

# Beneficial effects of vitamin D in the management of untreated hyperlipidemia in diabetic patients in Erbil, Iraq

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## Abstract

Hyperlipidemia is highly prevalent among type 2 diabetes mellitus (T2DM) patients. As hyperlipidemia plays a major part in atherosclerosis development and progression, this occurrence is linked to a significantly raised risk of cardiovascular disease. This study aims to assess the effects of vitamin D supplementation on lipid parameters in T2DM patients with untreated hyperlipidemia. Thirty-five T2DM patients with hyperlipidemia and vitamin D deficiency were supplemented with vitamin D for three months. Serum 25-hydroxyvitamin D (25[OH]D), calcium, lipid parameters, atherogenic indices, glucose, and HbA1c were recorded before and after the intervention. After supplementation, there was a statistically significant reduction in VLDL-C and triglycerides. Triglycerides showed a significant negative correlation with 25(OH)D. Atherogenic indices and HDL-C also improved significantly. Vitamin D supplementation had beneficial effects on the lipid profile of T2DM patients with untreated hyperlipidemia and vitamin D deficiency. Thus, vitamin D could be a valuable adjuvant therapy for these patients.

## Keywords

type 2 diabetes mellitus, hyperlipidemia, lipid profile, vitamin D

## Introduction

Diabetes is a significant driver of dyslipidemia, which is a metabolic disorder characterised by an increase in serum triglyceride (TG) levels or total cholesterol concentrations and/or serum high-density lipoprotein cholesterol (HDL-C) reduction (Ama Moor et al. 2017). The process of cholesterol, TG, and their derivatives is tightly regulated, which is interrupted due to continuous hyperglycemia in diabetes leading to hypertriglyceridemia and hypercholesterolemia (Závorková et al. 2018).

Dyslipidemia, hypertension, arteriosclerosis, and all these consequences associated with myocardial infarction and stroke are more common in type 2 diabetic

patients (Ginsberg 2000). Despite the increase in the use of lipid-lowering agents, dyslipidemia is poorly controlled (Alshamiri et al. 2018). Statins and fibrates are the most commonly prescribed lipid-lowering medicines (Blais et al. 2021). Although they are effective in achieving optimal concentrations of lipids, fibrates have been attributed to side effects, including myopathy and hepatotoxicity (Okopień et al. 2018). Furthermore, long-term statin use might lead to myopathy, new-onset T2DM, and perhaps a hemorrhagic stroke, which can affect treatment adherence and increase cardiovascular risk (Collins et al. 2016; Ward et al. 2019).

Vitamin D is a hormone that has an important role in maintaining mineral homeostasis and integrity of the

bone but also has numerous extraskeletal pleiotropic effects involving the endocrine system (Verstuyf et al. 2010). Many studies have reported that vitamin D deficiency is prevalent in patients with type 2 diabetes (Al-Zaharani 2013; Bashir et al. 2016; Nasr et al. 2022).

Studies also revealed that higher concentrations of serum 25-hydroxyvitamin D (25[OH]D) correlate with higher HDL-C, lower low-density lipoprotein cholesterol (LDL-C), total cholesterol, and TG levels (Wang et al. 2012; Tepper et al. 2014). In addition, a recent study in China reported that the incidence of dyslipidemia is higher in individuals with vitamin D deficiencies (Yang et al. 2020).

According to a meta-analysis of clinical trials, vitamin D supplementation has been shown to reduce TG, LDL-C, and total cholesterol serum levels (Dibaba 2019). A decade-long study discovered that serum 25(OH)D and serum TG have an inverse relationship (Jorde et al. 2010). Vitamin D might indirectly affect blood lipid levels by improving insulin sensitivity and secretion (Kamycheva et al. 2007).

Vitamin D may also help in maintaining glucose homeostasis via pancreatic beta-cell stimulation to increase insulin release (Pitocco et al. 2006). Improvement in insulin resistance as a result of reduced systemic inflammation, direct stimulation of insulin secretion via vitamin D receptors on pancreatic beta-cells, and reduction in peripheral insulin resistance in the liver and muscles have all been proposed as mechanisms to elucidate the possible role of vitamin D in the metabolism of glucose (Gysemans et al. 2005; Zhou et al. 2008; Park et al. 2016). Correcting vitamin D deficiency may improve glucose levels and have beneficial effects on preventing complications related to type 2 diabetes (Mirhosseini et al. 2018a; Hu et al. 2019).

Although vitamin D supplementation has been investigated for its effects on the lipid profile in type 2 diabetic individuals, experimental studies have provided inconsistent findings (Jorde and Grimnes 2011). Identifying effective ways of reducing microvascular and macrovascular complications and the risk of developing cardiovascular disease in type 2 diabetic patients is an important global health concern. There is a need for studies on the beneficial effects of vitamin D on blood lipids and glycemic control in diabetic patients. This study aims to evaluate the effects of correcting vitamin D deficiency with vitamin D supplementation in type 2 diabetic patients with untreated hyperlipidemia on lipid parameters and glycemic control.

## Materials and methods

### Study design and patients

This prospective clinical trial study was conducted among type 2 diabetes mellitus (T2DM) patients with untreated hyperlipidemia and vitamin D deficiency at Layla Qasim Diabetic Center, Erbil, Iraq, over a period of six months from 1 October 2021 to 1 April 2022. Out of two hundred

patients, thirty-five patients were eligible for the study. Patients were supplemented with a weekly oral 50,000 IU of vitamin D3 softgel capsule (Madamar Company, Warsaw, Poland) for three months to correct serum vitamin D deficiency. In addition, they were advised to continue their existing lifestyle and medications. Twenty-six patients completed the study, and the rest were excluded for various reasons (three patients started taking lipid-lowering agents, two patients were travelling, and four patients changed their antidiabetic medications). The study participants' mean age  $\pm$  standard deviation (SD) was  $55.4 \pm 9$  years and ranged from 38 to 72 years.

### Inclusion criteria

Both male and female type 2 diabetic patients aged  $\geq 18$  years attending Layla Qasim Diabetic Center with hyperlipidemia (triglyceride and/or total cholesterol  $> 200$  mg/dL) and serum 25(OH)D  $< 20$  ng/ml were included in this study.

### Exclusion criteria

The study excluded patients who were taking vitamin D supplements, lipid-lowering drugs, receiving insulin therapy, who had type 1 diabetes, and those who were known to have other lipid-altering diseases, such as hepato-biliary disease, hypothyroidism, chronic kidney disease, and nephrotic syndrome. Patients who consumed alcohol and women who were pregnant or breastfeeding were also excluded.

### Data collection

Patients' information including demographic characteristics, disease profiles including duration of diabetes, current medications used by the patients, presence of dyslipidemia and cardiovascular diseases (duration of the diseases and their treatments), height and weight to calculate body mass index (BMI).

Blood samples were taken from patients after fasting (for 12 hours) and divided into two parts. The first part was placed in an EDTA-test tube for glycated haemoglobin (HbA1c) measurement, and the second part was placed in a non-coagulant test tube at room temperature to allow clotting (for 15 minutes) then the sera were separated by centrifugation (3,000 rpm for 10 minutes). Finally, HbA1c, serum 25(OH)D, calcium, glucose, and lipid profile, including total cholesterol, TG, LDL-C, and HDL-C were measured by enzymatic methods using Cobas 6000 (Roche Diagnostics, Hitachi, Tokyo, Japan), which is a fully automated analyser for clinical chemistry analysis. The same procedures were carried out again after three months of supplementation with vitamin D.

### Ethical considerations

Informed consent was obtained from the patients who participated in this study and the study was approved by the Scientific and Research Committee of College

of Pharmacy, Erbil, Iraq. Reference number: HMU. PE.05.09.2021-332.

## Statistical analysis

The data were evaluated statistically using SPSS software (version 26.0). The data were presented as mean  $\pm$  SD or frequencies and percentages. A Student's *t*-test and the Mann-Whitney *U* test were used for data analysis. The Shapiro-Wilk test was used to identify the normal distribution of the data. A Pearson's correlation was used to examine the associations between serum 25(OH)D levels and blood lipid and glucose levels. A *P*-value of 0.05 or less was considered statistically significant.

## Results

Twenty-six patients completed the follow-up (13 females and 13 males) who had dyslipidemia and vitamin D deficiency with a diabetes duration of  $8.7 \pm 6$  years. Most participants (20) were non-smokers (76.9%) (Table 1).

**Table 1.** Baseline characteristics of the study participants.

Characteristics	Values
Age (years)	55.4 $\pm$ 9
Duration of diabetes (years)	8.7 $\pm$ 6
BMI (kg/m <sup>2</sup> )	30.31 $\pm$ 4.72
Height (cm)	163.94 $\pm$ 9.19
Weight (kg)	81.69 $\pm$ 15.53
Gender	
Male	13 (50)
Female	13 (50)
Smoking status	
Non-smoker	20 (76.9)
Smoker	6 (23.1)

Data presented as mean  $\pm$  SD or n (%); BMI: Body mass index.

There were no statistically significant differences in the mean serum 25(OH)D and calcium levels between male and female patients before and after the supplementation. Vitamin D supplementation over a period of three months led to a significant rise in serum 25(OH)D (from  $13.60 \pm 4.30$  to  $37.90 \pm 8.04$  ng/mL, *P* = 0.001). None of the patients developed hypercalcaemia ( $8.95 \pm 0.57$  mg/dL) after supplementation (Table 2).

After three months of follow-up, on the one hand, there was a statistically significant reduction in very-low-density lipoprotein cholesterol (VLDL-C) (from  $55.00 \pm 11.75$  to

**Table 2.** Assessment of serum 25(OH)D and calcium before and after vitamin D supplementation in T2DM patients with hyperlipidemia and vitamin D deficiency.

Parameters	Before vitamin D supplementation	After vitamin D supplementation	<i>P</i> -value
25(OH)D (ng/mL)	$13.60 \pm 4.30$	$37.90 \pm 8.04$	0.001
Calcium (mg/dL)	$8.92 \pm 0.50$	$8.95 \pm 0.57$	0.747

Data presented as mean  $\pm$  SD; 25(OH)D: 25-Hydroxyvitamin D.

$49.87 \pm 12.01$  mg/dL, *P* = 0.001) and TG (from  $274.98 \pm 58.74$  to  $249.34 \pm 60.06$  mg/dL, *P* = 0.001) with a mean serum level change of -9.31% and -9.32%, respectively. On the other hand, there was a statistically significant increase in HDL-C (from  $33.51 \pm 6.16$  to  $37.17 \pm 6.43$  mg/dL, *P* = 0.001) with a mean serum level change of 10.92% and atherogenic indices improved significantly. However, total cholesterol and LDL-C were decreased nonsignificantly (Table 3).

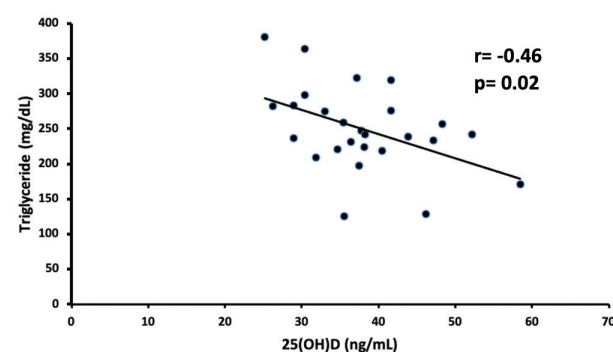
**Table 3.** The effect of vitamin D supplementation on lipid parameters and percentage change in serum lipid profile and atherogenic index following vitamin D supplementation.

Parameters	Before vitamin D supplementation	After vitamin D supplementation	% change	<i>P</i> -value
Total cholesterol (mg/dL)	$200.62 \pm 23.34$	$197.52 \pm 24.46$	-1.55%	0.184
LDL-C (mg/dL)	$122.72 \pm 19.68$	$120.72 \pm 20.93$	-1.63%	0.214
VLDL-C (mg/dL)	$55.00 \pm 11.75$	$49.88 \pm 12.01$	-9.31%	0.001
TG (mg/dL)	$274.98 \pm 58.74$	$249.34 \pm 60.06$	-9.32%	0.001
HDL-C (mg/dL)	$33.51 \pm 6.16$	$37.17 \pm 6.43$	10.92%	0.001
Cholesterol/HDL-C	$6.14 \pm 1.17$	$5.45 \pm 1.08$	-11.24%	0.001
TG/HDL-C	$8.56 \pm 2.73$	$6.99 \pm 2.42$	-18.34%	0.012
AIP (Log TG/HDL-C)	$0.55 \pm 0.15$	$0.46 \pm 0.15$	-16.36%	0.001

Data presented as mean  $\pm$  SD.

LDL-C: low-density lipoprotein cholesterol; VLDL-C: very-low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; AIP: atherogenic index of plasma.

Pearson's correlation analysis between serum levels of 25(OH)D and other parameters was performed in which serum levels of 25(OH)D had a nonsignificant negative correlation with fasting blood glucose (FBG) (*r* = -0.14, *P* = 0.49) and HbA1c (*r* = -0.03, *P* = 0.88). Regarding lipid parameters, TG showed a significant negative correlation with serum 25(OH)D (*r* = -0.46, *P* = 0.02) (Fig. 1) while other lipid parameters showed nonsignificant correlations with 25(OH)D levels.



**Figure 1.** Correlation between serum 25(OH)D and triglyceride levels after three months of supplementation with vitamin D.

Additionally, HbA1c was significantly improved (from  $8.44 \pm 0.93\%$  to  $7.95 \pm 0.86\%$ , *P* = 0.001) while FBG was decreased nonsignificantly (Table 4).

**Table 4.** Assessment of glycemic status before and after vitamin D supplementation in T2DM patients with hyperlipidemia and vitamin D deficiency.

Parameters	Before vitamin D supplementation	After vitamin D supplementation	P-value
FBG (mg/dL)	174.67 ± 37.58	160.13 ± 28.40	0.113
HbA1c (%)	8.44 ± 0.93	7.95 ± 0.86	0.001

Data presented as mean ± SD; FBG: fasting blood glucose; HbA1c: glycated haemoglobin.

## Discussion

The deficiency of vitamin D has been linked to a higher risk of developing several chronic diseases, including T2DM (Wang et al. 2017). Type 2 diabetics, especially those with poorly controlled diabetes, are highly prone to hyperlipidemia (Shahwan et al. 2019). Compared to those who do not have diabetes, hyperlipidemia is significantly associated with an increased risk of cardiovascular disease due to the role it plays in atherosclerosis development and progression (Miao et al. 2020; Merkhani et al. 2021).

In this study, 25(OH)D levels were measured to determine vitamin D deficiency, since it is the most accurate indicator of vitamin D status (Sempos et al. 2018).

The present study involved T2DM patients with vitamin D deficiency and dyslipidemia. They were on oral hypoglycaemic agents and not taking lipid-lowering agents. To our knowledge, no research has been conducted on the effects of vitamin D supplementation on the lipid profile in T2DM patients with untreated hyperlipidemia and vitamin D deficiency. Supplementing vitamin D for three months led to a substantial rise in levels of 25(OH)D and a significant decrease in VLDL-C, TG levels, and atherogenic indices (cholesterol/HDL-C, TG/HDL-C, and AIP), and a significant rise in HDL-C levels.

The available studies' findings regarding the impact of vitamin D administration on lipid profile are uncertain. A study conducted on hyperlipidemic patients on statin therapy found a significant improvement in total cholesterol, TG, LDL-C, and HDL-C levels after taking daily 2,000 IU of vitamin D for six months (Qin et al. 2015).

The present study's result of reduced levels of TG after vitamin D supplementation is consistent with the findings of Barzegari et al. (2019). In their study, an eight-week administration of weekly 50,000 IU of vitamin D as a supplement in diabetic nephropathy patients showed a significant reduction in TG, LDL-C, and total cholesterol levels in participants with a marginal vitamin D deficiency. In another study on T2DM patients who had been advised not to change the dose of their antidiabetic and antihyperlipidemic drugs throughout the study period, Mohammed et al. (2016) showed no significant improvement in lipid profile after receiving daily 4,500 IU of vitamin D for two months, except for female patients whose TG levels were significantly reduced.

In the present study, the participants showed a significant rise in HDL-C levels after the supplementation with vitamin D. A similar increase in HDL-C levels was

observed in several other studies (Rad et al. 2014; Razzaghi et al. 2017; Wenclewska et al. 2019). Similarly, Mirhosseini et al. (2018b) confirmed the favourable impact of vitamin D on HDL-C in their meta-analysis. This positive influence of 25(OH)D on HDL-C might result from the increased concentration of apolipoprotein AI in the blood, which plays an important role in the reverse cholesterol transport process (Kazlauskaite et al. 2010). Pearson's correlation revealed a significant negative correlation between serum TG and 25(OH)D, which is similar to the findings of some other studies (Elmi et al. 2021; Elshebiny et al. 2021; Gong et al. 2022). In contrast to this finding, Ramiro-Lozano and Calvo-Romero (2015) concluded that supplementing T2DM patients with 16,000 IU of vitamin D once a week for eight weeks did not significantly alter their blood TG, cholesterol, and HDL levels.

The variations in these results may be attributed to study participants' vitamin D levels and blood lipid levels at baseline, variations in dosage of vitamin D supplementation, and discrepancies in the design and duration of the studies.

Numerous mechanisms have been proposed for vitamin D's effect on lipid levels. Vitamin D may affect lipid metabolism by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase expression, which in turn lowers the synthesis of cholesterol (Li et al. 2016). Vitamin D increases the absorption of calcium in the intestine and the intestinal calcium influences the absorption of fats resulting from the binding of calcium to intestinal bile acids and fatty acids to make soaps of calcium-fatty acid, which are eventually eliminated from the body in the faeces (Wang et al. 2016). Zittermann et al. (2009) have proposed that the increased calcium absorption could affect hepatocellular calcium to lower serum TG by lowering hepatic TG formation or secretion. Theoretically, vitamin D could have an immediate effect on serum lipid levels, but it could also have an indirect effect on calcium balance and/or serum parathyroid hormone (PTH) (Jorde and Grimnes 2011). Additionally, serum levels of 25(OH)D and PTH are inversely related, and serum PTH levels are suppressed by vitamin D supplementation (Suplotova et al. 2019). This suppressive effect of vitamin D on serum concentrations of PTH might cause a reduction in serum levels of TG as a result of enhanced peripheral removal (Wang et al. 2016). Furthermore, vitamin D may also influence insulin secretion and sensitivity, thus indirectly affecting lipid metabolism (Lemieux et al. 2019).

Regarding glycemic status, following three months of vitamin D supplementation, participants had a significant reduction in HbA1c levels. The reduction in FBG was not significant. The effect of vitamin D supplementation on glucose levels in our study was similar to results in several other studies (Krul-Poel et al. 2015; Ghadiri-Anari et al. 2019; Safarpour et al. 2020).

In parallel with this study, various studies reported a significant reduction in HbA1c levels in diabetic patients after receiving vitamin D supplementations (Razzaghi et al. 2017; Upreti et al. 2018; Almaghrbi et al. 2021). Vitamin D may enhance the function of beta-cells (Mitri et al. 2011) and reduce insulin resistance (Guclu et al. 2016).

Conversely, some other studies on diabetic patients were not documented with similar effects of vitamin D supplementation on glycemic control (Witham et al. 2010; Heshmat et al. 2012; Al-Sofiani et al. 2015). The likely explanations for these inconsistent findings might be the different study designs, differences in diet and lifestyle, type and/or dose and the schedule of hypoglycaemic agents, and genetic variation of populations. Overall, vitamin D supplementation has improved lipid profile and glycemic control, thus, it might reduce the risk of diabetic complications, especially in those with hyperlipidemia and vitamin D deficiency.

It is still unclear exactly how vitamin D influences blood glucose levels. It is possible that the improvement in glycemic status might be due to the presence of vitamin D receptors and 1-alpha-hydroxylase in the pancreas (Bland et al. 2004). In a recent experiment, Kjalarsdottir et al. (2019) discovered that preincubating human and mouse islets with calcitriol increases glucose-stimulated insulin secretion and glucose-stimulated calcium influx via upregulation of the voltage-gated calcium channel gene, consequently modulating the beta-cell capacity to secrete insulin. Additionally, Chen et al. (2016) found that in mice lacking functional vitamin D receptors

in their skeletal muscles, forkhead box O1 (FOXO1), a transcription factor that negatively regulates insulin signalling, is expressed and activated at higher levels. They also showed that the overexpression of FOXO1 results in skeletal muscle vitamin D signalling deficiency that contributes significantly to insulin resistance and glucose intolerance development.

The present study has some limitations due to time constraints, including a relatively small sample size and a short intervention period. Additionally, this study did not analyse subgroups.

## Conclusions

Oral vitamin D supplementation of 50,000 IU once weekly for three months significantly decreased VLDL-C, TG, atherogenic indices, and HbA1c and led to a significant rise in HDL-C levels in T2DM patients with untreated hyperlipidemia and vitamin D deficiency. Therefore, vitamin D supplementation to restore normal levels of vitamin D in such patients could be a valuable adjuvant therapy. However, further studies with larger patient samples and longer durations are needed to substantiate our findings.

## References

- Almaghrbi A, Altarrani M, Elmighrabi N, Bakoush HM, Elmabsout AA (2021) Effect of Vitamin D Supplementation on Blood Glucose Homeostasis, BMI and Lipid Profile in Diabetic Patients with Vitamin D Deficiency. *Asian Journal of Basic Science & Research* 3: 25–35. <https://doi.org/10.38177/ajbsr.2021.3303>
- Alshamiri M, Ghanaim MMA, Barter P, Chang K-C, Li J-J, Matawaran BJ, Santoso A, Shaheen S, Suastika K, Thongtang N (2018) Expert opinion on the applicability of dyslipidemia guidelines in Asia and the Middle East. *International journal of general medicine* 11: 313. <https://doi.org/10.2147/ijgm.s160555>
- Al-Sofiani ME, Jammah A, Racz M, Khawaja RA, Hasanato R, El-Fawal HA, Mousa SA, Mason DL (2015) Effect of vitamin D supplementation on glucose control and inflammatory response in type II diabetes: a double blind, randomized clinical trial. *International journal of endocrinology and metabolism* 13: e22604. <https://doi.org/10.5812/ijem.22604>
- Al-Zaharani M (2013) The Prevalence of vitamin D deficiency in type 2 diabetic patients. *Majmaah Journal of Health Sciences* 1: 18–22. <https://doi.org/10.12816/0004767>
- Ama Moor VJ, Ndongo Amougou S, Ombotto S, Ntone F, Wouamba DE, Ngo Nonga B (2017) Dyslipidemia in patients with a cardiovascular risk and disease at the University Teaching Hospital of Yaoundé, Cameroon. *International journal of vascular medicine* 2017: e6061306. <https://doi.org/10.1155/2017/6061306>
- Barzegari M, Sarbakhsh P, Mobasser M, Noshad H, Esfandiari A, Khodadadi B, Gargari BP (2019) The effects of vitamin D supplementation on lipid profiles and oxidative indices among diabetic nephropathy patients with marginal vitamin D status. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 13: 542–547. <https://doi.org/10.1016/j.dsx.2018.11.008>
- Bashir F, Khan ZU, Qureshi S, Seetlani NK, Sheikh Z (2016) Prevalence of hypovitaminosis D in type 2 diabetes mellitus and its relationship with glycemic control. *Journal of Liaquat University of Medical & Health Sciences* 15: 83–9. <https://doi.org/10.22442/jlums.161520470>
- Blais JE, Tong GKY, Pathadka S, Mok M, Wong IC, Chan EW (2021) Comparative efficacy and safety of statin and fibrate monotherapy: A systematic review and meta-analysis of head-to-head randomized controlled trials. *PLoS ONE* 16: e0246480. <https://doi.org/10.1371/journal.pone.0246480>
- Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M (2004) Expression of 25-hydroxyvitamin D3-1 $\alpha$ -hydroxylase in pancreatic islets. *The Journal of steroid biochemistry and molecular biology* 89: 121–125. <https://doi.org/10.1016/j.jsbmb.2004.03.115>
- Borissova A, Tankova T, Kirilov G, Dakovska L, Kovacheva R (2003) The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *International journal of clinical practice* 57: 258–261.
- Chen S, Villalta SA, Agrawal DK (2016) FOXO1 mediates vitamin D deficiency-induced insulin resistance in skeletal muscle. *Journal of bone and mineral research* 31: 585–595. <https://doi.org/10.1002/jbmr.2729>
- Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D (2016) Interpretation of the evidence for the efficacy and safety of statin therapy. *The Lancet* 388: 2532–2561. [https://doi.org/10.1016/s0140-6736\(16\)31357-5](https://doi.org/10.1016/s0140-6736(16)31357-5)
- Dibaba DT (2019) Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis. *Nutrition reviews* 77: 890–902. <https://doi.org/10.1093/nutrit/nuz037>

- Elmi C, Fan MM, Le M, Cheng G, Khalighi K (2021) Association of serum 25-Hydroxy Vitamin D level with lipid, lipoprotein, and apolipoprotein level. *Journal of Community Hospital Internal Medicine Perspectives* 11: 812–816. <https://doi.org/10.1080/20009666.2021.1968571>
- Elshebiny A, AlHewishel MA, Al Ghadeer HA, Alosaif N, Al Furaikh BF, ALHejji MS, Alsahaf HAA (2021) Correlation of 25-Hydroxyvitamin D and Serum Lipid Levels Among Patients With Type 2 Diabetes. *Cureus* 13: e19667. <https://doi.org/10.7759/cureus.19667>
- Ghadiri-Anari A, Mozafari Z, Gholami S, Khodaei S-A, Aboutorabi-Zarchi M, Sepehri F, Nadjarzade A, Rahmanian M, Namiranian N (2019) Dose vitamin D supplementations improve peripheral diabetic neuropathy? A before-after clinical trial. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 13: 890–893. <https://doi.org/10.1016/j.dsx.2018.12.014>
- Ginsberg HN (2000) Insulin resistance and cardiovascular disease. *The Journal of clinical investigation* 106: 453–458. <https://doi.org/10.1172/jci10762>
- Gong T, Di H, Han X, Hu X, Liu C, Chen G (2022) Vitamin D is negatively associated with triglyceride in overweight/obese patients with type 2 diabetes. *Endocrine* 76: 304–311. <https://doi.org/10.1007/s12020-022-03009-8>
- Guclu A, Erdur F, Turkmen K (2016) The emerging role of sirtuin 1 in cellular metabolism, diabetes mellitus, diabetic kidney disease and hypertension. *Experimental and Clinical Endocrinology & Diabetes* 124: 131–139. <https://doi.org/10.1055/s-0035-1565067>
- Gysemans CA, Cardozo AK, Callewaert H, Giulietti A, Hulshagen L, Bouillon R, Eizirik DL, Mathieu C (2005) 1, 25-Dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: implications for prevention of diabetes in nonobese diabetic mice. *Endocrinology* 146: 1956–1964. <https://doi.org/10.1210/en.2004-1322>
- Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, Shahbazi S, Khooshehchin G, Bandarian F, 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: 1–6. <https://doi.org/10.1186/2008-2231-20-10>
- Hu Z, Jin'an Chen XS, Wang L, Wang A (2019) Efficacy of vitamin D supplementation on glycemic control in type 2 diabetes patients: a meta-analysis of interventional studies. *Medicine* 98: e14970. [98 pp] <https://doi.org/10.1097/md.00000000000014970>
- Jorde R, Grimnes G (2011) Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Progress in lipid research* 50: 303–312. <https://doi.org/10.1016/j.plipres.2011.05.001>
- Jorde R, Figenschau Y, Hutchinson M, Emaus N, Grimnes G (2010) High serum 25-hydroxyvitamin D concentrations are associated with a favorable serum lipid profile. *European journal of clinical nutrition* 64: 1457–1464. <https://doi.org/10.1038/ejcn.2010.176>
- Kamycheva E, Jorde R, Figenschau Y, Haug E (2007) Insulin sensitivity in subjects with secondary hyperparathyroidism and the effect of a low serum 25-hydroxyvitamin D level on insulin sensitivity. *Journal of endocrinological investigation* 30: 126–132. <https://doi.org/10.1007/bf03347410>
- Kazlauskaitė R, Powell LH, Mandapakala C, Cursio JF, Avery EF, Calvin J (2010) Vitamin D is associated with atheroprotective high-density lipoprotein profile in postmenopausal women. *Journal of clinical lipidology* 4: 113–119. <https://doi.org/10.1016/j.jacl.2010.01.006>
- Kjalarsdottir L, Tersey SA, Vishwanath M, Chuang J-C, Posner BA, Mirmira RG, Repa JJ (2019) 1, 25-Dihydroxyvitamin D3 enhances glucose-stimulated insulin secretion in mouse and human islets: a role for transcriptional regulation of voltage-gated calcium channels by the vitamin D receptor. *The Journal of steroid biochemistry and molecular biology* 185: 17–26. <https://doi.org/10.1016/j.jsbmb.2018.07.004>
- Krull-Poel YH, Westra S, ten Boekel E, ter Wee MM, van Schoor NM, van Wijland H, Stam F, Lips PT, Simsek S (2015) Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY trial): a randomized placebo-controlled trial. *Diabetes care* 38: 1420–1426. <https://doi.org/10.2337/dc15-0323>
- Lemieux P, Weisnagel SJ, Caron AZ, Julien A-S, Morisset A-S, Carreau A-M, Poirier J, Tchernof A, Robitaille J, Bergeron J (2019) Effects of 6-month vitamin D supplementation on insulin sensitivity and secretion: a randomised, placebo-controlled trial. *European journal of endocrinology* 181: 287–299. <https://doi.org/10.1530/eje-19-0156>
- Merkhan M, Mohammad J, Fathi Z, Younus Z, Mahmood SM, Mohammed M (2021) Silent hyperlipidaemia modulated vascular endothelial markers. *Pharmacia* 68: 479–484. <https://doi.org/10.3897/pharmacia.68.e67959>
- Miao J, Zang X, Cui X, Zhang J (2020) Autophagy, hyperlipidemia, and atherosclerosis. In: Le W (Ed.) *Autophagy: Biology and Diseases. Advances in Experimental Medicine and Biology*, vol. 1207. Springer, Singapore, 237–264. [https://doi.org/10.1007/978-981-15-4272-5\\_18](https://doi.org/10.1007/978-981-15-4272-5_18)
- Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM (2018a) Vitamin D Supplementation, Glycemic Control, and Insulin Resistance in Prediabetics: A Meta-Analysis. *Journal of the Endocrine Society* 2: 687–709. <https://doi.org/10.1210/js.2017-00472>
- Mirhosseini N, Rainsbury J, Kimball SM (2018b) Vitamin D supplementation, serum 25 (OH) D concentrations and cardiovascular disease risk factors: a systematic review and meta-analysis. *Frontiers in cardiovascular medicine* 5: 87. <https://doi.org/10.3389/fcvm.2018.00087>
- Mitri J, Dawson-Hughes B, Hu FB, Pittas AG (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>
- Mohamad MI, El-Sherbeny EE, Bekhet MM (2016) The effect of vitamin D supplementation on glycemic control and lipid profile in patients with type 2 diabetes mellitus. *Journal of the American college of nutrition* 35: 399–404. <https://doi.org/10.1080/07315724.2015.1026427>
- Nasr MH, Hassan BAR, Othman N, Karuppanan M, binti Abdulaziz N, Mohammed AH, Alsarani MA, Eskembaji MH, Aman AM, Othman G (2022) Prevalence of Vitamin D Deficiency Between Type 2 Diabetes Mellitus Patients and Non-Diabetics in the Arab Gulf. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 15: 647. <https://doi.org/10.2147/dms0.s350626>
- Okopień B, Bułdak Ł, Bóldys A (2018) Benefits and risks of the treatment with fibrates—a comprehensive summary. *Expert review of clinical pharmacology* 11: 1099–1112. <https://doi.org/10.1080/17512433.2018.1537780>
- Park S, Kim DS, Kang S (2016) Vitamin D deficiency impairs glucose-stimulated insulin secretion and increases insulin resistance by reducing PPAR- $\gamma$  expression in nonobese Type 2 diabetic rats. *The Journal of nutritional biochemistry* 27: 257–265. <https://doi.org/10.1016/j.jnutbio.2015.09.013>

- Pitocco D, Crino A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, Angiusola GB, Visalli N, Suraci C, Matteoli M (2006) The effects of calcitriol and nicotinamide on residual pancreatic  $\beta$ -cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI). *Diabetic Medicine* 23: 920–923. <https://doi.org/10.1111/j.1464-5491.2006.01921.x>
- Qin XF, Zhao LS, Chen WR, Wang H (2015) Effects of vitamin D on plasma lipid profiles in statin-treated patients with hypercholesterolemia: A randomized placebo-controlled trial. *Clinical Nutrition* 34: 201–206. <https://doi.org/10.1016/j.clnu.2014.04.017>
- Rad EY, Djalali M, Koohdani F, Saboor-Yaraghi AA, Eshraghian MR, Javanbakht MH, Saboori S, Zarei M, Hosseinzadeh-Attar MJ (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.
- Ramiro-Lozano JM, Calvo-Romero JM (2015) Effects on lipid profile of supplementation with vitamin D in type 2 diabetic patients with vitamin D deficiency. *Therapeutic advances in endocrinology and metabolism* 6: 245–248. <https://doi.org/10.1177/2042018815599874>
- Razzaghi R, Pourbagheri H, Momen-Heravi M, Bahmani F, Shadi J, Soleimani Z, Asemi Z (2017) The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *Journal of Diabetes and its Complications* 31: 766–772. <https://doi.org/10.1016/j.jdiacomp.2016.06.017>
- Safarpour P, Daneshi-Maskooni M, Vafa M, Nourbakhsh M, Janani L, Maddah M, Amiri F-S, Mohammadi F, Sadeghi H (2020) Vitamin D supplementation improves SIRT1, Irisin, and glucose indices in overweight or obese type 2 diabetic patients: a double-blind randomized placebo-controlled clinical trial. *BMC family practice* 21: 1–10. <https://doi.org/10.1186/s12875-020-1096-3>
- Sampos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, DeLuca HF, Jones G, Munns CF, Bilezikian JP (2018) Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. *British journal of clinical pharmacology* 84: 2194–2207. <https://doi.org/10.1111/bcp.13652>
- Shahwan MJ, Jairoun AA, Farajallah A, Shanabli S (2019) Prevalence of dyslipidemia and factors affecting lipid profile in patients with type 2 diabetes. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 13: 2387–2392. <https://doi.org/10.1016/j.dsx.2019.06.009>
- Suplotova LA, Avdeeva VA, Pigarova EA, Rozhinskaya LY (2019) The «cut-off point» of vitamin D: a method of suppressing excessive secretion of PTH. *Obesity and metabolism* 16: 88–93. <https://doi.org/10.14341/omet10196>
- Tepper S, Shahar D, Geva D, Avizohar O, Nodelman M, Segal E, Ish-Shalom S (2014) Identifying the threshold for vitamin D insufficiency in relation to cardiometabolic markers. *Nutrition, metabolism and cardiovascular diseases* 24: 489–494. <https://doi.org/10.1016/j.numecd.2013.10.025>
- Upreti V, Maitri V, Dhull P, Handa A, Prakash M, Behl A (2018) Effect of oral vitamin D supplementation on glycemic control in patients with type 2 diabetes mellitus with coexisting hypovitaminosis D: A parallel group placebo controlled randomized controlled pilot study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 12: 509–512. <https://doi.org/10.1016/j.dsx.2018.03.008>
- Verstuyf A, Carmeliet G, Bouillon R, Mathieu C (2010) Vitamin D: a pleiotropic hormone. *Kidney international* 78: 140–145. <https://doi.org/10.1038/ki.2010.17>
- Wang H, Xia N, Yang Y, Peng D-Q (2012) Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids in health and disease* 11: 1–9. <https://doi.org/10.1186/1476-511x-11-42>
- Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, Zheng SG (2017) Vitamin D and chronic diseases. *Aging and disease* 8: 346. <https://doi.org/10.14336/ad.2016.1021>
- Wang Y, Si S, Liu J, Wang Z, Jia H, Feng K, Sun L, Song SJ (2016) The associations of serum lipids with vitamin D status. *PLoS ONE* 11(10): e0165157. <https://doi.org/10.1371/journal.pone.0165157>
- Ward NC, Watts GF, Eckel RH (2019) Statin toxicity: mechanistic insights and clinical implications. *Circulation research* 124: 328–350. <https://doi.org/10.1161/circresaha.118.312782>
- Wenclewska S, Szymczak-Pajor I, Drzewoski J, Bunk M, Śliwińska A (2019) Vitamin D supplementation reduces both oxidative DNA damage and insulin resistance in the elderly with metabolic disorders. *International journal of molecular sciences* 20: 2891. <https://doi.org/10.3390/ijms20122891>
- Witham M, Dove F, Dryburgh M, Sugden J, Morris A, Struthers A (2010) The effect of different doses of vitamin D3 on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* 53: 2112–2119. <https://doi.org/10.1007/s00125-010-1838-1>
- Yang K, Liu J, Fu S, Tang X, Ma L, Sun W, Niu Y, Jing G, Niu Q (2020) Vitamin D status and correlation with glucose and lipid metabolism in Gansu Province, China. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 13: 1555–1563. <https://doi.org/10.2147/dmso.s249049>
- Závorková M, Vetricka V, Richter J, Kral V, Liehnova I, Rajnohova DL (2018) Effects of glucan and vitamin D supplementation on obesity and lipid metabolism in diabetic retinopathy. *The open biochemistry journal* 12: 36–45. <https://doi.org/10.2174/1874091x01812010036>
- Zhou QG, Hou FF, Guo ZJ, Liang M, Wang GB, Zhang X (2008) 1, 25-Dihydroxyvitamin D improved the free fatty-acid-induced insulin resistance in cultured C2C12 cells. *Diabetes/metabolism research and reviews* 24: 459–464. <https://doi.org/10.1002/dmrr.873>
- Zittermann A, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R (2009) Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *The American journal of clinical nutrition* 89: 1321–1327. <https://doi.org/10.3945/ajcn.2008.27004>