

# Evaluating the Use of Vitamin D Supplementation to Improve Glycaemic Outcome in Type 2 Diabetes Mellitus Patients: A Systematic Review of Evidence

Mzwandile A. Mabhala<sup>1\*</sup>, Adetoyosi Babanumi<sup>1</sup>, Anthony Olagunju<sup>1</sup>, Eloho Akata<sup>1</sup>, Asmait Yohannes<sup>2</sup>

<sup>1</sup>Department of Public Health and Wellbeing, Faculty of Health and Social Care, University of CHESTER, Riverside Campus, Chester, UK

<sup>2</sup>Department of Surgery, Mount Sinai Hospital, Ambulatory Surgery Centre, New York, NY, USA

Email: \*a.mabhala@chester.ac.uk, adetoyosibabanumi@gmail.com, 1220673@chester.ac.uk, eloho3@yahoo.co.uk, asmait.yohannes@mountsinai.org

**How to cite this paper:** Mabhala, M.A., Babanumi, A., Olagunju, A., Akata, E. and Yohannes, A. (2017) Evaluating the Use of Vitamin D Supplementation to Improve Glycaemic Outcome in Type 2 Diabetes Mellitus Patients: A Systematic Review of Evidence. *Journal of Diabetes Mellitus*, 7, 223-240.

<https://doi.org/10.4236/jdm.2017.74018>

**Received:** August 25, 2017

**Accepted:** September 18, 2017

**Published:** September 22, 2017

Copyright © 2017 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

---

## Abstract

**Background:** The evidence indicates that vitamin D [25(OH)D] improves glycaemic outcomes in type 2 Diabetes mellitus patients. The outcome measures used to determine the accuracy of this hypothesis are: glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG) and homeostasis model assessment-insulin resistance (HOMA-IR). **Methods:** We performed a systematic review and meta-analysis which included all previous randomised controlled trial (RCT) studies that assessed the effects of vitamin D on glucose metabolism. We carried out an extensive electronic database search of published and unpublished RCTs, evaluating the association between vitamin D and glycaemic outcomes in type 2 diabetes mellitus patients. We searched Cochrane Library, PubMed, EMBASE, CINAHL Plus with Full Text, MEDLINE, BioMed Central, Turning Research Into Practice (TRIP), Health Technology Assessment (HTA), and Latin American and Caribbean Health Sciences (LILACS) between the years 2005 and 2016. The full texts of relevant studies were retrieved and a snowballing technique was used to discover further studies missed from the initial database search. This was done by hand-searching for references within the retrieved articles. **Results:** A total of 17 studies were included in the review. The pooled effect of 15 studies that measured HbA1c showed an insignificant effect of vitamin D on HbA1c (Mean difference (MD) = -0.06 mmol/l; 95% CI = -0.26 to 0.14; I<sup>2</sup> = 76%). A pooled analysis of seven studies that measured the effect of vitamin D on

---

blood glucose also found no significant effect of vitamin D on T2DM (MD =  $-0.03$  mmol/l; 95% CI =  $-0.69$  to  $0.63$ ;  $I^2 = 76\%$ ). Three studies that analysed the effect of vitamin D on insulin sensitivity also observed no significant effect (MD =  $-1.51$  mmol/l; 95% CI =  $-3.61$  to  $0.60$ ;  $I^2 = 67\%$ ). **Conclusion:** In conclusion, although vitamin D has been extensively studied in relation to some glycaemic outcomes and some indications that increased plasma vitamin D concentrations might be linked to prevention of T2DM, firm universal conclusions about its benefits cannot be drawn. Further studies with better designed trials and larger sample sizes are needed to draw firmer conclusions.

## Keywords

Vitamin D, Type 2 Diabetes Mellitus, Glycaemic, Public Health

---

## 1. Introduction

Globally, type 2 diabetes mellitus (T2DM) is shifting in two directions: first, from being predominantly a disease of the affluent toward disadvantaged populations and nations; and second, from being a disease of old age toward exponential growth among young people [1] [2] [3]. Some of the factors associated with these shifting patterns include uneven distribution of health determinants and the unintended consequences of phenomena such as aging populations, growing industrialization, urbanization, and market globalization [4] [5] [6] [7] [8]. While the high-income countries have benefited from these phenomena, the low-income countries have paid the price with their health including increased obesity and its associated co-morbidities [7] [8]. In low and middle-income countries, T2DM has shifted from being the 15<sup>th</sup> biggest cause of death in 1990 to the 7<sup>th</sup> greatest in 2016 [8] [9] [10]. It has been reported that 80% of people diagnosed with T2DM are from low and middle-income countries [10].

The growing prevalence of obesity, and particularly childhood obesity, has led to a shift in T2DM to younger populations [3] [6] [11] [12] [13]. The estimate from the International Obesity Task Force indicates that about 155 million school-going children worldwide are obese [14]. It has also been observed that T2DM now accounts for about 45% of new onset diabetes in adolescents, as against 3% about 10 years ago [15].

New evidence is emerging indicating an association between hypovitaminosis D and insulin resistance amongst T2DM patients [12] [16]-[32]. Studies by researchers including Lips *et al.* [33] found that in patients with established T2DM and in the general population, low levels of calcidiol (also known as calcifediol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D [25(OH)D]) were associated with higher fasting glucose, insulin resistance and the metabolic syndrome [12]. 25(OH)D exists in two major forms: ergocalciferol (vitamin D<sub>2</sub>) which is largely ingested, and cholecalciferol (vitamin D<sub>3</sub>) which is synthesized in the human body [16] [34]. Both forms are inactive, but are converted into an active form by

two enzymatic hydroxylation reactions: first, in the liver, forming 25-hydroxyvitamin D mediated by 25-hydroxylase; and second in the kidneys mediated by 1  $\alpha$ -hydroxylase, forming the final activated product calcitriol (1,25 dihydroxyvitamin D) [16] [34]. 25-hydroxyvitamin D is the circulating form of vitamin D in plasma, and an inverse relationship has been established between this and the prevalence of T2DM and impaired glucose tolerance [12] [35]. Several prospective studies showed that a low serum 25(OH)D baseline was associated with incidence of T2DM [36]-[42]. A meta-analysis of prospective studies by Song *et al.* [43] also indicated an association between low circulating 25(OH)D levels and risk of T2DM.

Several studies have explained the mechanisms through which vitamin D levels are associated with T2DM [16] [33] [34] [44]. It has been proposed that vitamin D influences T2DM in two ways: first, the active form 1,25 dihydroxyvitamin D directly binds to  $\beta$  cell vitamin D receptors, thus facilitating insulin's response to glucose [45] [46]; and second, through the regulation of calcium homeostasis through  $\beta$  cell membranes [34]. In this second case, vitamin D deficiency (which alters the extracellular and intracellular  $\beta$  cell calcium pool) will adversely affect insulin secretion [39] [44].

Vitamin D is present in some diets in micro-quantities, albeit rarely [45]. The major source of vitamin D (over 80%) is endogenous, but this requires ultraviolet B radiation from sunlight to activate its precursor 7-dehydrocholesterol in the skin [45]. The evidence indicates that indoor lifestyles and protection from the sun's rays have led to vitamin D deficiency even in countries with abundant sunlight [45].

In response to this vitamin D/T2DM theory, several studies have evaluated the effect of vitamin D supplementation on a variety of glycaemic outcomes, including the effect of 25(OH)D on glycosylated haemoglobin (HbA1c) levels, plasma glucose levels and homeostatic model assessment insulin resistance (HOMA-IR). These reported conflicting results. For example, studies have found 25(OH)D to be inversely related to HbA1c levels in diabetes mellitus [19] [28] [31]. Some studies reported a decrease in HbA1c and an increase in insulin sensitivity on vitamin D supplementation [47]. Others, such as Ahmadi *et al.* [22], found no significant relationship between vitamin D and levels of HbA1c, while Elkassaby *et al.* [20] in a study on T2DM patients with vitamin D deficiency observed a slight improvement in glycaemic outcomes measured by plasma glucose.

The few studies that measured the effects of vitamin D on HOMA-IR had varying outcomes. Some showed that vitamin D has a slight improvement effect on HOMA-IR [18] [32]; others showed that vitamin D supplementation in patients with T2DM did not significantly reduce insulin resistance [17].

Owing to inconsistencies in these results and because these RCTs suffer the same shortcomings (low statistical power, lack of precision and small sample size), this study will systematically review the effects of vitamin D on glycaemic outcomes in T2DM patients. A systematic review is used because the pooled ef-

fect of considering all RCTs increases the power of the research.

## 2. Methods

### 2.1 Search Strategy

We performed a systematic review and meta-analysis in accordance with the standards set by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISM) checklist (Figure 1). We carried out an extensive electronic database search of published and unpublished RCTs, evaluating the association between vitamin D and glycaemic outcomes in T2DM patients. We searched Cochrane Library (Issue 6, 2014), PubMed, EMBASE, CINAHL Plus with Full Text, MEDLINE, BioMed Central, Turning Research Into Practice (TRIP), Health Technology Assessment (HTA), and Latin American and Caribbean Health Sciences (LILIACS) between the years 2005 and 2016. The full texts of relevant studies were retrieved, and references within them were followed up (“snowballing”) to discover studies missed in the initial search.

We used keywords that followed the PICO guidelines (population, interven-

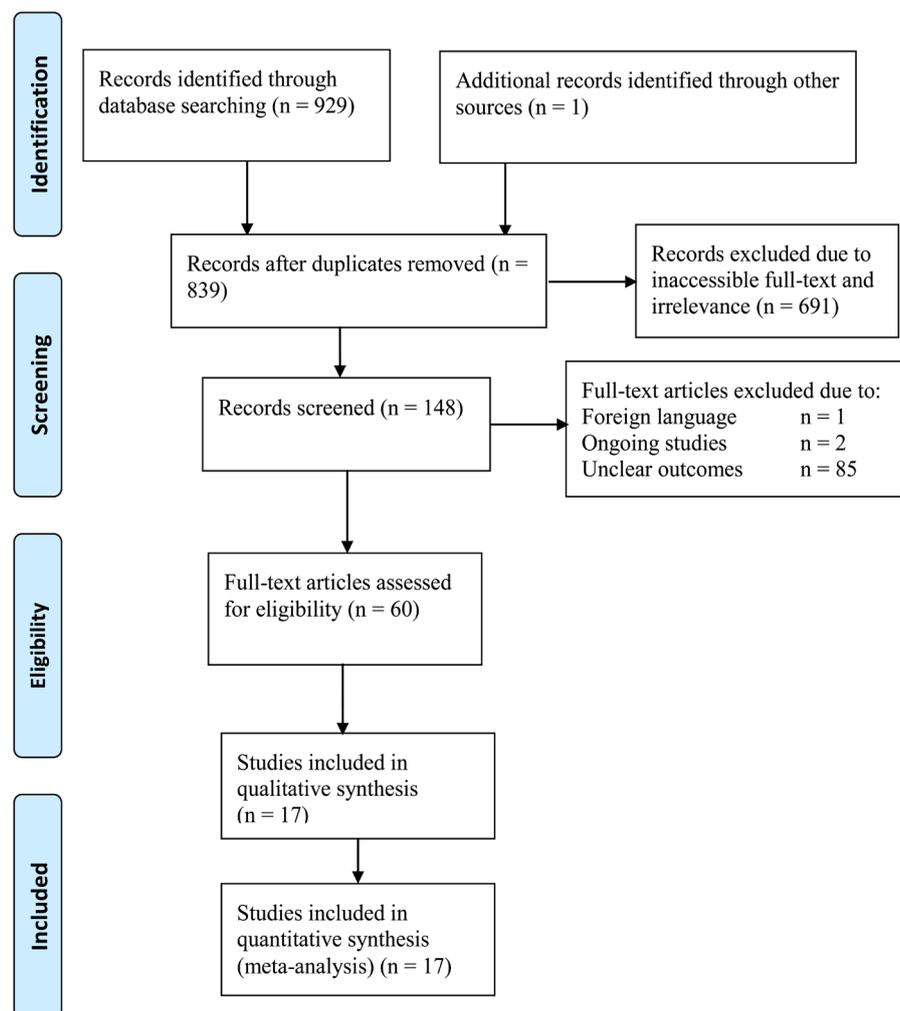


Figure 1. Flow diagram showing the study selection process.

tion, comparison and outcome): “type 2 diabetes patients” AND “vitamin D” OR “ergocalciferol” OR “cholecalciferol” AND “glucose metabolism” AND “glycosylated hemoglobin” AND “randomized controlled trials”. The Boolean operators “AND” and “OR” were used to focus the search strategy.

## 2.2. Study Selection

**Figure 1** illustrates how the PRISM checklist was used to document the process of study selection. The inclusion criteria were: a) participants were patients with T2DM irrespective of their age; b) the study design was RCT; c) the treatment group included patients who received vitamin D without calcium as an intervention, compared with a control group who received placebo or non-vitamin D supplements; d) the studies measured changes in at least one of HbA1c, plasma glucose or HOMA-IR.

The following studies were excluded: non-RCT studies; non-peer-reviewed studies; not enough detail given to judge the rigour of the methodology; studies that included patients with gestational diabetes; studies that included patients with pre-diabetes; studies where the full text cannot be assessed; and studies that compared supplementation of vitamin D with calcium.

## 2.3. Data Extraction and Quality Assessment

Data were extracted in duplicate by four independent reviewers (MAM, AB, EA and AO) [9]. **Table 1** shows the data that were abstracted regarding the baseline characteristics of the included studies [9]—author, year of publication, study design, country of study, intervention and comparison, study size, participant age and loss to follow-up. Data were extracted and appraised with reference to methodological quality, outcome measures and predetermined criteria relevant to the research questions.

**Table 2** indicates data for glycosylated hemoglobin, blood glucose and HOMA-IR extracted from the included studies. Means and standard deviations are presented at a 95% confidence interval. It should be noted that some of the included studies reported blood glucose and HbA1c in different units; all units were converted to mg/dl for blood glucose (1 mmol/l = 18 mg/dl) and % for HbA1c.

**Figure 2 & Figure 3** illustrates how the internal and external validity, including appraisal of random sequence generation, blinding treatment for subjects and personnel, outcome assessments, completeness of outcomes data, objective reporting and risks of potential bias, were evaluated using Review Manager (Revman) Version 5.3 [Computer program] the Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

## 2.4. Statistical Analysis

The extracted data were analysed using revman. RevMan is statistical software used by the Cochrane Collaboration to prepare, analyse and interpret data for

systematic review and meta-analyses.

**Table 2** presents the data that were extracted analysed using revman 5.1. Heterogeneity was estimated statistically using Chi-squared tests (where  $P > 0.1$  suggested a lack of heterogeneity for continuous variables) and I-squared tests (where  $I^2 > 75\%$  was regarded as great heterogeneity). In addition, homogeneity was visually assessed using interpretation of forest plots.

**Table 1.** Characteristics and quality assessment of included studies.

Author	Study design	Country of study	Age of participants	Study size/comparison		Dose of vitamin D	Loss to follow-up
				Vitamin D	Placebo		
Ahmadi <i>et al.</i> , 2013	RCT	Iran (Isfahan)	Older than 20 years	30	30	50,000 IU/week	9
Al-Zahrani, 2014	RCT	Saudi Arabia	Not specified	100	100	45,000 IU/week for two months, and a single dose of 45,000 IU in the last month	17
Breslavsky <i>et al.</i> , 2013	RCT	Not specified	Mean age of 66.8	24	23	1000 IU/day for 12 months	15
Elkassaby <i>et al.</i> , 2014	RCT	Australia	30 - 60	26	24	6000 IU/day	Not specified
Ghavamzadeh <i>et al.</i> , 2013	RCT	Iran	Mean age of 49.28	26	25	400 IU/day of vitamin D3	Not specified
Heshmat <i>et al.</i> , 2012	RCT	Iran (Tehran)	37 - 79	21	21	Single intramuscular injection of 300,000 IU of vitamin D3	Not specified
Jehle <i>et al.</i> , 2014	RCT	Switzerland	>16	29	26	300,000 IU of vitamin D3	Not specified
Jorde <i>et al.</i> , 2009	RCT	North Norway	21 - 76	16	16	40,000 IU/week cholecalciferol	4
Kampmann, 2014	RCT	Denmark	>18	7	8	11,200 IU/day cholecalciferol for two weeks and 5600 IU/day for 10 weeks	1
Kota <i>et al.</i> , 2012	RCT	India (Hyderabad)	22 - 63	15	15	Not specified	Not specified
Neyestani <i>et al.</i> , 2012	RCT		30 - 60	30	30	500 IU/day vitamin D and 150 mg calcium/250ml/day	Not specified
Ryu <i>et al.</i> , 2013	RCT	South Korea	Not specified	79	79	1000 IU cholecalciferol daily combined with 100mg of elemental calcium twice daily	29
Shar-Bidar <i>et al.</i> , 2011	RCT	Iran (Tehran)	29 - 67	50	50	Vitamin D fortified yoghurt (170 mg calcium and 150 IU vitamin D)	Not specified
Strobel <i>et al.</i> , 2014	RCT	Germany	30 - 78	39	33	20 drops of Vigantol oil/ week (1904 IU/day)	14
Sugden <i>et al.</i> , 2007	RCT	Scotland	Mean age of 64.2	17	17	A single dose of 100,000 IU vitamin D2	9
Thethi <i>et al.</i> , 2015	RCT	USA	18 - 70	30	30	1 mcg paricalcitol	5
Yousefi Rad <i>et al.</i> , 2015	RCT	Iran	30 - 60	28	30	4000 IU/day	7

**Table 2.** Data extraction.

Author	Outcomes	Intervention			Control		
		Number of participants (N1)	Mean	SD	Number of participants (N2)	Mean	SD
Ahmadi <i>et al.</i> , 2013	HbA1c (%)	28	7.22	1.2	23	7.09	1.4
Al-Zahrani, 2014	HbA1c (%)	91	8.6	1.6	92	8.7	1.8
	FBG (mmol/l)		9.3	3.1		10	3.7
Breslavsky <i>et al.</i> , 2013	HbA1c (%)	19	7.3	1.1	13	7.2	1.7
	FBG (mmol/l)		8.66	3.06		8.36	3.53
Elkassaby <i>et al.</i> , 2014	HbA1c (%)	26	6.15	0.25	24	6.1	0.2
	FBG (mmol/l)		6.85	0.25		6.43	0.33
Ghavamzadeh <i>et al.</i> , 2013	HbA1c (%)	26	6.6	2.35	25	8.42	3.35
Heshmat <i>et al.</i> , 2012	HbA1c (%)	21	6.49	0.9	21	6.5	0.9
	FBG		8.32	1.62		7.18	1.67
Jehle <i>et al.</i> , 2014	HbA1c	29	7.2	1.1	26	7.7	0.9
	HOMA-IR		3.9	2.2		4.4	2.5
	HbA1c (%)		7.8	0.9		7.7	0.5
Jorde <i>et al.</i> , 2009	FBG (mmol/l)	16	9.6	3.1	16	9.6	1
	HOMA-IR		27.9	23.5		24.8	13.7
Kampmann, 2014	HbA1c (%)	7	0.0678	0.005	8	0.083	0.006
	FBG (mmol/l)		7.17	1.06		10.03	1.7
Kota <i>et al.</i> , 2012	HbA1c (%)	15	7.7	0.9	15	7.8	1.1
	FBG (mmol/l)		7.96	1.24		8.14	1.19
Neyestani <i>et al.</i> , 2012	HOMA-IR	30	2.7	1.5	30	5.5	3.7
Ryu <i>et al.</i> , 2013	HbA1c (%)	64	7.4	0.9	65	7.27	0.87
Shar-Bidar <i>et al.</i> , 2011	HbA1c (%)	50	7.8	1.3	50	8.5	1.6
Strobel <i>et al.</i> , 2014	HbA1c (%)	39	6.1	0.76	33	6.68	1
	FBG (mmol/l)		7	1.31		6.82	1.7
Sugden <i>et al.</i> , 2007	HbA1c (%)	17	7.51	0.6	17	6.25	0.39
Thethi <i>et al.</i> , 2015	HbA1c (%)	23	7.85	1.3	23	7.73	1.13
Yousefi Rad <i>et al.</i> , 2015	HbA1c (%)	28	6.76	0.95	30	7.73	1.26

### 3. Results

This research hypothesized that vitamin D will effectively improve glucose metabolism in type 2 Diabetes mellitus patients. **Figure 4** is the forest plot of 15 trials that compared the effect of vitamin D on HbA1c. An increase in glycosylated hemoglobin (HbA1c) means that glucose metabolism was not improved with vitamin D supplementation. Conversely, a decrease in HbA1c depicts an improvement in glucose metabolism with vitamin D supplementation. The average HbA1c was slightly lower in the 25(OH)D than control, but the difference was

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmadi et al, 2013	+	+	+	+	+	+	+
Al-Zahrani et al, 2014	+	+			+	+	+
Breslavsky et al, 2013			+		+	+	+
Elkassaby et al, 2014	+	+	+	+	+	+	+
Ghavamzadeh et al, 2013			+	+	+	+	+
Heshmat et al 2012		+	+	+	+	+	+
Jehle et al, 2014	+	+	+	+	+	+	+
Jorde et al 2009	-				+	+	+
Kampmann, 2014	+	+	+	+	+	+	+
Kota et al, 2012					+	+	+
Neyestani, 2012			+	+	+	+	+
Ryu et al, 2013	+	+	+	+	+	+	+
Shar- Bidar et al, 2011		+	+	+	+	+	+
Strobel et al, 2014	-		+	+	+	+	+
Sugden et al, 2007		+	+	+	+	+	+
Thethi et al, 2015	-	+	+	+	+	+	+
Yousefi Rad et al, 2015	+	+	+	+	+	+	+

**Figure 2.** Assessment of risk of bias of individual studies.

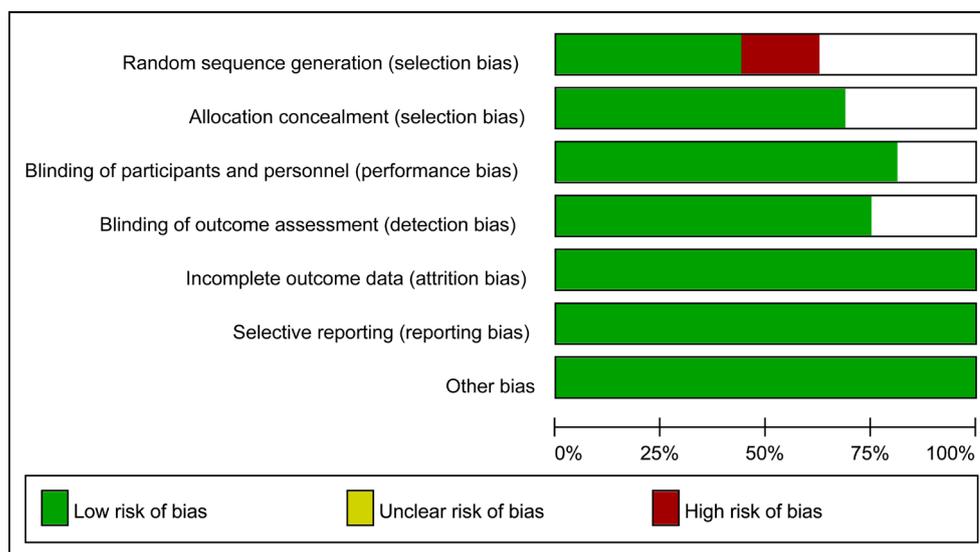


Figure 3. Graphic summary of assessment risk of bias for included studies.

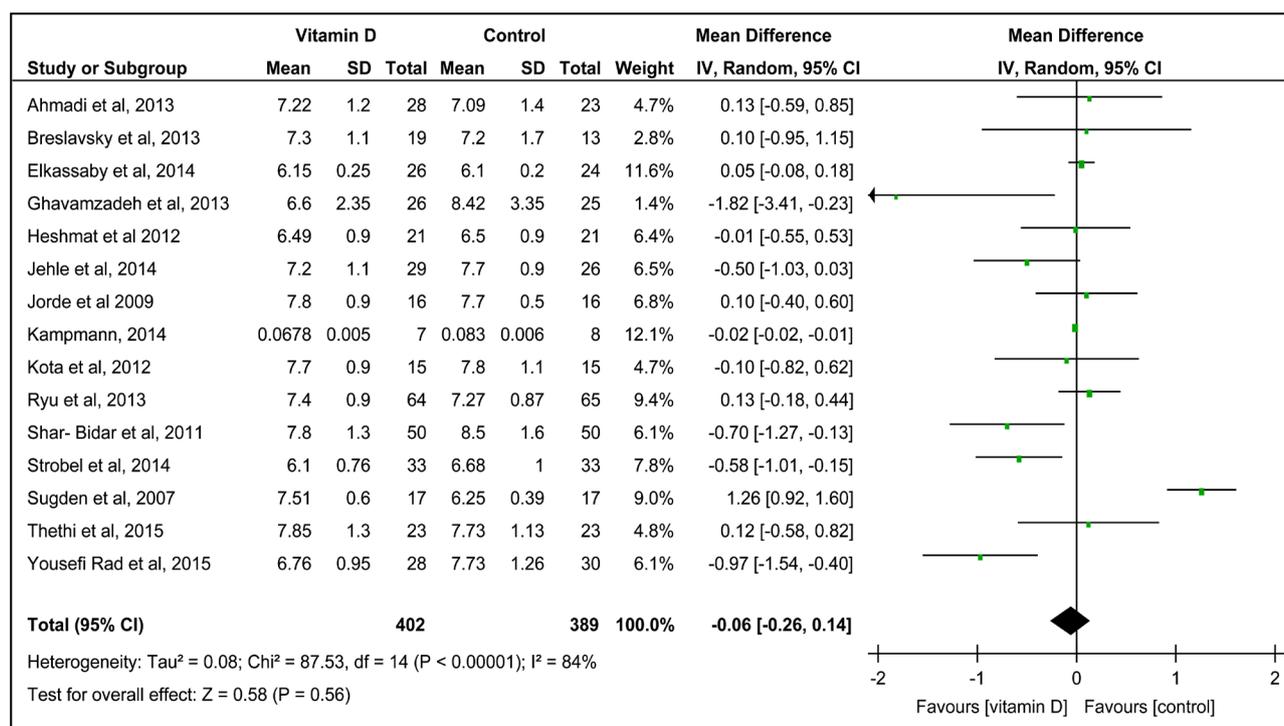


Figure 4. Forest plot of 15 trials that compared effect of vitamin D and placebo on the levels of glycosylated haemoglobin (HbA1c).

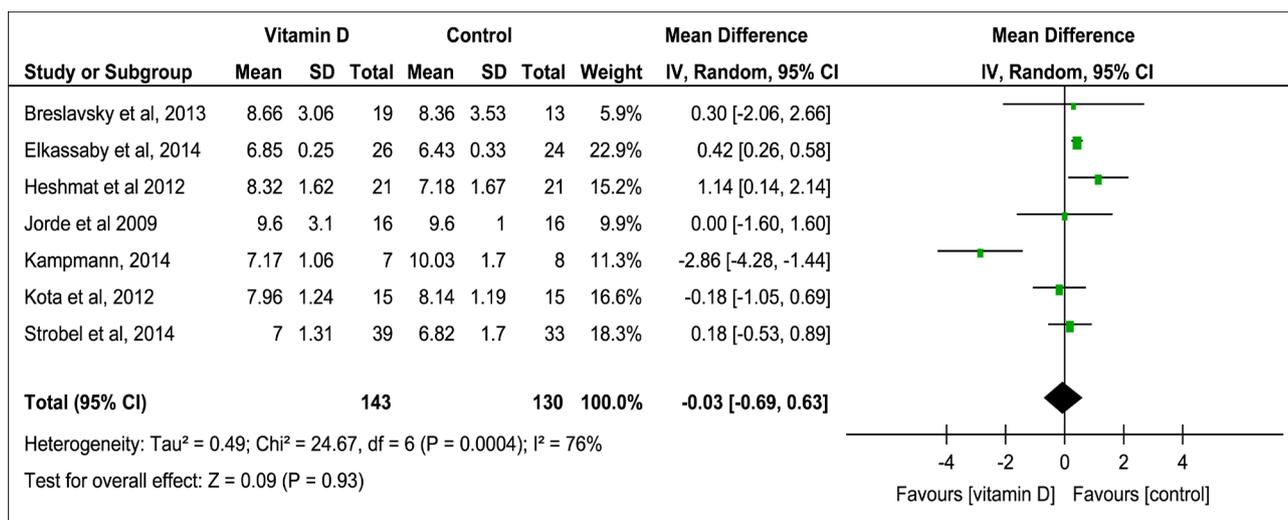
not statistically significant (P = 0.56; MD = -0.06; 95% CI = -0.26 to 0.14); the 95% confidence interval crosses the line of no effect.

Figure 5 is a forest plot of seven studies that compared the effect of vitamin D and placebo on blood glucose. An increase in blood glucose indicates that vitamin D supplementation did not improve glucose metabolism, while a decrease indicates an improvement. The figure shows a pooled estimated mean of -0.03 indicating an average decrease in plasma glucose in the 25(OH)D group com-

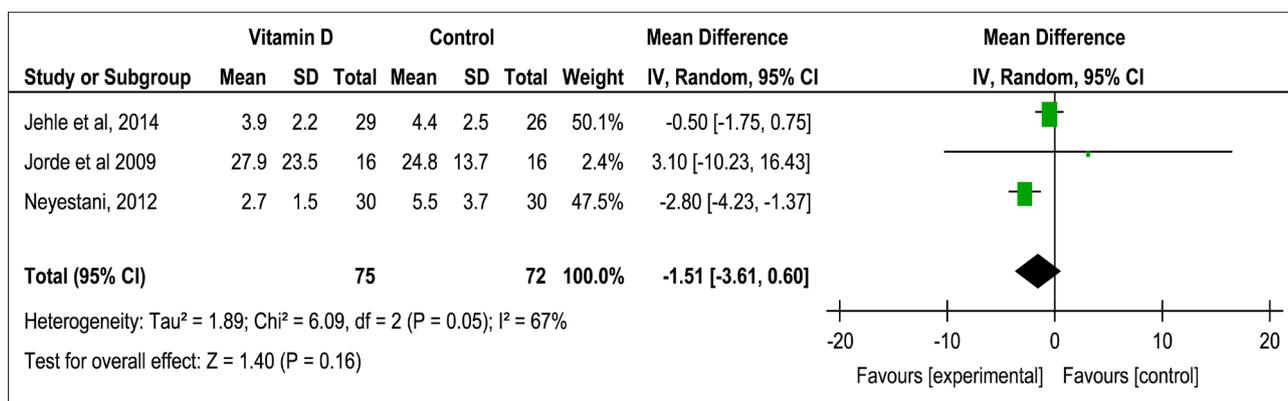
pared to control. However, the difference was not statistically significant ( $P = 0.95$ ; 95% CI:  $-0.69$  to  $0.63$ ); the 95% confidence interval crosses the line of no effect.

**Figure 6** is a forest plot of studies that compared the effect of vitamin D and placebo on homeostatic model assessment insulin resistance (HOMA-IR). The data show a pooled estimate of MD =  $-1.51$ , indicating an improvement in average HOMA-IR in the 25(OH)D group compared to control. However, the difference was not statistically significant ( $P = 0.16$ ; 95% CI =  $-3.61$  to  $0.60$ ), and the 95% confidence interval crosses the line of no effect.

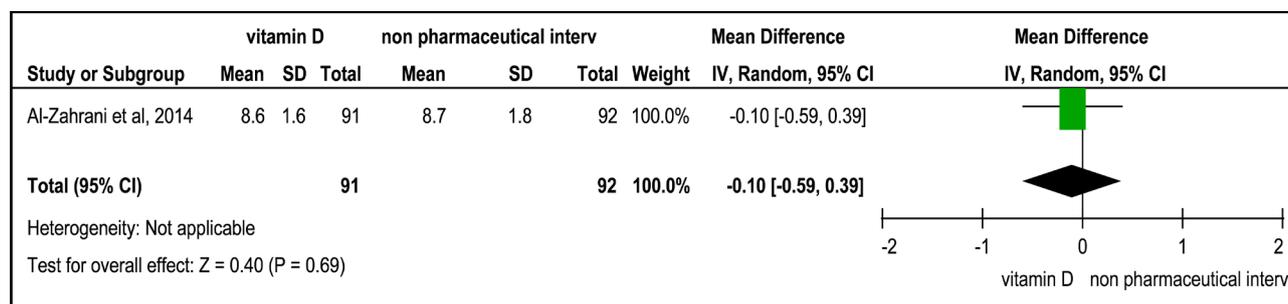
**Figure 7** and **Figure 8** show a single study that compared the effect of vitamin D and non-pharmaceutical intervention (counselling) on glycosylated haemoglobin and blood glucose respectively. Nothing was administered to the control group in this study; however, participants were counselled on how to naturally increase vitamin D levels. The authors thought to separate this study from the studies that compared vitamin D with placebo, since the study has a different comparator which may affect the heterogeneity of the study results.



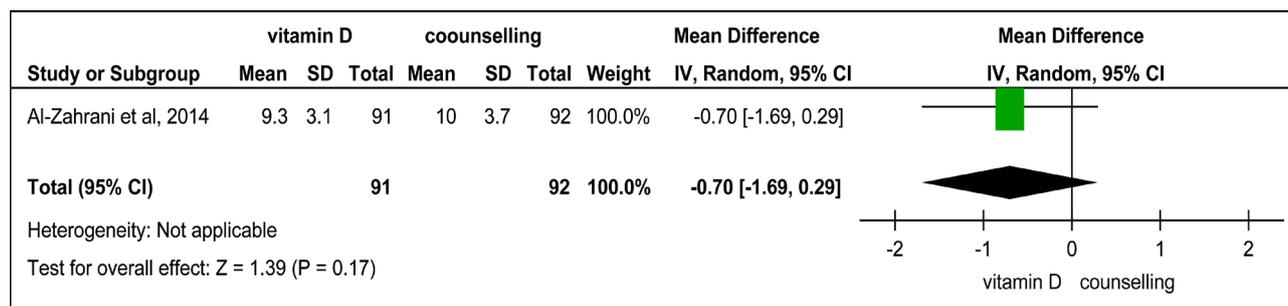
**Figure 5.** Forest plot of 7 trials that compared effect of vitamin D and placebo on blood glucose.



**Figure 6.** Forest plot of 3 trials that compared effect of vitamin D and placebo on homeostatic model assessment insulin resistance (HOMA-IR).



**Figure 7.** Study that compared effect of vitamin D and non-pharmaceutical intervention on glycosylated hemoglobin.



**Figure 8.** Study that compared effect of vitamin D and non-pharmaceutical intervention on blood glucose.

#### 4. Discussion

Our systematic review identified 929 studies and 148 RCTs that evaluated the effect of vitamin D supplementation on three glycaemic outcomes – plasma glucose, HbA1c and HOMA-IR. A total of 15 studies compared vitamin D with placebo and measured glycosylated haemoglobin (HbA1c) as the endpoint outcome with a total of 791 participants, 402 in the vitamin D group and 389 in the placebo group. In relation to vitamin D and HbA1c, the results showed a slight reduction in HbA1c in the vitamin D group compared to the placebo group (mean difference =  $-0.06$ ; 95% CI =  $-0.26$  to  $0.14$ ;  $I^2 = 84\%$ ). However, the reduction was not statistically significant ( $P = 0.56$ ). These findings are typical of most intervention studies evaluating the effect of vitamin D on T2DM, which give signals of nominal significance for diverse outcomes that are inconclusive and subject to caveats [48] [49]. It is also consistent with previous systematic reviews, including one by Seida *et al.* which included 15 RCTs and examined the effects of vitamin D on HbA1c in individuals with normal glucose tolerance and individuals with T2DM [49].

The conclusive evidence of association between increases in 25(OH)D and decreases in HbA1c levels come from observational studies [50] [51] [52] [53]. For example, a longitudinal study by Munasinghe *et al.* [50] found that the mean serum 25(OH)D concentrations of participants on vitamin D supplementation increased from 90.8 nmol/L at baseline to 121.3 nmol/L at follow-up, while the mean HbA1c values decreased from 5.6% at baseline to 5.5% at follow-up. The prevalence of participants with increased diabetes risk, *i.e.* those with HbA1c values  $\geq 5.8\%$ , decreased from 29.5% to 17.4% [50]. This signifies the need for

further investment into research in this area.

For effects of vitamin D on plasma glucose, a total of seven studies [17] [20] [21] [24] [25] [29] were examined; these had a total of 273 participants, 143 in the vitamin D group and 130 in the control group. The study showed a MD = -0.03 mmol/l and a 95% CI = -0.69 to 0.63 in favour of the 25(OH)D group. Consistent with previous intervention studies which showed nominal improvements in plasma glucose, these findings were statistically insignificant (P = 0.93; 95% CI = -0.69 to 0.63). Similarly, Seida *et al.*'s [49] systematic review of 25 RCTs showed minimal effects (MD = -0.18 mg/dL; 95% CI = -1.26 to 0.90; I<sup>2</sup> = 21%) of vitamin D on blood glucose in individuals with normal glucose tolerance, pre-diabetes and patients with T2DM. Similar results were shown in another systematic review by George, Pearson and Witham, [54]. More conclusive evidence of the link between vitamin D and FPG came from an observational study by Pannu *et al.* [52] which showed that every 10 nmol/L increment in serum 25(OH)D significantly reduced the adjusted odds ratio (AOR) of a higher FPG (AOR = 0.91, (0.86, 0.97); P = 0.002] and a higher HbA1c (AOR 0.94, (0.90, 0.98); P = 0.009).

Homeostatic Model Assessment Insulin Resistance (HOMA-IR) is the most common measure of insulin sensitivity. We found three studies which met our inclusion criteria [17] [18] [32] and measured effects of vitamin D on HOMA-IR. Together these had 147 participants, 67 in the vitamin D group and 65 in the control group. The result showed that vitamin D has a slight improvement effect on HOMA-IR (MD = -1.51; 95% CI = -3.61 to 0.60; I<sup>2</sup> = 67%); however, a P value = 0.16 shows that the effect of vitamin D was not significant. This study showed that vitamin D supplementation in patients with T2DM did not significantly reduce insulin resistance. Comparably, Seida *et al.* [49] included six studies that examined the effects of vitamin D supplementation on HOMA-IR in T2DM patients [55]. They also found no significant difference in the vitamin D group compared to the placebo group (MD = -1.46; 95% CI = -4.27 to 1.34).

Overall, a lack of consensus on the effect of vitamin D supplementation continues to exist among the intervention studies. The consistent feature amongst all of them is lack of statistical significance. Even systematic reviews that combine several RCTs failed to increase statistical power and estimates of precision [49] [56]. This calls for further research into this issue using larger sample sizes.

## 5. Conclusion

In conclusion, although vitamin D has been extensively studied in relation to glycaemic outcomes and indications that increased plasma vitamin D concentrations might be linked to prevention of T2DM, firm universal conclusions about its benefits cannot be drawn. Further studies with better designed trials and larger sample sizes are needed to draw firmer conclusions.

## 6. Limitations of the Study

It is important to note that the major strength of this review is its strict adherence to the methods and guidelines included in the Cochrane handbook of systematic reviews. It also included the most recent RCTs which provide up-to-date evidence. However, it was not without its limitations: the funding for this study only covered the lead researcher's time and did not cover resources; consequently, several studies that looked promising from the reviews of their abstracts were excluded due to limited funds to purchase the full text.

## Acknowledgements

The authors would like to thank Roger Whiteley for proofreading and editorial support. Our very special gratitude goes to the reviewers of this paper, who will have expended considerable effort on our behalf.

## Conflict of Interest

The authors declare no conflicts of interest.

## Funding

There was no funding allocated to the study. However, the University of Chester provided time for the lead author to do this research.

## Consent for Publication

Not applicable to this paper.

## Ethical Approval

Not applicable to this paper.

## Authors' Contributions

- MM wrote the entire manuscript.
- AB wrote the protocol for the study and contributed to writing the manuscript.
- AO and EA contributed in data analysis and
- AY did all the editing of the manuscript.

## References

- [1] Hwang, C.K., Han, P.V., Zabetian, A., Ali, M.K. and Narayan, K.V. (2012) Rural Diabetes Prevalence Quintuples over Twenty-Five Years in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *Diabetes Research and Clinical Practice*, **96**, 271-285. <https://doi.org/10.1016/j.diabres.2011.12.001>
- [2] Guariguata, L., Whiting, D.R., Hambleton, I., Beagley, J., Linnenkampa, U. and Shawd, J.E. (2014) Global Estimates of Diabetes Prevalence for 2013 and Projections for 2035. *Diabetes Research and Clinical Practice*, **103**, 137-149. <https://doi.org/10.1016/j.diabres.2013.11.002>

- [3] Choukem, S.-P., Kamdeu-Chedeu, J., Leary, S.D., Mboue-Djieka, Y., Nebongo, D.N., Akazong, C., Mapoure, Y.N., Hamilton-Shield, J.P., Gautier, J.-F. and Mbanya, J.C. (2017) Overweight and Obesity in Children Aged 3 - 13 Years in Urban Cameroon: A Cross-Sectional Study of Prevalence and Association with Socio-Economic Status. *BMC Obesity*, 2017, **4**, 2-8. <https://doi.org/10.1186/s40608-017-0146-4>
- [4] Cowie, C.C., Rust, K.F., Byrd-Holt, D.D., Eberhardt, M.S., Flegal, K.M., Engelgau, M.M. and Gregg, E.W. (2006) Prevalence of Diabetes and Impaired Fasting Glucose in Adults in the US Population: National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care*, **29**, 1263-1268. <https://doi.org/10.2337/dc06-0062>
- [5] Gunasekaran, U. and Gannon, M. (2011) Type 2 Diabetes and the Aging Pancreatic Beta Cell. *Aging*, **3**, 565-575. <https://doi.org/10.18632/aging.100350>
- [6] Gebremichael, B. and Chere, A. (2015) Prevalence of Childhood Overweight and Obesity and Its Determinant Factors among Elementary School Children in Addis Ababa, Ethiopia: A Cross Sectional Study. *Journal of Nutritional Disorders & Therapy*. <https://doi.org/10.4172/2161-0509.S1-002>
- [7] Pang, T. and Guindon, G.E. (2004) Globalization and Risks to Health. *European Molecular Biology Organisation*, **5**, s11. <https://doi.org/10.1038/sj.embor.7400226>
- [8] Huynen, M.M.T.E., Martens, P. and Hilderink, H.B.M. (2005) The Health Impacts of Globalisation: A Conceptual Framework. *Globalization and Health*, **1**, 14-14. <https://doi.org/10.1186/1744-8603-1-14>
- [9] Leading Causes of Death by Economy Income Group. <http://www.who.int/mediacentre/factsheets/fs310/en/index1.html>
- [10] Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V. and Cross, M. (2013) Global and Regional Mortality from 235 Causes of Death for 20 Age Groups in 1990 and 2010: A Systematic Analysis for the Global Burden of Disease Study 2010. *The Lancet*, **380**, 2095-2128. [https://doi.org/10.1016/S0140-6736\(12\)61728-0](https://doi.org/10.1016/S0140-6736(12)61728-0)
- [11] Zhang, T., Zhang, H., Li, Y., Li, S., Fernandez, C., Bazzano, L., He, J., Xue, F. and Chen, W. (2017) Long-Term Impact of Temporal Sequence from Childhood Obesity to Hyperinsulinemia on Adult Metabolic Syndrome and Diabetes: The Bogalusa Heart Study. *Scientific Reports*, **7**, 1-7.
- [12] Haimi, M. and Kremer, R. (2017) Vitamin D Deficiency/Insufficiency from Childhood to Adulthood: Insights from a Sunny Country. *World Journal of Clinical Pediatrics*, **8**, 1-9.
- [13] Han, J.C., Lawlor, D.A. and Kimm, S.Y. (2010) Childhood Obesity. *The Lancet*, **375**, 1737-1748.
- [14] Lobstein, T., Baur, L. and Uauy, R. (2004) Obesity in Children and Young People: A Crisis in Public Health. *Obesity Reviews*, **5**, 4-85. <https://doi.org/10.1111/j.1467-789X.2004.00133.x>
- [15] Pinhas-Hamiel, O. and Zeitler, P. (2007) Acute and Chronic Complications of Type 2 Diabetes Mellitus in Children and Adolescents. *The Lancet*, **369**, 1823-1831.
- [16] Talaie, A., Mohamadi, M. and Adgi, Z. (2013) The Effect of Vitamin D on Insulin Resistance in Patients with Type 2 Diabetes. *Diabetology & Metabolic Syndrome*, **5**.
- [17] Jorde, R. and Figenschau, Y. (2009) Supplementation with Cholecalciferol Does Not Improve Glycaemic Control in Diabetic Subjects with Normal Serum 25-Hydroxyvitamin D Levels. *European Journal of Nutrition*, **48**, 349-354. <https://doi.org/10.1007/s00394-009-0020-3>

- [18] Jehlea, S., Lardi, A., Felixa, B., Hulter, H.N., Stettler, C. and Krapfa, R. (2014) Effect of Large Doses of Parenteral Vitamin D on Glycaemic Control and Calcium/Phosphate Metabolism in Patients with Stable Type 2 Diabetes Mellitus: A Randomised, Placebo-Controlled, Prospective Pilot Study. *The European Journal of Medical Sciences*, **144**, 1-10. <https://doi.org/10.4414/smw.2014.13942>
- [19] Ghavamzadeh, S., Mobasseri, M. and Mahdavi, R. (2014) The Effect of Vitamin D Supplementation on Adiposity, Blood Glycated Hemoglobin, Serum Leptin and Tumor Necrosis Factor- $\alpha$  in Type 2 Diabetic Patients. *International Journal of Preventive Medicine*, **5**, 1091-1098.
- [20] Elkassaby, S., Harrison, L.C., Mazzitelli, N., Wentworth, J.M., Colman, P.G., Spelman, T. and Furlanos, S. (2014) A Randomised Controlled Trial of High Dose Vitamin D in Recent-Onset Type 2 Diabetes. *Diabetes Research and Clinical Practice*, **106**, 576-582.
- [21] Heshmat, R., Tabatabaei-Malazy, O., Abbaszadeh-Ahnanjani, S., Shahbazi, S., Khooshehchin, G., Bandarian, F. and Larijani, B. (2012) Effect of Vitamin D on Insulin Resistance and Anthropometric Parameters in Type 2 Diabetes; A Randomized Double-Blind Clinical Trial. *DARU Journal of Pharmaceutical Sciences*, **20**, 10. <https://doi.org/10.1186/2008-2231-20-10>
- [22] Ahmadi, N., Mortazavi, M., Iraj, B. and Askari, G. (2013) Whether Vitamin D(3) Is Effective in Reducing Proteinuria in Type 2 Diabetic Patients? *Journal of Research in Medical Sciences. The Official Journal of Isfahan University of Medical Sciences*, **18**, 374-377.
- [23] Al-Zahrani, M.K., Elnasieh, A.M., Alenezi, F.M., Almoushawah, A.A., Almansour, M., Alshahrani, F., Rahman, S.U. and Al-Zahrani, A. (2014) A 3-Month Oral Vitamin D Supplementation Marginally Improves Diastolic Blood Pressure in Saudi Patients with Type 2 Diabetes Mellitus. *International Journal of Clinical and Experimental Medicine*, **7**, 5421-5428.
- [24] Breslavsky, A., Frand, J., Matas, Z., Boaz, M., Barnea, Z. and Shargorodsky, M. (2013) Effect of High Doses of Vitamin D on Arterial Properties, Adiponectin, Leptin and Glucose Homeostasis in Type 2 Diabetic Patients. *Clinical Nutrition*, **32**, 970-975.
- [25] Kota, S.K., Jammula, S., Kota, S.K., Tripathy, P.R., Panda, S. and Modi, K.D. (2011) Effect of Vitamin D Supplementation in Type 2 Diabetes Patients with Pulmonary Tuberculosis. *Diabetes & Metabolic Syndrome. Clinical Research & Reviews*, **5**, 85-89.
- [26] Ryu, O.-H., Lee, S., Yu, J., Choi, M.-G., Yoo, H.J. and Mantero, F. (2014) A Prospective Randomized Controlled Trial of the Effects of Vitamin D Supplementation on Long-Term Glycemic Control in Type 2 Diabetes Mellitus of Korea. *Endocrine Journal*, **61**, 167-176. <https://doi.org/10.1507/endocrj.EJ13-0356>
- [27] Sugden, J.A., Davies, J.I., Witham, M.D., Morris, A.D. and Struthers, A.D. (2008) Vitamin D Improves Endothelial Function in Patients with Type 2 Diabetes Mellitus and Low Vitamin D Levels. *Diabetic Medicine*, **25**, 320-325. <https://doi.org/10.1111/j.1464-5491.2007.02360.x>
- [28] Shab-Bidar, S., Neyestani, T.R., Djazayeri, A., Eshraghian, M.-R., Houshiarrad, A., Gharavi, A., Kalayi, A., Shariatzadeh, N., Zahedirad, M., Khalaji, N. and Haidari, H. (2011) Regular Consumption of Vitamin D-Fortified Yogurt Drink (Doogh) Improved Endothelial Biomarkers in Subjects with Type 2 Diabetes: A Randomized Double-Blind Clinical Trial. *BMC Medicine*, **9**, 125. <https://doi.org/10.1186/1741-7015-9-125>
- [29] Strobel, F., Reusch, J., Penna-Martinez, M., Ramos-Lopez, E., Klahold, E., Klepzig,

- C., Wehrle, J., Kahles, H. and Badenhoop, K. (2014) Effect of a Randomised Controlled Vitamin D Trial on Insulin Resistance and Glucose Metabolism in Patients with Type 2 Diabetes Mellitus. *Hormone and Metabolic Research*, **46**, 54-58.
- [30] Thethi, T.K., Bajwa, M.A., Ghanim, H., Jo, C., Weir, M., Goldfine, A.B., Umpierrez, G., Desouza, C., Dandona, P., Fang-Hollingsworth, Y., et al. (2015) Effect of Paricalcitol on Endothelial Function and Inflammation in Type 2 Diabetes and Chronic Kidney Disease. *Journal of Diabetes and its Complications*, **29**, 433-437.
- [31] Yousefi Rad, E., Djalali, M., Koohdani, F., Saboor-Yaraghi, A.A., Eshraghian, M.R., Javanbakht, M.H., Saboori, S., Zarei, M. and Hosseinzadeh-Attar, M.J. (2014) The Effects of Vitamin D Supplementation on Glucose Control and Insulin Resistance in Patients with Diabetes Type 2: A Randomized Clinical Trial Study. *Iranian Journal of Public Health*, **43**, 1651-1656.
- [32] Neyestani, T.R., Nikooyeh, B., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., Tayebinejad, N., Heravifard, S., Salekzamani, S. and Zahedirad, M. (2012) Improvement of Vitamin D Status via Daily Intake of Fortified Yogurt Drink Either with or without Extra Calcium Ameliorates Systemic Inflammatory Biomarkers, Including Adipokines, in the Subjects with Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, **97**, 2005-2011. <https://doi.org/10.1210/jc.2011-3465>
- [33] Lips, P., Marelise, E., van Schoor, N., Oosterwerffa, M., de Jongha, R., Krul-Poeld, Y. and Simseka, S. (2016) Vitamin D and Type 2 Diabetes. *Journal of Steroid Biochemistry & Molecular Biology*.
- [34] Papandreou, D. and Hamid, Z.-T.-N. (2015) The Role of Vitamin D in Diabetes and Cardiovascular Disease: An Updated Review of the Literature. *Disease Markers*, **2015**, Article ID: 580474. <https://doi.org/10.1155/2015/580474>
- [35] Targher, G., Bertolini, L., Padovani, R., Zenari, L., Scala, L., Cigolini, M. and Arcaro, G. (2006) Serum 25-Hydroxyvitamin D3 Concentrations and Carotid Artery Intima-Media Thickness among Type 2 Diabetic Patients. *Clinical Endocrinology*, **65**, 593-597. <https://doi.org/10.1111/j.1365-2265.2006.02633.x>
- [36] Deleskog, A., Hilding, A., Brismar, K., Hamsten, A., Efendic, S. and Ostenson, C.G. (2012) Low Serum 25-Hydroxyvitamin D Level Predicts Progression to Type 2 Diabetes in Individuals with Prediabetes But Not with Normal Glucose Tolerance. *Diabetologia*, **55**, 1668-1678. <https://doi.org/10.1007/s00125-012-2529-x>
- [37] Forouhi, N.G., Ye, Z., Rickard, A.P., Khaw, K.T., Luben, R., Langenberg, C. and Wareham, N.J. (2012) Circulating 25-Hydroxyvitamin D Concentration and the Risk of Type 2 Diabetes: Results from the European Prospective Investigation into Cancer (EPIC)-Norfolk Cohort and Updated Metaanalysis of Prospective Studies. *Diabetologia*, **55**, 2173-2182. <https://doi.org/10.1007/s00125-012-2544-y>
- [38] Liu, E., Meigs, J.B., Pittas, A.G., Economos, C.D., McKeown, N.M., Booth, S.L. and Jacques, P.F. (2010) Predicted 25-Hydroxyvitamin D Score and Incident Type 2 Diabetes in the Framingham Offspring Study. *American Journal of Clinical Nutrition*, **91**, 1627-1633.
- [39] Pittas, A.G., Nelson, J., Mitri, J., Hillmann, W., Garganta, C. and Dawson-Hughes, B. (2012) Plasma 25-Hydroxyvitamin D and Progression to Diabetes in Patients at Risk for Diabetes: An Ancillary Analysis in the Diabetes Prevention Program. *Diabetes Care*, **35**, 565-573. <https://doi.org/10.2337/dc11-1795>
- [40] Mattila, C., Knekt, P., Mannisto, S., Rissanen, H., Laaksonen, M.A., Montonen, J. and Reunanen, A. (2007) Serum 25-Hydroxyvitamin D Concentration and Subsequent Risk of Type 2 Diabetes. *Diabetes Care*, **30**, 2569-2570. <https://doi.org/10.2337/dc07-0292>

- [41] Knekt, P., Laaksonen, M., Mattila, C., Harkanen, T., Marniemi, J., Heliovaara, M., Rissanen, H., Montonen, J. and Reunanen, A. (2008) Serum Vitamin D and Subsequent Occurrence of Type 2 Diabetes. *Epidemiology*, **19**, 666-671. <https://doi.org/10.1097/EDE.0b013e318176b8ad>
- [42] Gagnon, C., Lu, Z.X., Magliano, D.J., Dunstan, D.W., Shaw, J.E., Zimmet, P.Z., Sikaris, K., Grantham, N., Ebeling, P.R. and Daly, R.M. (2011) Serum 25-Hydroxyvitamin D, Calcium Intake, and Risk of Type 2 Diabetes after 5 Years: Results from a National, Population-Based Prospective Study (the Australian Diabetes, Obesity and Lifestyle Study). *Diabetes Care*, **34**, 1133-1138. <https://doi.org/10.2337/dc10-2167>
- [43] Song, Y., Wang, L., Pittas, A.G., del Gobo, L.C., Zhang, C., Manson, J.E. and Hu, F.B. (2013) Blood 25-Hydroxy Vitamin D Levels and Incident Type 2 Diabetes: A Meta-Analysis of Prospective Studies. *Diabetes Care*, **36**, 1422-1428. <https://doi.org/10.2337/dc12-0962>
- [44] Pittas, A.G., Harris, S.S., Stark, P.C. and Dawson-Hughes, B. (2007) The Effects of Calcium and Vitamin D Supplementation on Blood Glucose and Markers of Inflammation in Nondiabetic Adults. *Diabetes Care*, **30**, 980-986. <https://doi.org/10.2337/dc06-1994>
- [45] Van der Mei, I.A., Ponsonby, A.L., Engelsen, O., Pasco, J.A., McGrath, J.J., Eyles, D.W. and Jones, G. (2007) The High Prevalence of Vitamin D Insufficiency across Australian Populations Is only Partly Explained by Season and Latitude. In: *Environmental Health Perspectives*, Routledge, London, 1132-1139. <https://doi.org/10.1289/ehp.9937>
- [46] Bland, R., Markovic, D., Hills, C.E., Hughes, S.V., Chan, S.L., Squires, P.E. and Hewison, M. (2004) Expression of 25-Hydroxyvitamin D3-1 $\alpha$ -Hydroxylase in Pancreatic Islets. *Journal Steroid Biochemical Molecillar Biology*, **89**, 121-125.
- [47] Kostoglou-Athanassiou, I., Athanassiou, P., Gkountouvas, A. and Kaldrymides, P. (2013) Vitamin D and Glycemic Control in Diabetes Mellitus Type 2. *Therapeutic Advances in Endocrinology and Metabolism*, **4**, 122-128. <https://doi.org/10.1177/2042018813501189>
- [48] Theodoratou, E., Tzoulaki, I., Zgaga, L. and Ioannidis, J.P.A. (2014) Vitamin D and Multiple Health Outcomes: Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies and Randomised Trials. *The BMJ*, **348**, g2035. <https://doi.org/10.1136/bmj.g2035>
- [49] Seida, J.C., Mitri, J., Colmers, I.N., Majumdar, S.R., Davidson, M.B., Edwards, A.L., Hanley, D.A., Pittas, A.G., Tjosvold, L. and Johnson, J.A. (2014) Effect of Vitamin D(3) Supplementation on Improving Glucose Homeostasis and Preventing Diabetes: A Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology and Metabolism*, **99**, 3551-3560. <https://doi.org/10.1210/jc.2014-2136>
- [50] Munasinghe, L., Mastroeni, M., Mastroeni, S., Loehr, S., Ekwaru, J. and Veugelers, P. (2017) The Association of Serum 25-Hydroxyvitamin D Concentrations and Elevated Glycated Hemoglobin Values: A Longitudinal Study of Non-Diabetic Participants of a Preventive Health Program. *Nutrients*, **9**, 640. <https://doi.org/10.3390/nu9070640>
- [51] Koch, A., Grammatikos, G., Trautmann, S., Schreiber, Y., Thomas, D., Bruns, F., Pfeilschifter, J., Badenhop, K. and Penna-Martinez, M. (2017) Vitamin D Supplementation Enhances C18(dihydro)ceramide Levels in Type 2 Diabetes Patients. *International Journal of Molecular Sciences*, **18**, 1532. <https://doi.org/10.3390/ijms18071532>
- [52] Pannu, P.K., Piers, L.S., Soares, M.J., Zhao, Y. and Ansari, Z. (2017) Vitamin D Sta-

tus Is Inversely Associated with Markers of Risk for Type 2 Diabetes: A Population Based Study in Victoria, Australia. *PLoS ONE*, **12**, e0178825.

<https://doi.org/10.1371/journal.pone.0178825>

- [53] Nam, H., Kim, H.-Y., Choi, J.-S., Kweon, S.-S., Lee, Y.-H., Nam, H.-S., Park, K.-S., Ryu, S.-Y., Choi, S.-W., Oh, S.-H., *et al.* (2017) Association between Serum 25-Hydroxyvitamin D Levels and Type 2 Diabetes in Korean Adults. *Chonnam Medical Journal*, **53**, 73-77. <https://doi.org/10.4068/cmj.2017.53.1.73>
- [54] George, P.S., Pearson, E.R. and Witham, M.D. (2012) Effect of Vitamin D Supplementation on Glycaemic Control and Insulin Resistance: A Systematic Review and Meta-Analysis. *Diabetic Medicine*, **29**, e142-e150. <https://doi.org/10.1111/j.1464-5491.2012.03672.x>
- [55] Fondjo, L.A., Owiredu, W.K.B.A., Sakyi, S.A., Laing, E.F., Adotey-Kwofie, M.A., Antoh, E.O. and Detoh, E. (2017) Vitamin D Status and Its Association with Insulin Resistance among Type 2 Diabetics: A Case-Control Study in Ghana. *PLoS ONE*, **12**, e0175388. <https://doi.org/10.1371/journal.pone.0175388>
- [56] Mitri, J., Dawson-Hughes, B., Hu, F.B. and Pittas, A.G. (2011) Effects of Vitamin D and Calcium Supplementation on Pancreatic  $\beta$  Cell Function, Insulin Sensitivity, and Glycemia in Adults at High Risk of Diabetes: The Calcium and Vitamin D for Diabetes Mellitus (CaDDM) Randomized Controlled Trial. *The American Journal of Clinical Nutrition*, **94**, 486-494. <https://doi.org/10.3945/ajcn.111.011684>