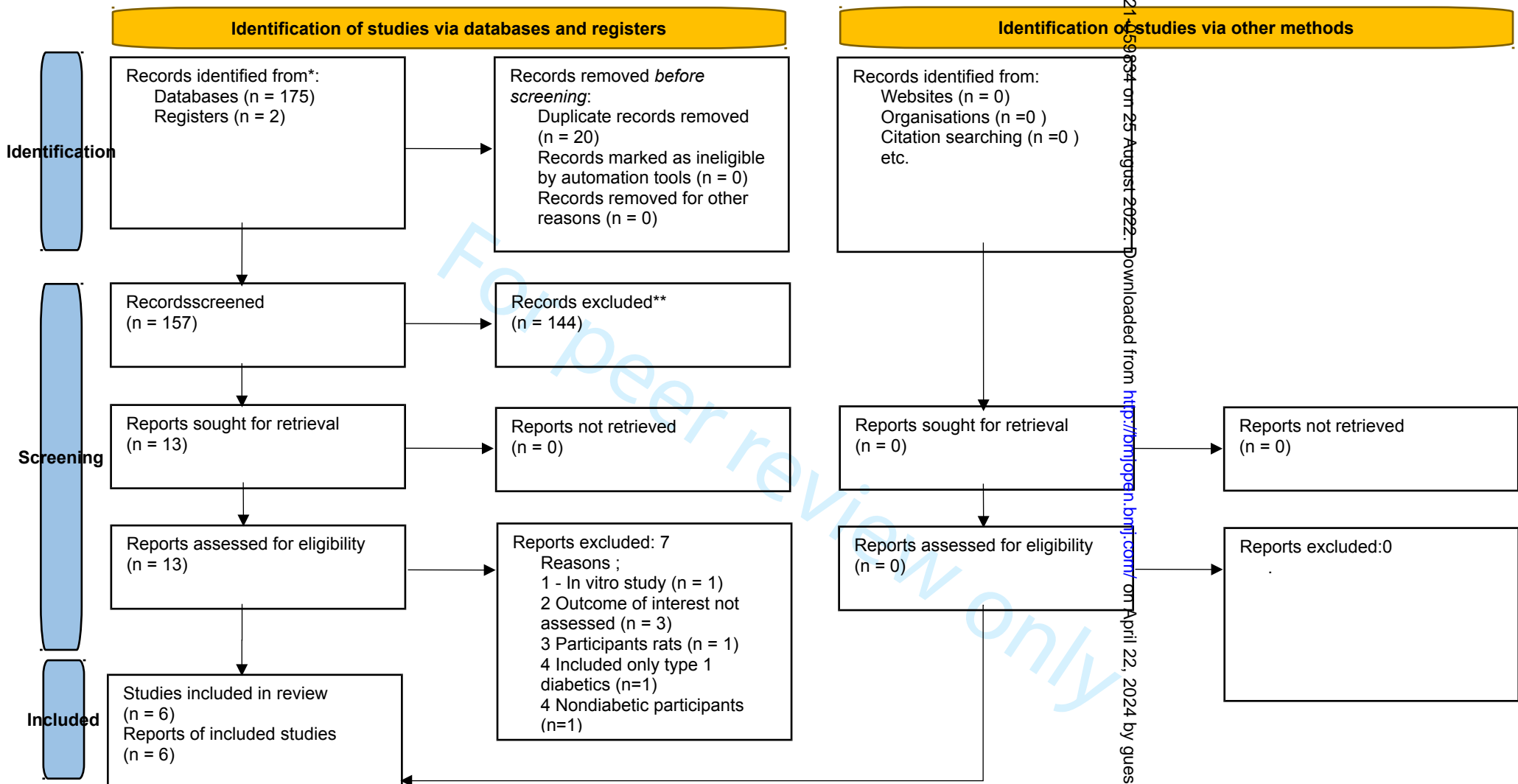


Fig 1: PRISMA 2020 Flow diagram showing searching results

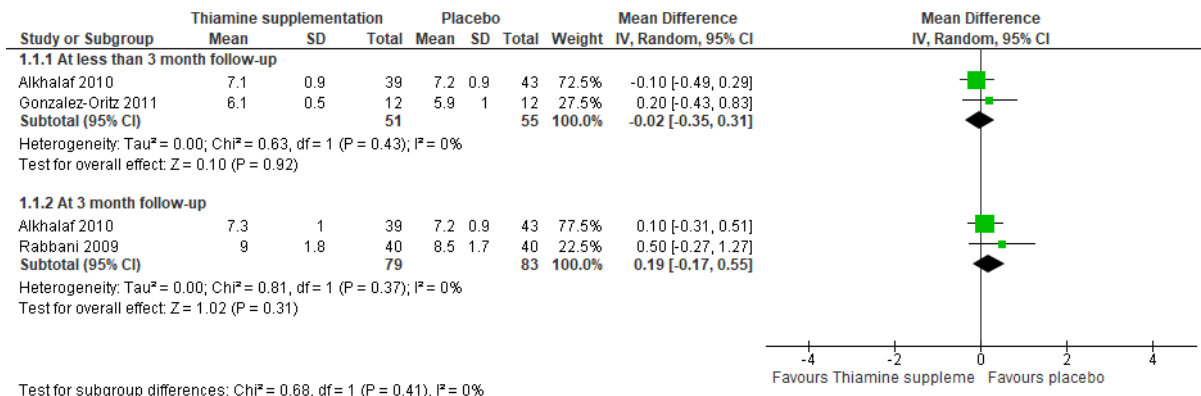
\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

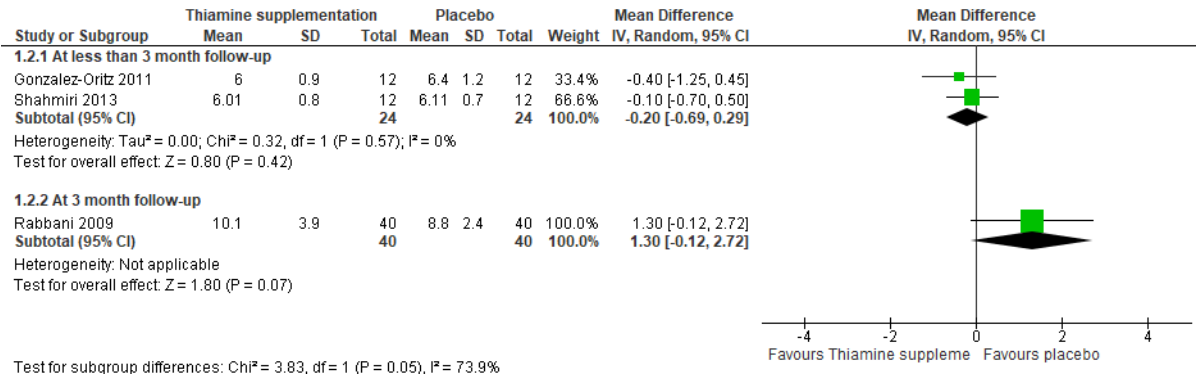
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

bmjopen-2021-0159834 on 25 August 2022. Downloaded from <http://bmjopen.bmj.com/> on April 22, 2024 by guest. Protected by copyright.



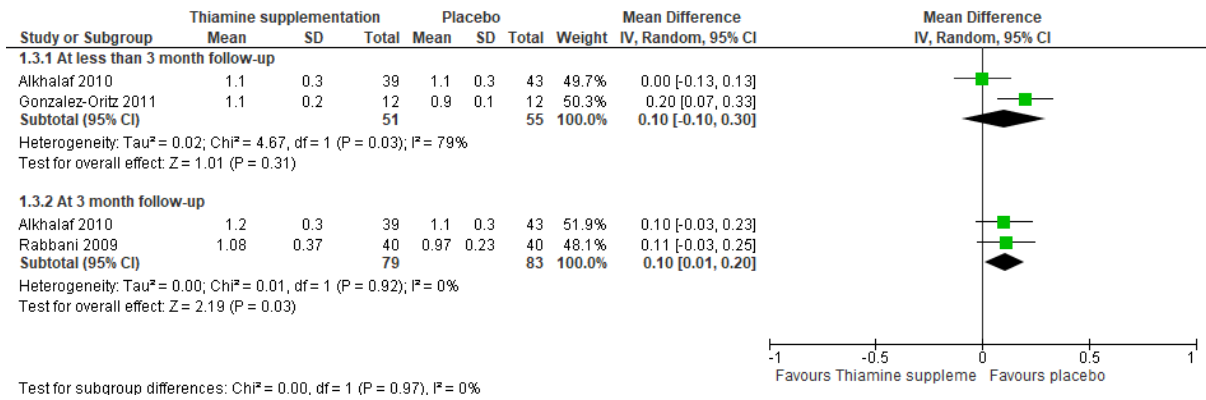


**Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.**

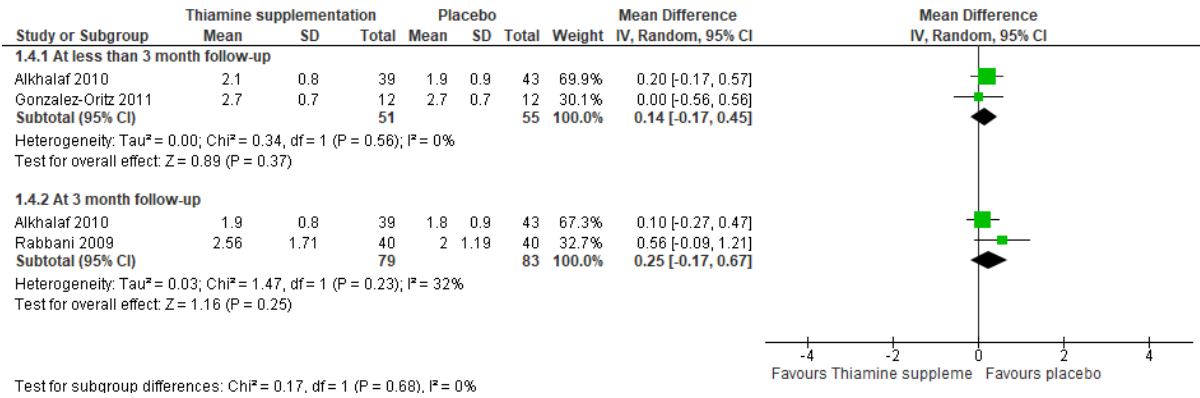


**Fig 3: Effect on FBG at less than 3 months and at 3 months follow up**

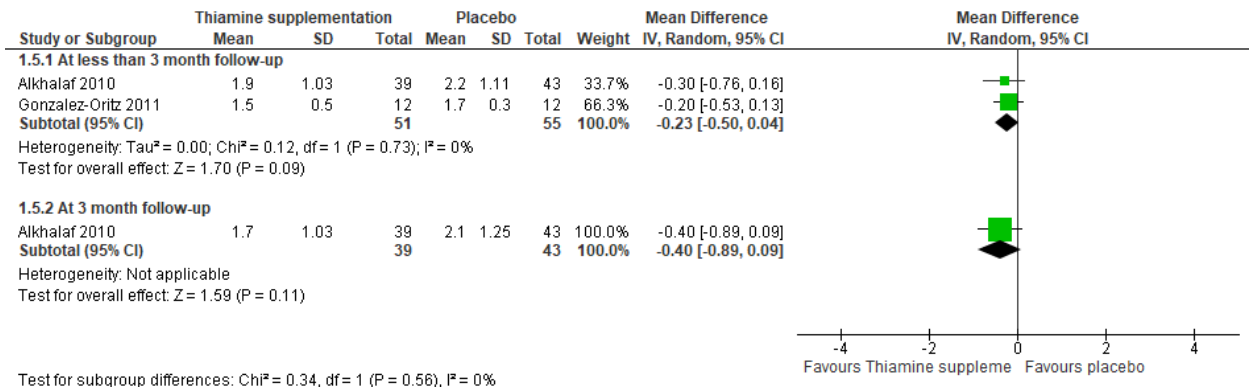
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**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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 <input type="checkbox"/> 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

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**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

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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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16 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
17 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
18 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

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

24 **Reason for exclusion: Outcome of interest not assessed.**  
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27 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
28 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

29 **Reason for exclusion: Participants rats.**  
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33 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
34 *Metabolic brain disease*. 1996;11(1):95-106.

35 **Reason for exclusion: Outcome of interest not assessed.**  
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38 Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, Seljeflot I, et al. The effects of long-  
39 term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers  
40 in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial.  
41 *Diabetes Care*. 2012;35(5):1095-7.

42 **Reason for exclusion: Included only type 1 diabetics.**  
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46 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
47 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
48 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

49 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC 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, FBC 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride at 6 weeks.	No differences in metabolic outcomes between the three groups.

Table of included study characteristics

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

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Nutritional support < GASTROENTEROLOGY, Nutrition < TROPICAL MEDICINE

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3 **Title:** Effect of Thiamine supplementation on glycemc outcomes in adults with Type 2  
4 diabetes: A systematic review and meta-analysis  
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8 Running title: Type 2 Diabetes and thiamine  
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10 Authors:

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12 Ritin Fernandez<sup>2,3,4</sup>

13 Heidi Green<sup>3</sup>

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23 Excellence, NSW, Australia  
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27 4. School of Nursing, University of Wollongong, Sydney, Australia.  
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31 Key words: Type 2 diabetes mellitus; Thiamine; Glycaemic outcomes; Systematic review

32 Word count:

33 Abstract: 244

34 Main text: 4868

35 No. of references: 52  
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4 diabetes: A systematic review and meta-analysis  
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7 **ABSTRACT**  
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10 **Background:** Patients with Type 2 diabetes mellitus (T2DM) have been shown to have  
11 thiamine deficiency. Dietary supplementation is an economic strategy to control blood  
12 glucose. *Objective:* To evaluate effectiveness of thiamine supplementation on glycemc  
13 outcomes in patients with T2DM.  
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19 **Methods:**  
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23 *Eligibility criteria:* Studies that assessed effect of thiamine supplementation in adults with  
24 T2DM which measured glycemc outcomes - HbA1C, fasting blood glucose (FBG), and/or  
25 post prandial blood glucose (PPG) were included.  
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30 *Information sources:* PUBMED, Tripdatabase, the Cochrane Central Register, National  
31 Institute of Health Clinical Database and Google Scholar were searched until December 2021  
32 for RCTs.  
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37 *Risk of bias:* It was assessed using standardized critical appraisal instruments from the Joanna  
38 Briggs Institute for RCTs.  
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43 *Synthesis of results:* Where possible, studies were pooled in a meta-analysis. Results were  
44 presented in a narrative format if statistical pooling was not possible.  
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49 **Results:**  
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52 *Included studies:* Six trials involving 364 participants.  
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55 *Synthesis of results:* No significant beneficial effects were observed on glycemc outcomes  
56 with 100 – 900 mg/day of Thiamine or benfotiamine for up to 3 months (HbA1C: MD -0.02  
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3 %, 95% CI -0.35, 0.31; FBG: MD -0.20 mmol/l; CI -0.69, 0.29; PPG : MD - 0.20 mmol/l, CI  
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5 -2.05, 1.65). There was a significant increase in HDL (MD 0.10; CI 0.10, 0.20) at 3 months  
6  
7 follow-up. Benfotiamine reduced triglyceride level (MD -1.10; 95% CI -1.90,-0.30) in  
8  
9 120mg/day dose as compared to placebo 150 mg/day, however this was not demonstrated in  
10  
11 higher doses.  
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### 14 15 **Discussion:**

16  
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18 *Limitations of evidence:* Inclusion of single-centre trials published only in English, small  
19  
20 sample sizes of included studies, lack of trials investigating outcomes for some comparisons  
21  
22 and varying follow-up periods.  
23  
24

25  
26 *Interpretation:* Thiamine supplementation doesn't affect glycaemic outcomes, however  
27  
28 reduces triglycerides while increasing HDL. Multicentre well designed RCT with higher  
29  
30 doses of thiamine and a follow-up period of 1-2 years will provide better evidence.  
31  
32

### 33 34 **Strengths:**

- 35  
36 • Addresses an important topic of control of diabetes with thiamine supplementation  
37  
38 including secondary outcomes as well like LDL and triglyceride levels.  
39  
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- 41  
42 • Included only good quality RCTs, hence the results can be relied upon to give  
43  
44 direction to future research.  
45  
46

### 47 48 **Limitations:**

- 49  
50 • The review includes single-centre trials published only in the English language.  
51  
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- 53  
54 • Sample sizes of the included studies were small although some had addressed this  
55  
56 issue using statistical power.  
57  
58  
59  
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- 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

For peer review only

## 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.<sup>1</sup>

T2DM resulted in 59,258,034 disability adjusted life years (DALYs) in 2012 and became the third most common cause of fatal complications.<sup>2</sup> It is a known risk factor for ischemic heart disease with approximately 20% to 30% of patients undergoing coronary artery bypass graft (CABG).<sup>3,4</sup> 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.<sup>5</sup> Thiamine diphosphate (TDP) is its metabolically active form that acts as a coenzyme for transketolase (TK), pyruvate dehydrogenase and  $\alpha$ -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.<sup>6</sup> The pancreas also has high concentration of thiamine. Here, the uptake of thiamine is carrier mediated, regulated by the prevailing vitamin level.<sup>7</sup> Given its physiological action, thiamine deficiency can lead to a marked decrease in synthesis and secretion of insulin.<sup>8</sup>

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.<sup>9</sup>It also has a role in blocking pathways responsible for

1  
2  
3 hyperglycaemia induced damage, such as the hexosamine pathway, formation of Advanced  
4 Glycation End Products (AGEs) and activation of protein kinase C. It also works by  
5  
6 activating transketolase which is the rate limiting enzyme of the non-oxidative branch of the  
7  
8 pentose phosphate pathway.<sup>10</sup>  
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### 12 13 *How the intervention might work* 14

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

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

1  
2  
3 Many studies have investigated the association between fasting blood sugar (FBS), post  
4 prandial blood sugar (PP2BS), glycosylated haemoglobin (HbA1C), BP, cholesterol, LDL,  
5 HDL, triglycerides and various vitamins (including thiamine) and minerals<sup>13,15,17-28</sup> but with  
6 inconsistent results. Some studies reported significant inverse association for thiamine  
7 supplementation<sup>19-21,23</sup> while other intervention studies did not find any significant association  
8 with thiamine.<sup>13,15,17,18,20,29-31</sup>

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

## 28 29 30 31 32 33 34 35 36 37 38 39 40 41 **Methods**

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

### 50 51 52 53 54 55 56 57 *Literature search strategy*

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3 The search strategy aimed to find both published and unpublished studies which included a  
4 three-step search strategy to include all relevant articles published till 31<sup>st</sup> December 2019  
5 and updated later till 31<sup>st</sup> December 2021. A final update search was done till 30<sup>th</sup> June 2022.  
6  
7 No additional article was found in the updated search. An initial limited search of PUBMED  
8 using the keywords: vitamin B1, thiamine, benfotiamine, diabetes mellitus and blood glucose  
9 was undertaken. Text words contained in the title, abstract and index terms of the studies  
10 identified were used to inform the development of a search strategy for the second step which  
11 was tailored for each information source. Published studies were searched for including the  
12 databases: PUBMED, Tripdatabase and the Cochrane Central Register of Controlled Trials  
13 (CENTRAL) (The Cochrane Library). A full search strategy for the databases is detailed in  
14 Appendix I. The following databases were searched to find any unpublished studies: the  
15 National Institute of Health Clinical Database (<http://ClinicalTrials.gov>) and Google Scholar.  
16 The final step of the search strategy included a review of the reference list of all trials  
17 selected for critical appraisal. The search was restricted to papers published in the English  
18 language.

### 19 *Inclusion and exclusion criteria*

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



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2  
3 review. The following secondary outcomes were also included in the review: serum  
4 triglycerides level, HDL, LDL, systolic BP, diastolic BP and BMI. Trials in which the  
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6 outcomes were measured in different units were included and results were converted to  
7  
8 desired units for meta-analysis. Reviews, retrospective studies, observational studies, letters  
9  
10 to the editors, and conference abstracts were excluded. Any discrepancies were resolved by  
11  
12 discussion with a third author (HG). The results of the search is presented in a PRISMA flow  
13  
14 diagram (Figure 1).  
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### 20 *Screening*

21  
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23 The titles and abstracts of all the identified citations were independently screened by two  
24  
25 authors (AM and RF) for assessment against the inclusion criteria. The full text of eligible  
26  
27 studies were assessed for inclusion and critically appraised independently reviewed by two  
28  
29 authors (AM and RF).  
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### 33 *Data extraction*

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35  
36 Quantitative data was extracted from all trials included in the review by two independent  
37  
38 reviewers (RF and HG) using the data extraction tool outlined in JBI SUMARI. The data  
39  
40 extracted included specific details about the type of intervention, populations, context, study  
41  
42 design and duration, study methods and other outcomes of significance to the review question  
43  
44 and specific objectives.  
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### 48 *Quality assessment*

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51 Methodological quality of parallel group RCTs was assessed using the widely used critical  
52  
53 JBI checklist for randomised controlled trials.<sup>32</sup> This checklist comprises of 13 items that  
54  
55 assesses bias relating to design, conduct, analysis and reporting of RCTs. Items were scored  
56  
57 as '2' when the criteria were found adequately reported for the study, '1' when the  
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3 information was unclear and '0' when there was no reporting based on the criteria. The  
4 minimal obtainable score was 0 and the maximum 26. For unclear information, authors were  
5 contacted for more information and a decision made accordingly. An additional risk of bias  
6 exists in cross-over RCTs, therefore a further four questions were used to assess the  
7 additional risk of bias exists in cross-over RCTs, therefore a further four questions were used  
8 to assess the methodological quality of these RCTs as recommended in the Cochrane  
9 Handbook for Systematic Reviews of Interventions.  
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### 20 *Data synthesis and analysis*

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23 Data from included studies were pooled in a statistical meta-analysis model using Review  
24 Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).<sup>34</sup> The continuous data  
25 extracted from the cross-over RCTs were treated as if from a parallel trial.<sup>35</sup> All pooled  
26 statistics were subject to double data entry with two independent reviewers. For continuous  
27 data, effect sizes are expressed as mean differences and corresponding 95% confidence  
28 intervals (CI) were calculated. Post-intervention mean (SD) was used in meta-analysis.  
29  
30 Statistical heterogeneity was assessed in the meta-analysis using the  $I^2$  and chi-squared  
31 statistics, and heterogeneity was considered substantial if  $I^2 > 50\%$  and P value  $< 0.10$  in the  
32 chi-square test for heterogeneity.<sup>36</sup> A random effects model was used in the meta-analysis.  
33  
34 Subgroup-analysis according to type of intervention and length of intervention period were  
35 performed. For results which were not possible to present in a meta-analysis, the findings  
36 have been presented in a narrative form.  
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### 50 *Patient and public involvement:*

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52 No patient involved.  
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## 58 **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<sup>37</sup> or non-diabetic<sup>38</sup>, in vitro study<sup>39</sup>, did not assess the outcome of interest<sup>30,40,41</sup> and study done on rats.<sup>42</sup>

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Insert Figure1 here

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### *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 <sup>16</sup>	U	U	U	N	N	U	Y	Y	Y	Y	Y	Y	Y	18/26
Gonzalez-Ortiz 2010 <sup>15</sup>	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Stracke 2008 <sup>31</sup>	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	23/26
Rabbani 2009 <sup>19</sup>	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	24/26
Shahmiri <sup>43</sup>	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	25/26
Alkhalaf 2010 <sup>29</sup>	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

JBIC 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<sup>16</sup> to 26/26<sup>19</sup> (Table

1). Whilst all trials reported that participants were randomized, the precise method of randomization was reported by only one<sup>19</sup> 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,<sup>43</sup> 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)

	<b>Citation</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Score</b>
1	Shahmiri 2013 <sup>43</sup>	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<sup>15,16,19,29,31</sup> and one was cross-over RCT.<sup>43</sup> The six trials were conducted in six different countries – Germany<sup>31</sup>, Pakistan<sup>19</sup>, Netherlands<sup>29</sup>, Australia<sup>43</sup>, Mexico/USA<sup>15</sup> and Hungary<sup>16</sup>. The number of participants in parallel RCTs varied from 12<sup>43</sup> to 165<sup>31</sup> 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.<sup>16,29</sup> One trial<sup>29</sup> had male predominance (77% vs 33%) while the other<sup>16</sup> had female predominance (61% vs 39%). The mean age of the patients ranged from 52 ± 8 years<sup>16</sup> to 65.3 ± 5.9 years.<sup>29</sup>

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

Fasting blood glucose was reported in four trials,<sup>15,16,19,43</sup> PPG in two trials,<sup>16,43</sup> HbA1c in five trials,<sup>15,16,19,29,31</sup> HDL in four trials,<sup>15,16,19,29</sup> LDL in three trials,<sup>15,19,29</sup> triglycerides in four trials,<sup>15,16,19,29</sup>, systolic and diastolic BP in three trials<sup>15,19,29</sup> and BMI in two trials.<sup>15,43</sup> 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<sup>15,29</sup> 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<sup>19,29,31</sup> 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<sup>31</sup> reported no statistically significant differences in the HbA1C levels among those who received thiamine supplementation compared to those who received placebo.

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Insert Figure 2

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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; 95% CI -1.09, 0.49).

## FBG

### *Comparison between Thiamine supplementation vs Placebo*

Pooled results from three trials<sup>15,19,43</sup> 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).

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**Insert Fig 3 here**

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### *Comparisons between various dosages of Benfotiamine supplementation*

One trial<sup>16</sup> 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 mmol/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<sup>43</sup> 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<sup>16</sup> 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<sup>15,19,29</sup> 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



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

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11 *Comparisons between various dosages of Benfotiamine supplementation*

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13  
14 One trial <sup>16</sup> compared two dosages of Benfotiamine demonstrated no statistically significant  
15 differences in the HDL levels among those who received 320 mg/day benfotiamine compared  
16 to those who received 120 mg/day benfotiamine (MD 0.00 mmol/l; CI -0.36, 0.36 ).  
17  
18 Similarly, there were no statistically significant differences in the HDL levels among those  
19 who received 320 mg/day benfotiamine compared to those who received 150 mg/day  
20 benfotiamine (MD -0.20 mmol/l, CI -0.60, 0.20). There were also no statistically significant  
21 differences in the HDL levels among those who received 120 mg/day benfotiamine compared  
22 to those who received 150 mg/day benfotiamine (MD -0.20 mmol/l, CI -0.56, 0.16).  
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33 **LDL**

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36 *Comparison between Thiamine supplementation vs Placebo*

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

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55 **Triglycerides**

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58 *Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on  
4 triglyceride levels. The results demonstrated no statistically significant differences in the  
5 triglyceride levels between the groups at less than 3 month (MD -0.23 mmol/l; CI -0.50, 0.04)  
6 (Fig 6) as well as the 3 month follow-up period (MD -0.40 mmol/l; CI -0.89, 0.09) (Fig 6) .  
7  
8 The study by Rabbani provided Median and minimum and maximum scores and hence could  
9 not be included in the meta-analysis. The results however demonstrated no statistically  
10 significant differences in the triglyceride levels between the groups at the 3 month follow-up.  
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**Insert Fig 6**

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### *Comparisons between various dosages of Benfotiamine supplementation*

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25  
26 One trial<sup>16</sup> that compared various dosages of Benfotiamine demonstrated no statistically  
27 significant differences in the triglyceride levels among those who received 320 mg/day  
28 benfotiamine compared to those who received 120 mg/day benfotiamine (MD 0.30 mmol/l;  
29 95% CI -0.46, 1.06). Similarly, there were no statistically significant differences in the  
30 HbA1C levels among those who received 320 mg/day benfotiamine compared to those who  
31 received 150 mg/day benfotiamine (MD -0.80 mmol/l; 95% CI -1.64, 0.04). HbA1C levels  
32 among those who received 120 mg/day benfotiamine compared was significantly lower  
33 compared to those who received 150 mg/day benfotiamine (MD -1.10 mmol/l; 95% CI -  
34 1.90,-0.30)  
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### **BMI**

#### *Comparison between Thiamine supplementation vs Placebo*

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3 Three trials <sup>15,19,29</sup> investigated the effect of thiamine supplementation vs placebo on BMI  
4 levels. Pooled results demonstrated no statistically significant differences in the BMI levels  
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6 between the groups at less than 3 month (MD -0.22 kg/m<sup>2</sup>; 95% CI -2.23, 1.79).  
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### 10 **Systolic BP**

#### 11 *Comparison between Thiamine supplementation vs Placebo*

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

#### 27 *Comparison between Thiamine supplementation vs Placebo*

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30 Three trials <sup>15,27,34</sup> investigated the effect of thiamine supplementation vs placebo on diastolic  
31 BP levels. Pooled results demonstrated no statistically significant differences in the diastolic  
32 BP levels between the groups at less than 3 month (MD 0.71 mmHg; 95% CI -2.77,4.18) as  
33 well as the 3 month follow up period (MD 0.55 mmHg; 95% CI -2.22, 3.31).  
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### 45 **Discussion**

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48 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
49 outcomes at doses 100 to 900mg/day for up to 3 months, however it reduces triglycerides  
50 while increasing HDL. It was conducted to investigate the effects of thiamine and its lipid  
51 soluble derivative benfotiamine on various glycaemic parameters including FBG, PPG and  
52 HbA1C in people with T2DM. Secondary outcomes included HDL, LDL, systolic and  
53 diastolic BP and BMI. Since this review only included trials that were undertaken in people  
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3 with T2DM, only six trials were eligible for inclusion of which one was a cross over trial.  
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5 The overall methodological quality of the trials was variable as the assessment criteria  
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7 regarding the method of randomization and allocation concealment was not reported in four  
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9 trials.  
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13 For HbA1C, the meta-analysis demonstrated a non-statistically significant overall treatment  
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15 effect size of 0.02% and for FBG the effect size was 0.2mmol/L. Evidence from the  
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17 literature indicates that a difference of 0.5% HbA1C and 1mmol/L in FBG <sup>44,45</sup> is considered  
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19 as clinically significant. In our review, the treatment effect sizes did not reach the point of  
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21 clinical significance for both HbA1C and FBG which could be due to the small sample sizes  
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23 in the included studies. Nevertheless, the small reductions identified in HbA1C and blood  
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25 glucose levels can reduce the health impacts associated with T2DM <sup>46</sup>.  
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32 The results of the review also demonstrated no significant differences in FBG, LDL, and BMI  
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34 in T2DM patients receiving 100 to 900 mg/day thiamine or benfotiamine supplementation  
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36 compared to those receiving placebo at less than three months or at three months follow-up.  
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38 These results could be due the fact that the outcomes were assessed within three months of  
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40 administration of thiamine. It has been established that plasma thiamine level is associated  
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42 with increased fractional excretion of thiamine resulting in decreased thiamine concentration  
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44 by about 75% in type 2 diabetic patients <sup>7</sup>. Therefore, trials with longer term follow-up are  
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46 required to assess the effect of thiamine on glycemic outcomes.  
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52 A significant reduction in triglyceride level was demonstrated with a 120mg/day  
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54 benfotiamine dose compared to 150mg/day dose. However, when compared to 320mg/day  
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56 dosage there were no differences in triglyceride levels <sup>16</sup> indicating that the benefit decreased  
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3 as the dose was escalated. This result should be interpreted with caution as these results are  
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5 based on a single study with a sample size of 36 participants.  
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10 Various other factors could have influenced the results of the review including different  
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12 populations in different studies (with different diabetes risk) and the presence of underlying  
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14 health conditions (like presence of autoimmune diseases) which can cause high blood glucose  
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16 despite thiamine supplementation. It has been shown that people with poorly controlled  
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18 diabetes often experience micronutrient deficiencies <sup>47</sup>. Hence there is substantial interest  
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20 globally to find easily accessible and inexpensive treatments such as thiamine  
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22 supplementation for T2DM.  
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### 28 *Limitations of this review*

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

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51 This review demonstrates that there is no benefit of thiamine supplementation on glycaemic  
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53 outcomes at doses 100 to 900mg/day for up to 3 months. Further research is warranted to  
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55 change practices. Therefore, existing practices will be dictated by current policies. However,  
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57 some important points have been identified such as, the studies published to date have been  
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3 single centric studies, with small sample size, varying doses and follow-up for only 3 months.  
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5 Therefore, more robust designed multicentre RCTs with higher doses of thiamine for longer  
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7 follow-up of 1-2 years using sample size based on power calculation should be undertaken to  
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9 address the confusion regarding benefit of thiamine supplementation on glycemic outcomes  
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11 in T2DM. One such study if undertaken would be able to give specific recommendations on  
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13 whether or not to consider thiamine supplementation for improving glycemic outcomes in  
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15 T2DM patients.  
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23 *Ethics statement:* This study does not involve any human or animal participant.  
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26 *Funding:* No additional sources of funding.  
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29 *Data availability:* No additional data available.  
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32 *Disclosure of Interest:* The authors declare that they have no competing interests.  
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35 *Contribution:* AM, RF formulated the study concept and design and contributed in data  
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37 analysis and manuscript preparation; GH : did data acquisition, manuscript preparation and  
38  
39 analysis; PM collected data and contributed in manuscript preparation and analysis.  
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42 *Acknowledgements:* The authors would like to thank Ms Sofia Russo for secretarial support.  
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56 Figure Legends:

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59 Fig 1: PRISMA 2009 Flow Diagram for searching  
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3 Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3  
4 months follow up.  
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8 Fig 3: Effect on FBG at less than 3 months and at 3 months follow up.  
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11 Fig 4: Effect on HDL at less than 3 months and at 3 months follow up.  
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14 Fig 5: Effect on LDL at less than 3 months and at 3 months follow up.  
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17 Fig 6: Effect on triglycerides at less than 3 months and at 3 months follow up  
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### PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

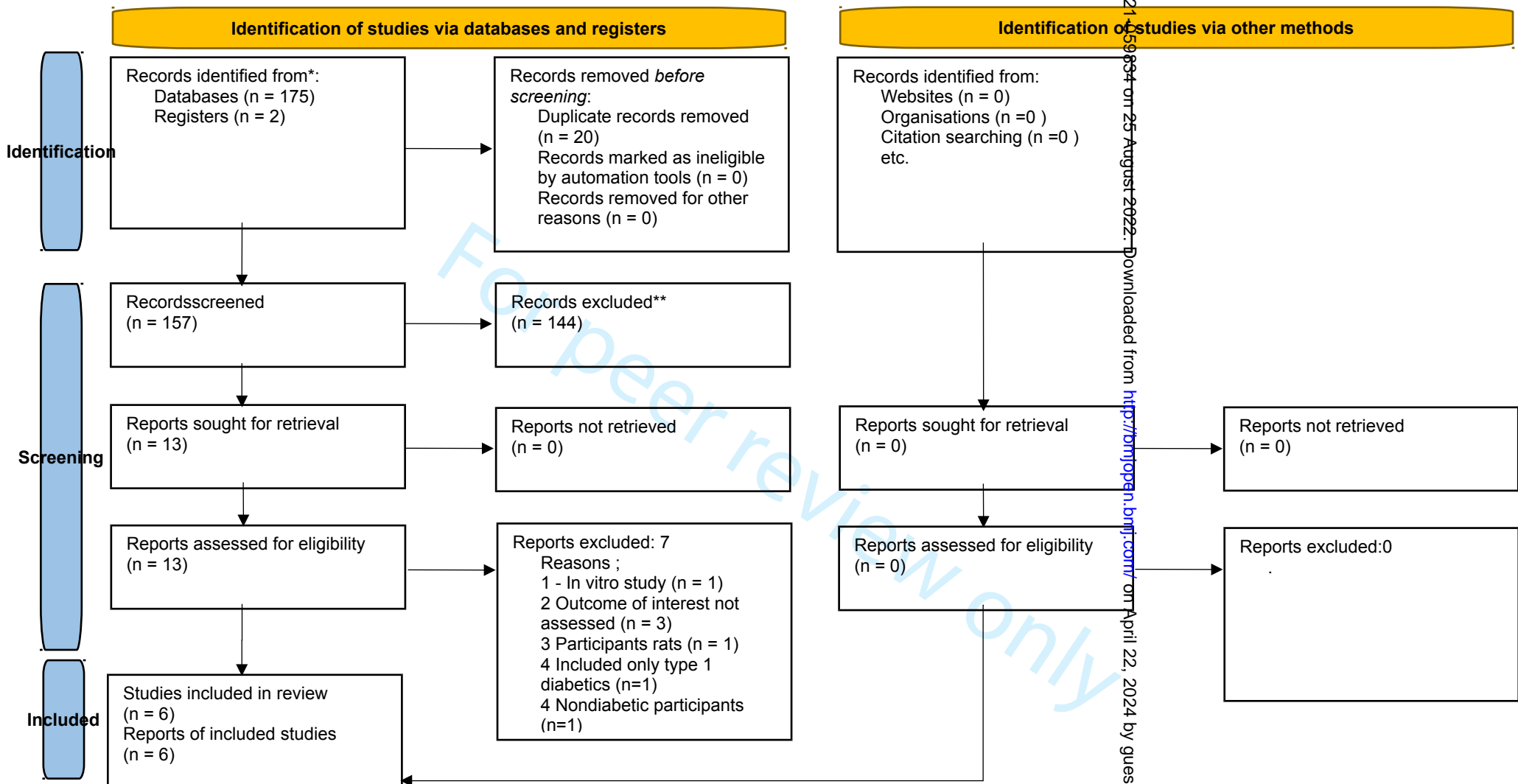


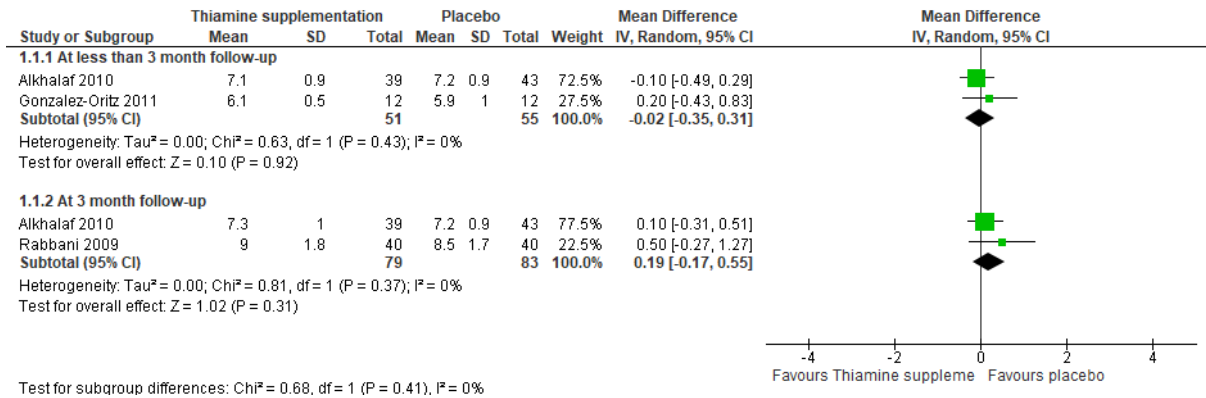
Fig 1: PRISMA 2020 Flow diagram showing searching results

\*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).

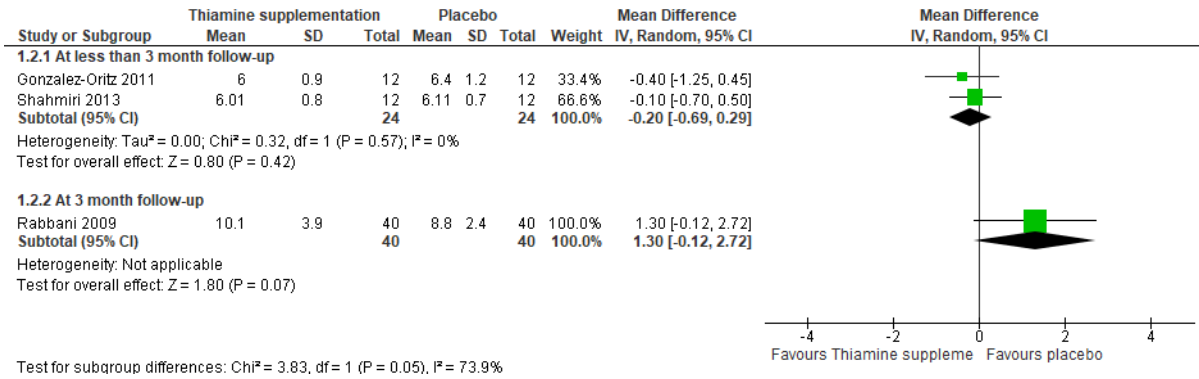
\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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/>

bmjopen-2021-015984 on 25 August 2022. Downloaded from <http://bmjopen.bmj.com/> on April 22, 2024 by guest. Protected by copyright.



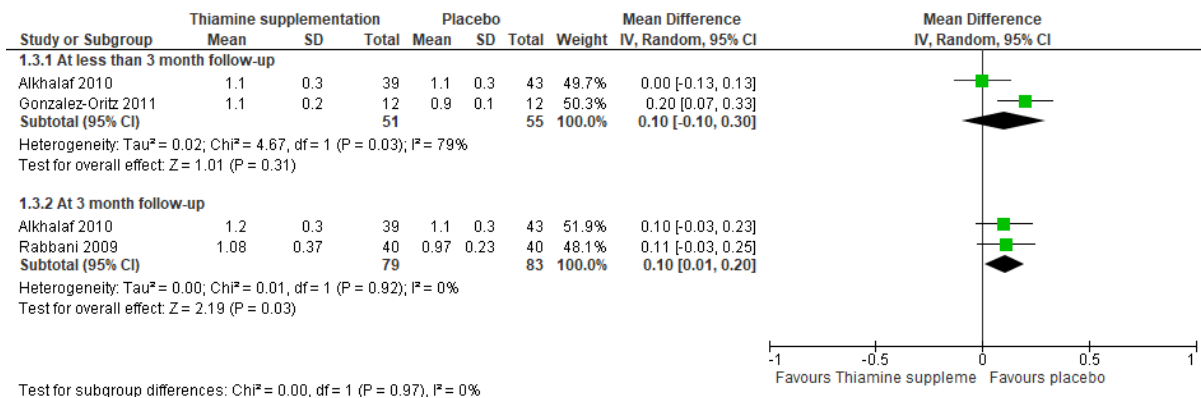
**Fig 2: Effect of thiamine supplementation on HbA1C level at less than 3 months and at 3 months follow up.**



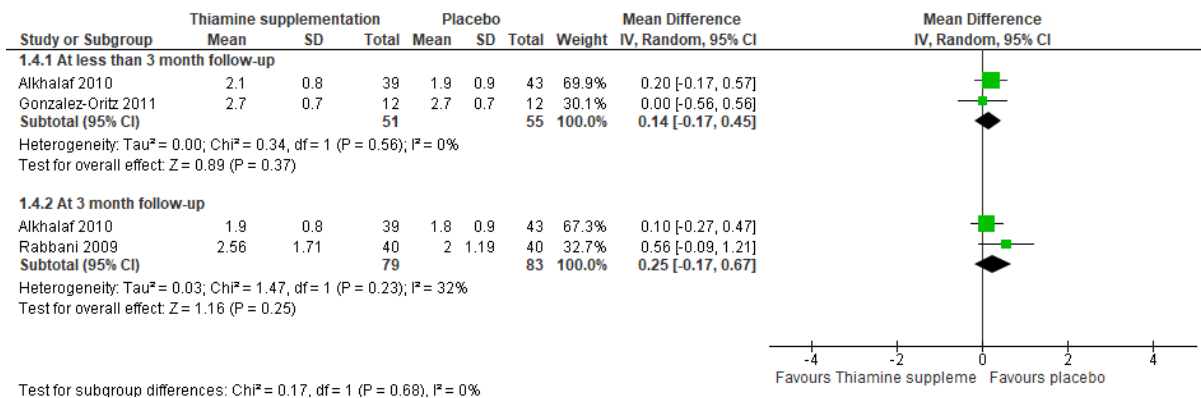
**Fig 3: Effect on FBG at less than 3 months and at 3 months follow up**

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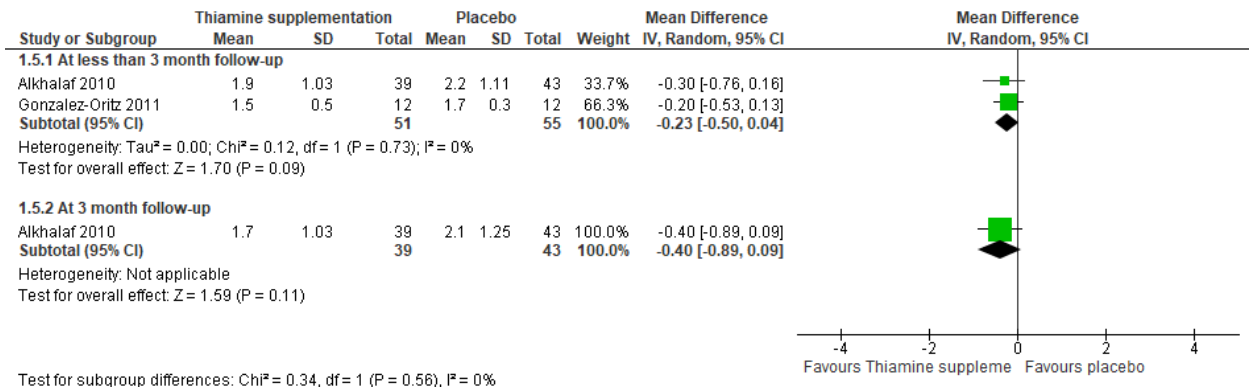




**Fig 4: Effect on HDL at less than 3 months and at 3 months follow up**



**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**

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4 *Appendix I: Search strategy*  
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7 **Search strategy for PubMed**

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No.	Search terms
1.	Diabetes Mellitus, Adult-Onset <input type="checkbox"/> 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

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**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

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5 *Appendix II: List of excluded studies*  
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7 **Excluded articles**  
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9 Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased  
10 formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in  
11 vitro. *The Journal of Biochemistry*. 2001;129(4):543-9.

12 **Reason for exclusion: In vitro study.**  
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16 Alkhalaf A, Kleefstra N, Groenier KH, Bilo HJ, Gans RO, Heeringa P, et al. Effect of  
17 benfotiamine on advanced glycationendproducts and markers of endothelial dysfunction and  
18 inflammation in diabetic nephropathy. *PLoS One*. 2012;7(7).

19 **Reason for exclusion: Outcome of interest not assessed.**  
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21  
22 Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic. *International*  
23 *journal of clinical pharmacology and therapeutics*. 2005;43(2):71-7.

24 **Reason for exclusion: Outcome of interest not assessed.**  
25

26  
27 Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ. Prevention of incipient  
28 diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes*. 2003;52(8):2110-20.

29 **Reason for exclusion: Participants rats.**  
30

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33 Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue.  
34 *Metabolic brain disease*. 1996;11(1):95-106.

35 **Reason for exclusion: Outcome of interest not assessed.**  
36

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

42 **Reason for exclusion: Included only type 1 diabetics.**  
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46 Schwab S, Zierer A, Heier M, Fischer B, Huth C, Baumert J, et al. Intake of vitamin and mineral  
47 supplements and longitudinal association with HbA1c levels in the general non-diabetic  
48 population—results from the MONICA/KORA S3/F3 study. *PloS one*. 2015;10(10).

49 **Reason for exclusion: Participants nondiabetic.**  
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Table of included study characteristics

Study	Country	Setting/context	Participant characteristics	Groups	Outcomes measured	Description of main results
Stracke 2008 <sup>34</sup>	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, FBC, BP at six weeks	The mean HbA1c was 7.7 %.
Rabbani 2008 <sup>25</sup>	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/m <sup>2</sup> .	Group 1: High-dose thiamine therapy (300 mg/day) Group 2: placebo	HbA1c, FBC, 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, FBC, 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 <sup>48</sup>	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/m <sup>2</sup>	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 <sup>15</sup>	Mexico/USA	Community	24 patients with T2DM or overweight or obesity Age range 30 – 65 years BMI 25–40 kg/m <sup>2</sup>	Group 1: Thiamine orally (150 mg), once daily for one month (n=12) Group 2: placebo (n=12)	HbA1c, FBG, HDL-c, LDL-c, Triglyceride, BP, BMI at 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 <sup>24</sup>	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, Triglyceride 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)		

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# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Pg 1, Line 2
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Done
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

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## 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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>OTHER INFORMATION</b>			
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/>

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