

Cholecalciferol Effects on Lipid Profile of Experimental Animals: A Scoping Review

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Abstract

Vitamin D is an essential nutrient that has various beneficial effects on the human body. The results of cholecalciferol supplementation are varied, and there has yet to be a comprehensive review regarding its effect on animal models. Therefore, this scoping review aims to summarize the evidence regarding the effect of cholecalciferol (vitamin D3) supplementation on the lipid profiles of animal subjects. PubMed, Scopus, and DOAJ were searched for original research articles published until 2022. Studies were included if they were experimental studies, cholecalciferol was used as a supplement, and the changes in the lipid profile were analyzed. A total of 260 articles were collected, of which 250 articles were excluded, and 10 articles were included for qualitative synthesis. All studies used oral routes to supplement cholecalciferol with various doses and duration ranging from several weeks to several months. Most studies reported reduced lipid parameters in serum or organ-specific animals supplemented with cholecalciferol. As conclusion, cholecalciferol reduces lipid content in animal subjects and may have a beneficial effect on populations with metabolic diseases such as diabetes and dyslipidemia. Further research is required to explore the mechanism of how cholecalciferol affects the lipid profiles of experimental animals.

Keywords: Cholecalciferol; Cholesterol; Lipid

1. INTRODUCTION

Dyslipidemias are quantitative changes in cholesterol concentrations, respective fractions, or triglycerides in the plasma. This condition may increase the risk of atherosclerosis in adults and lead to cardiovascular diseases (Mosca et al., 2022). Approximately 50% of the adult population has dyslipidemia (Hedayatnia et al., 2020). The primary causes of dyslipidemia are gene mutations causing overproduction or inadequate clearance of triglycerides (TG) and low-density lipoprotein (LDL) or underproduction or excessive clearance of high-density lipoprotein (HDL). Secondary causes of dyslipidemia may be caused by various diseases such as hypothyroidism, nephrotic syndrome, chronic kidney disease, diabetes, obesity, and lifestyle causes such as abnormal alcohol intake and smoking (Yanai and Yoshida, 2021).

Vitamin D has been shown in various studies to play a role in various diseases, including dyslipidemia, in which observational studies showed that low vitamin D levels were associated with lipid abnormalities (Surdu et al., 2021; Kim and Jeong, 2019). Cholecalciferol (Vitamin

D3) is a native vitamin D obtained by food ingestion that has various roles in the metabolism of the musculoskeletal, respiratory, endocrine, renal, cardiovascular, and immune systems (Sosa and Gómez, 2020). Previous scoping studies have analyzed the effect of vitamin D on lipid profiles, which found that vitamin D and calcium have a beneficial effect on total cholesterol (TC), triglycerides (TG), and HDL-C using placebo-controlled randomized controlled trials (RCTs) (Morvaridzadeh et al., 2021). Another review found that vitamin D administration in postmenopausal women reduces triglycerides, but LDL-C, HDL-C, and TC changes are negligible (Zhang et al., 2022).

Numerous research studies regarding the effect of cholecalciferol supplementation on lipid profiles in animal models have varying results. However, there still needs to be a comprehensive review of its effect and what parameters of lipid profiles are affected. The purpose of this review is to address the knowledge gap by reviewing the literature on cholecalciferol supplementation in healthy or disease-induced animal models which reported changes in lipid profiles

2. MATERIAL AND METHODS

This scoping review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018).

2.1. Eligibility criteria

To be included in the review, peer-reviewed journal papers needed to (1) involve supplementation of cholecalciferol, (2) analyze the changes in lipid profiles which comprised of either total cholesterol, triglycerides, low-density lipoprotein or high-density lipoprotein, (3) experimental studies using mice as animal subjects. Studies were excluded if they (1) did not report cholecalciferol dose and (2) did not report quantitative changes in the lipid profile. All the studies had to be fully completed and published; abstract-only, presentation-only, and unpublished studies were excluded.

2.2. Information sources

Searches were conducted on the electronic databases of PubMed, Scopus, and the Directory of Open Access Journals (DOAJ) for studies published from its inception until February 2023. (The last search was conducted in February 2023). The databases are chosen considering their advantages, and Pubmed is considered one of the most frequently updated websites with a comprehensive follow-up of a specific subject. Scopus provides more citations, and with proper search strategies, false positives can be eliminated from the search. DOAJ is one of the leading multidisciplinary open-access databases and may provide additional articles that would otherwise not be published under a paid-model database. The search was restricted to papers written or translated into English. Reference lists of all retrieved articles and the profiles of authors with extensive experience in dietary supplement research were scanned for

additional relevant articles. All databases were searched for the earliest known published articles in the database up until the articles were published in December 2022.

2.3. Search strategy

The search strategy involved a combination of keywords limited to the title and abstract. For different databases, the search strategy was adapted according to the search feature of each database. Search strategy in PUBMED includes (Vitamin D3 OR cholecalciferol OR hydroxycholecalciferol OR dihydroxy vitamin D3), AND (Lipid OR cholesterol OR lipid panel OR VLDL OR HDL OR VLDL OR IDL OR very low-density lipoprotein OR intermediate-density lipoprotein OR low-density lipoprotein OR high-density lipoprotein). Search strategy in DOAJ and Scopus includes (Cholecalciferol) AND (Lipid).

2.4. Selection process

Two of the authors screened the studies for eligibility. Any disagreements on study selection or data extraction were resolved by consensus.

2.5. Data charting and items

The first author developed the data charting table and further improved and approved by the other two authors to finally include the authors' names, year of publication, animal model, amount of cholecalciferol supplementation, route of supplementation, comparison group, duration, results analyzed, the health status of animal model, comparison with controls, and comparison with other treatment.

3. RESULTS AND DISCUSSION

3.1. Selection of studies

In total, 260 articles were identified by database searches, whereas manual searches identified no articles. After removing duplicates, 245 articles remained; 221 articles were removed during the initial screening, and 24 articles were removed during full-text screening. Ten articles were included in the analysis (Figure 1).

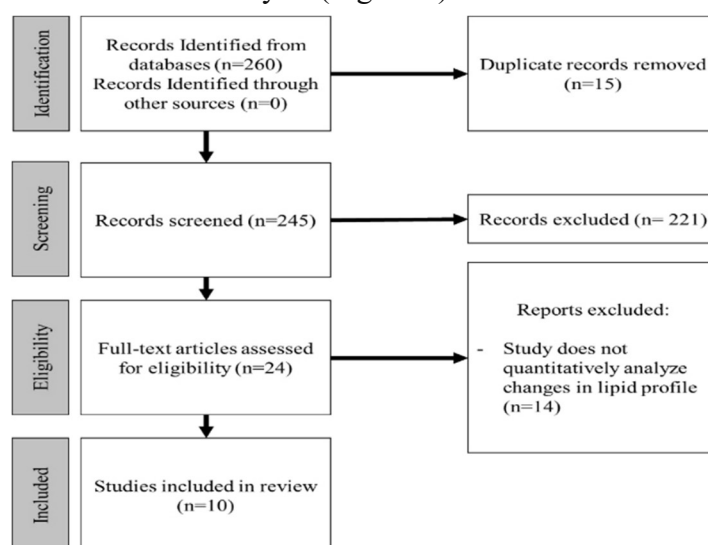


Figure 1. Flow chart for the study selection that searched in PubMed PMC, Scopus, and DOAJ.

3.2. Characteristics of vitamin D3 supplementation

All studies used the oral route to administer cholecalciferol using various vehicles (Tsuruki et al., 1986; Quach et al., 2018; Lee et al., 2020; Lim et al., 2021; Surdu et al., 2021; Wahba et al., 2021; Abd and Sallam, 2022; Atia et al., 2022; Elseweidy et al., 2022; Philouze et al., 2022). Cholecalciferol was either administered as a single treatment or with other supplements. Tsuruki et al. (1986) administered vitamin D3 orally, dissolved in 0.1 ml of propylene glycol and ethanol solution. Philouze et al. (2022) used a vitamin D3-enriched (15000 IU/kg) HFS diet for over 15 weeks. Lee et al. (2020) administered vitamin D3 300 ng/kg orally for 12 weeks. Lim et al. (2021) fed HFD supplemented with vitamin D3 in 300 ng/kg or 600 ng/kg dissolved in olive oil over 12 weeks by oral gavage. Wahba et al. (2021) administered vitamin D3 orally for six weeks in a dose of 10 µg/kg/day along with the same fructose/salt feeding concentration. Abd and Sallam (2022) administered cholecalciferol in two groups, one in 500 IU/KG/day dose by oral route for six weeks and the other group by pretreatment of cholecalciferol 500 IU/Kg/day orally for four weeks, followed by Tamoxifen and cholecalciferol oral administration for the remaining two weeks. Atia et al. (2022) administered vitamin D3 in 500 IU/kg using corn oil via orogastric lavage. Elseweidy et al. (2022) supplemented 170 IU cholecalciferol weekly for eight weeks. Quach et al. (2018) treated hypercholesterolemia mice using 1625 nmol/kg cholecalciferol for eight days. Calgaroto et al. (2015) supplemented 90 µg/kg/day of oral cholecalciferol for 30 days on diabetic rats.

3.2. Changes in lipid profile

Most of the studies reported a significant decrease in lipid parameters, whether it is total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), or high-density lipoprotein (HDL) (10,13,14,15,16,17,19). Cholecalciferol supplementation was reported to impair lipid metabolism, which resulted in a significant decrease of LDL-c ($P < 0.0001$) and triglycerides ($P = 0.001$) by 140 and 74%, respectively, along with a decrease in HCL-c ($P = 0.00002$) by 18% in saline-treated diabetic rats (Calgaroto et al., 2015). Another study plotted plasma and liver cholesterol levels against plasma 1,25(OH)₂ D₃ and liver concentration, which showed an inverse correlation. A significant correlation was found when liver cholesterol was plotted against 1,25(OH)₂ D. However, the study showed a very shallow and insignificant correlation between plasma 1,25(OH)₂ D and plasma cholesterol (Quach et al., 2018).

Other studies also reported a significant decrease in lipid-related parameters. A study reported that vitamin D3 administration significantly reduced plasma TG levels, with no significant alterations in TC levels. There was also an elevation of plasma HDL-C levels following a high dose of vitamin D3 in type 2 diabetic mice. The study also showed that vitamin D3 supplementation reduced liver TG content, while hepatic TC levels did not significantly change (Lim et al., 2021). Atia et al. (2022) showed a significant decrease ($p < 0.001$) in TC and TG levels in diabetic rats treated with eight weeks of cholecalciferol compared with untreated diabetic rats. Wahba et al. (2021) showed that vitamin D3 significantly improved the markers of obesity and serum lipids such as serum TG, TC, and TC/HDL-C ratio profile compared to

untreated metabolic syndrome rats ($p < 0.05$). In the study, vitamin D3 supplementation in normal animals almost exhibited non-significant parameters of the previous parameter compared to the control group. Philouze et al. (2022) showed that cholecalciferol supplementation in HFS-fed mice decreased cholesterol levels. However, there was no effect on TG, other sphingolipids, or cholesteryl esters.

A study by Abd and Sallam (2022) supplemented cholecalciferol as pretreatment analyzes lipid profiles in Tamoxifen (TAM)-induced steatohepatitis in female rats; the study showed that pretreatment using cholecalciferol alleviated the TAM-induced alterations in lipid profiles. Cholecalciferol also mitigated hepatic TG elevation by TAM and normalized hepatic cholesterol levels. Cholecalciferol alone for six weeks was also reported in the study to reduce serum TG ($F(3, 21) = 3.464, p = 0.0346$) and hepatic TG ($F(3, 20) = 788.7, p < 0.0001$). Compared with lipid-reducing drugs, cholecalciferol supplementation was also found to produce the same results, such as the study by Elseweidy et al. (2022), which showed that in diabetic hyperlipidaemic rats, rats treated with atorvastatin and vitamin D3 showed similar results where TC, TG, LDL-C were significantly decreased ($p < 0.001$) compared with non-diabetic hyperlipidemic rat control group.

There are also changes in lipid composition on several specific organs of rats supplemented with cholecalciferol. Tsuruki et al. (1986) reported the effect of vitamin D3 and cadmium on the lipid composition of rat intestinal brush border membranes. The total lipid content was found to be increased. Phospholipid duodenal content was increased significantly in vitamin-D3-treated rats without cadmium. Cholesterol and glycolipid levels were not significantly altered in these rats by vitamin D3 treatment. Lee et al. (2020) showed no significant reduction of serum TH and TC levels in mice supplemented with vitamin D3. However, there was a decrease in TG and TC levels in the kidney, while there was still no significant decline in renal LDL by vitamin D3 supplementation. No significant changes were found in renal HDL in vitamin D3-supplemented mice.

Cholecalciferol, or vitamin D3, is synthesized in the skin as the primary source in humans and increases proportionally with the intensity of ultraviolet radiation. The synthesis of vitamin D3 depends on the 7-dehydrocholesterol pathway to control the synthesis of cholesterol in cells. Radiation of ultraviolet B (UV-B) light ionizes the 7-dehydrocholesterol into pre-vitamin D3 thus converting to cholecalciferol. Vitamin D3 is transported with a serum protein vitamin D-binding protein (DBP) and hydroxylated into calcidiol. The calcidiol binds with the vitamin D receptor (VDR). The vitamin D-VDR complex is a primary circulating form in the blood. In the liver, vitamin D3 converts to an active form as calcifediol (25-hydroxycholecalciferol) and is hydroxylated into calcitriol (1,25-dihydroxycholecalciferol) in the kidney (Surdu et al., 2021).

Numerous studies suggest the active form, vitamin D, as a predictor of increased lipid by the adipogenesis process. It promotes adipogenesis by the differentiation of human and mouse adipose tissue-derived stem cells (ASCs) and bone marrow-derived mesenchymal stem cells (BM-MSCs) from pigs (Felicidade et al., 2018). Calcidiol will elevate the expression of the

enzyme CYP24A1 and promote adipogenesis. Atmani et al. (2003) observed calcitriol increase adipocytes by about 180%, presenting calcitriol has a stimulatory effect on proliferation in rat bone marrow-derived mesenchymal stem cells (BM-MSCs) stimulated with calcitriol for 14 days.

One of the significant forms of vitamin D is cholecalciferol, or vitamin D₃, which is human-made and can be found in food (Sosa and Gómez, 2021). However, contrary to the study of vitamin D, this primary form improved the lipid profile and enhanced the adipogenesis process. A study reported a significant decrease in LDL-c by cholecalciferol supplementation in diabetic Wistar rats. There is a negative correlation between serum vitamin D₃ and LDL-C levels. The same study also reported that cholecalciferol administration ameliorated lipid metabolism in healthy non-diabetic rats. (Calgaroto et al., 2015). Similarly, Aon et al. (2021) documented lower serum vitamin D₃ in the type 2 diabetes mellitus with cardiovascular disease group. This group has a high-level lipid profile, and it has been considered among the important risk factors for CVD in type 2 diabetes mellitus.

Type 2 diabetes mellitus is associated with elevated triglyceride, decreased HDL-c level, and increased LDL-c level (Elmi et al., 2021). Cholecalciferol supplementation on healthy subjects also resulted in beneficial results on lipid profiles, in which Abd and Sallam (2022) reported a significant decrease in serum TG of healthy Wistar rats, and another study by Tsuruki et al. (1986) showed a significant decrease of cholesterol and glycolipids in healthy Wistar rats supplemented with cholecalciferol.

Consistent with Atia et al. (2022), the study by Lim et al. (2021) reported lower plasma triglyceride and TC levels in the diabetic mice group after 12 weeks supplemented with 300 mg and 600 mg of vitamin D₃. This study also showed that vitamin D₃ supplementation lowers lipogenesis and inhibits lipid accumulation by improving β -oxidation. Moreover, the study subsequently showed elevated HDL-c levels after 600 mg vitamin D administration. Similarly, Abeer and Suzan (2019), vitamin D₃, also known as significantly improved plasma HDL-c in the gestational diabetes mellitus-induced rat group that injected IM with 20.000 IU/kg of vitamin D₃. The mechanism of these actions is also observed in another study (Ivkovic et al., 2022). They found that cholecalciferol did not directly modify the nuclear content of β -oxidation but improved β -oxidation by affecting the ACC/MCD expressions in malonyl-CoA-mediated regulation of β -oxidation (Wang et al. 2019). Ruiz-Ramírez et al. (2016) also noted the upregulating gene expression named uncoupling protein 3 (UCP3) proteins that act as lipotoxicity, reduce ROS production, and oxidative stress in 1000IU/kg of vitamin D₃ injected rat group.

In addition, Riek et al. (2013) documented that vitamin D₃ could inhibit formatting foam cells by reducing cholesterol deposition and improving cholesterol efflux in macrophages. Marino et al. (2022) found in their experiment that macrophages incubated with free fatty acid will increase PPAR- γ 1. Augmentating vitamin D₃ was able to downregulate PPAR- γ 1. Meanwhile, the deficit of PPAR- γ 1 could prevent intracellular lipid droplet accumulation in endothelial cells.

Table 1. Summary of articles on animal studies regarding cholecalciferol supplementation and results of lipid changes were searched in PubMed PMC, Scopus, and DOAJ

First author (year)	Animals	Amount of cholecalciferol supplementation	Route of cholecalciferol supplementation	Comparison group	Duration	Data presented	Health status	Results compared with controls	Results compared with other treatment
Elseweidy et al., 2022	Male Wistar rats	170 IU/week	Oral	Atorvastatin	8 weeks	TC, TG, HDL, LDL	Diabetes, hyperlipidemia	TC, TG, and LDL decreased significantly. HDL increased significantly	No significant difference
Lim, 2021	C57BL/6J mice	300 ng/kg (low cholecalciferol) or 600 ng/kg (high cholecalciferol)	Oral	- (Control only with HFD)	12 weeks	Plasma and hepatic TC, TG, HDL	Diabetes	Significant decrease in plasma TG levels. Significant increase in HDL levels. No significant change in TC levels.	-
Philouze et al., 2022	C57BL/6JRj mice	15.000 IU/kg	Oral	- (Control only with HFS)	15 weeks	Plasma TG	Diabetes	No significant change in TG levels	-
Lee et al., 2020	C57BL/6 mice	300 ng/kg	Oral	- (Control only with Streptozocin)	12 weeks	Plasma TG, TC, LDL, HDL	Diabetes	No significant change in TG, TC, LDL and HDL levels.	-
Wahba et al., 2021	Wistar rats	10 µg/kg/day	Oral	- (Control only with fructose)	6 weeks	Plasma TG, TC, TC/HDL ratio, HDL/LDL ratio	Metabolic Syndrome	Significant decrease in TG levels, TC levels, and TC/HDL ratio. Significant increase in HDL/LDL ratio	-
Abd and Sallam., 2022	Wistar rat	500 IU/kg/day	Oral	- (Control only)	6 weeks	Plasma TG, TC	Healthy rats	Significant decrease in serum TG	-

Table 1. Summary of articles of animal studies regarding cholecalciferol supplementation and results of lipid changes that were searched in PubMed PMC, Scopus, and DOAJ (*Continued*).

First author (year)	Animals	Amount of cholecalciferol supplementation	Route of cholecalciferol supplementation	Comparison group	Duration	Data presented	Health status	Results compared with controls	Results compared with other treatment
Quach et al., 2018	C57BL/6 mice	1625 nmol/kg	Oral	Vitamin D analogues (1 α (OH)D ₂ , 1 α (OH)D ₃ , 1,25(OH) ₂ D ₃ , 25(OH)D ₃)	8 days	Plasma TC	Hypercholesterolemia	No significant change in TC levels	-
Calgaroto et al., 2015	Wistar rat	90 μ g/kg/day	Oral	Metformin	30 days	Plasma TG, LDL, HDL	Diabetics	Vitamin D3 and Metformin + Vitamin D3: Significant decrease in LDL and TC levels. Significant increase in HDL levels and ameliorated lipid metabolism in non-diabetic rats	Not compared
Atia et al., 2022	Wistar rat	0.6 mg/kg	Oral (Orogastric lavage)	Glibenclamide	8 weeks	Plasma TC, TG	Diabetics	Significant decrease in TC and TG levels	Better result with Glibenclamide + Vitamin D than GLB-only
Tsuruki et al., 1986	Wistar rat	100 IU 5 times	Oral	-(Control only with cadmium)	2 weeks	Intestinal brush border cholesterol, phospholipid, glycolipid.	Healthy rats	Partial recovery of phospholipid contents. Cholesterol and glycolipids significantly decreased.	-

Most studies included in this review have shown that various doses and duration of cholecalciferol supplementation have beneficial effects on one or more lipid parameters, such as total cholesterol, triglycerides, LDL, and HDL. One study also showed that cholecalciferol supplementation has a similar effect with lipid-lowering medication, which is atorvastatin, resulting in a comparable beneficial effect on total cholesterol, triglycerides, HDL, and LDL. This review has several limitations. The first one is that the study is limited to experimental studies, which may reduce its applicability in a natural clinical setting. The second is language limitation, which limits the studies to only English. The third is that the study was not assessed for risk of bias, which can affect the quality of evidence. Lastly, all of the studies used an oral route, which cannot delineate the effect of cholecalciferol supplementation by other routes. Nevertheless, this review provides a comprehensive overview of the effect of cholecalciferol supplementation on the lipids of experimental animals.

4. CONCLUSION

Cholecalciferol administration ranging from 8 days to 15 weeks in animal subjects has beneficial effects on lipid profile, low-density lipoprotein, and high-density lipoprotein in most experimental studies. The addition of vitamin D3 showed a reduction of TC, TG, and LDL-c levels and also increased HDL-c levels. The lack of vitamin D3 showed vice versa. Several studies have provided the mechanism of vitamin D that alters lipid plasma. However, the direct mechanism of cholecalciferol on lipid profile changes was still unspecific and poorly understood. By reducing lipid content, cholecalciferol supplementation may benefit populations with various health risks, such as metabolic syndromes.

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CONFLICT OF INTEREST

The authors state that there is no conflict of interest in implementing this research from start to finish.

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