CASE REPORT

Effect of oral vitamin E supplementation on lipid profile in diabetes mellitus: evidence based case report

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Abstract

Introduction: Diabetes mellitus, a prominent non-communicable disease, presents as a chronic condition associated with various complications, including heart disease, nerve damage, chronic kidney disease, and dyslipidemia. A pivotal abnormality in diabetic dyslipidemia is insulin resistance, which stimulates the production of Hepatic VLDL1 (very-low-density lipoprotein 1). The resulting overproduction of VLDL1 is metabolically linked to an abundance of small, dense LDL (low-density lipoprotein) particles and a reduction in large, cholesterol-rich HDL2 (high-density lipoprotein). Conversely, vitamin E, known for its antioxidant and anti-inflammatory properties, acts as a remover of peroxyl radicals, preventing lipid oxidation and safeguarding polyunsaturated fatty acids (PUFA) within cells and plasma lipoproteins. **Method**: This study investigates the impact of oral vitamin E supplementation on the lipid profile in diabetic patients. Employing advanced search techniques on databases like PubMed, Cochrane Library, and Google Scholar, we conducted a comprehensive literature search using MeSH terms, advanced search methods, and specific eligibility criteria. The results yielded one systematic review with a meta-analysis and two randomized controlled trials (RCTs) that met the predefined PICO and eligibility criteria. **Results**: The systematic review and meta-analysis, along with one RCT, reported no significant reduction in lipid profiles with oral vitamin E supplementation in diabetic patients. In contrast, the other RCT observed an improvement in lipid profiles among diabetic patients receiving oral vitamin E supplementation. **Conclusion**: Supplementing with oral vitamin E does not enhance the lipid profile of individuals with diabetes mellitus.

Keywords : vitamin E, supplement, diabetes mellitus, lipid profile

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Case Scenario

A 62-year-old individual named Ms. LTE, who has been managing diabetes mellitus with a regular intake of 3x500 mg of metformin for the past seven years, was admitted to the hospital due to general weakness and reduced food intake. During her hospital stay, she underwent a series of laboratory tests, revealing elevated blood sugar levels (fasting blood glucose at 305 mg/dL) and dyslipidemia (with total cholesterol at 228 mg/dL, triglycerides at 197 mg/dL, HDL at 25 mg/dL, and LDL at 186 mg/dL). Upon the recommendation of an internal

medicine specialist, Ms. LTE was referred to a clinical nutrition specialist for tailored nutrition therapy and education suitable for her condition. Additionally, the consultation aimed to explore the potential benefits of oral vitamin E supplementation in improving her lipid profile.

Introduction

Diabetes mellitus is one of the four primary types of noncommunicable diseases characterized by its chronic nature and potential for causing severe harm to the body's systems.[1] As per the 2021 data from the International Diabetes Federation, approximately 537 million adults between the ages of 20 and 79 are currently dealing with diabetes on a global scale. It's noteworthy that more than three-quarters of these individuals reside in low to middle-income countries.[2] Individuals diagnosed with diabetes mellitus face a heightened risk, ranging from two to four times, of developing coronary artery disease (CAD), with CAD standing as the leading cause of mortality in the diabetic population. Dyslipidemia and hypertension represent significant controllable risk factors for diabetes mellitus and are closely linked to the occurrence of CAD. Furthermore, there is a notable association between metabolic syndrome, prediabetes, and diabetes mellitus, all of which elevate the risk of cardiovascular disease.[3]

According to clinical findings, dyslipidemia can lead to higher mortality rates in individuals with diabetes. It's often observed that diabetes patients commonly experience elevated triglyceride levels and reduced high-density lipoprotein (HDL-C) levels. Insulin resistance, a significant factor in diabetic dyslipidemia, plays a role in stimulating the production of Hepatic VLDL1. The liver primarily derives triglycerides (TG) from three major sources: 1) free fatty acids (FFA) originating from adipose tissue, 2) fatty acids derived from remnants of VLDL and chylomicron), and 3) De Novo Lipogenesis (DNL). The newly synthesized TG effectively inhibit the degradation of apoB within cells. In cases of insulin resistance, there is a diminished inhibition of hormone-sensitive lipase in adipose tissue, leading to an increased flow of FFA into the portal system. The synthesis of TG from FFA, or even FFA itself, strongly hinders apoB degradation in the liver, consequently promoting the production of VLDL. In an insulin-resistant state, VLDL1 production is specifically amplified, with no significant effect on VLDL2 production. This overproduction of VLDL1 is metabolically linked to an abundance of small, dense LDL particles and a reduction in large, cholesterol-rich HDL2.[4] On the other hand, vitamin E, being a fat-soluble vitamin with antioxidant and anti-inflammatory properties, has been demonstrated to function as a remover of peroxyl radicals, which aids in blocking the spread of free radicals and, as a result, prevents lipid oxidation. Within cells, vitamin E is present in the phospholipid layer of the cell membrane and in plasma lipoproteins, safeguarding polyunsaturated fatty acids (PUFA) from oxidation by peroxyl radicals, that would have beneficial effects on lipid profile in a high-risk population such as diabetic patients.[5,6]

According to Khabaz et al.'s study,[7] vitamin E administration in diabetic patients was observed to lower triglycerides, total cholesterol, and LDL (low-density lipoprotein) levels. In contrast, another study by Mohammad et al.,[8] reported a contentious outcome regarding the impact of oral vitamin E supplementation for more than 12 weeks did not have a significant effect on lipid profiles in diabetic patients. However, a separate study by Aghadavod et al.,[9] revealed a significant reduction in total cholesterol and LDL levels as a result of oral vitamin E supplementation.

Clinical question

P : Diabetes mellitus patients
I : Oral vitamin E supplement
C : Placebo
O : Lipid profile
Clinical question: can administering vitamin E orally enhance the lipid profile of individuals suffering from diabetes mellitus?

Methods

We conducted a comprehensive literature search on April 18, 2023, utilizing a combination of

MeSH terms and Title/Abstract searches across three major databases: PubMed, the Cochrane Library, and an advanced search on Google Scholar. The keywords employed in the search included "vitamin E," "supplements," "diabetes mellitus," and "lipid profile." Our evaluation of the identified literature was guided by critical assessment tools and levels of evidence in accordance with the criteria established by the Oxford Center for Evidence-Based Medicine.

Eligibility criteria

The inclusion criteria encompassed participants aged 18 years or older who had been diagnosed with diabetes mellitus, received oral vitamin E supplementation, and were part of a study designed as a randomized controlled trial (RCT), systematic review, or meta-analysis. These studies needed to report outcomes related to lipid profiles and have been published between 2018 and 2023, with the publication being in English. On the other hand, exclusion criteria consisted of animal studies, articles that were not accessible in full text, and studies in which participants received both intravenous and oral supplementation.

Results

A visual representation in figure 1, in the form of a PRISMA flowchart, from the advanced search methods, Pubmed, Cochrane and Google Scholar, that published between 2018-2023, total obtained 294 journals, after removing duplications, title and abstract screening according to PICO, we got 3 studies included.
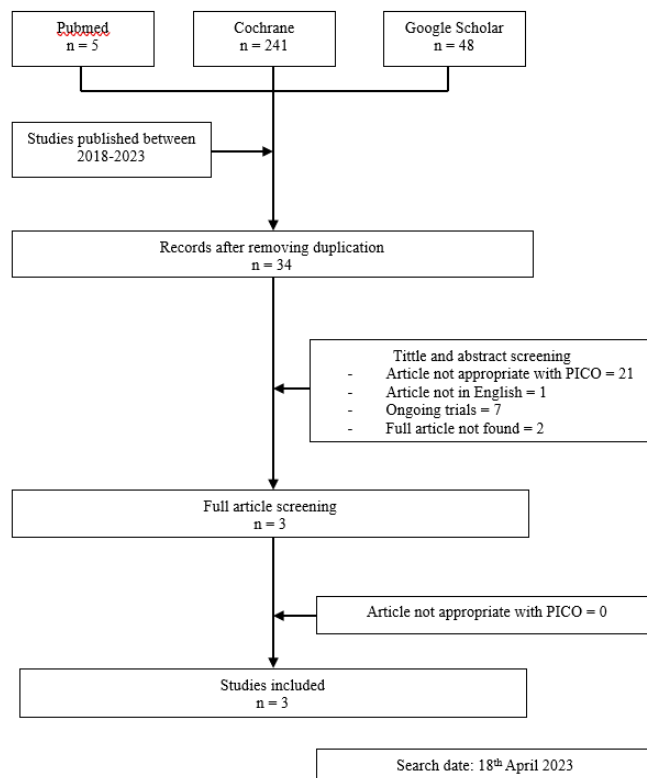

Figure 1. Prisma's Flow Chart

Table 1. Resources and Search Strategy

Database	Terminology	Hits	Eligible
PubMed	((oral vitamin E supplement) AND (diabetes mellitus)) AND (lipid profile)	5	1
Cochrane	#1 MeSH descriptor: [vitamin E] explode all trees #2 (vitamin E):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Diabetes Mellitus] explode all trees #4 (lipid profile):ti,ab,kw (Word variations have been searched) #5 MeSH descriptor: [Administration, Oral] explode all trees #6 (oral):ti,ab,kw (Word variations have been searched) #7 #1 OR #2 #8 #3 OR #4 #9 #6 AND #7 AND #8	241	1
Google Scholar	allintitle: oral vitamin E diabetes mellitus lipid profile	48	1

In table 1, Pubmed search strategy using keywords: oral vitamin E supplement, diabetes mellitus, and lipid profile, obtained 5 journals and 1 eligible criteria. From Cochrane search strategy using MeSH descriptor vitamin E, diabetes mellitus, and oral, obtained 241 journals and 1 eligible criteria. From Google Scholar, using all in title: oral vitamin E diabetes mellitus lipid profile, obtained 48 journals and 1 eligible criteria.

Table 2. Study Characteristic

No	Author	Study design	Population characteristic	Total participants	Outcome	Key results
1	Mohammad, et al (2021)[8]	Systematic review and Meta-analysis RCT	Patients age 18–75 years old with diabetes mellitus who were given oral vitamin E supplementation 700 IU for 6-27 weeks.	613 (10 studies)	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation (αTF) did not have effect on TC (WMD: -0.69 mg/dl; 95% CI: -15.03, 13.65; p = 0.93), TG (WMD: 1.33 mg/dl; 95% CI: -9.19, 11.85; p = 0.80), HDL-C (WMD: 0.68 mg/dl; 95% CI: -1.25, 2.61; p = 0.51), and LDL-C (WMD: -0.52 mg/dl; 95% CI: -8.30, 7.25; p = 0.90) after supplementation >12 weeks
2	Aghadavod, et al (2018)[9]	RCT, double blind	Patients with diabetic nephropathy (DN) who were given oral vitamin E supplementation 800 IU for 12 weeks	54	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation has significant reduction in TC (-14.3 ± 29.9 mg/dL versus -0.8 ± 13.1 mg/L, P = .03), LDL-C (-16.4 ± 28.5 mg/dL versus 0.1 ± 17.2 mg/L, P = .01), and TC-HDL-C ratio (-0.5 ± 0.7 versus 0.1 ± 0.5, P = .001)., LDL-C, and TC-HDL-C ratio
3	Dalan, et al (2020)[10]	RCT, double blind	Patients with diabetes mellitus who were given oral vitamin E supplementation 400 IU for 24 weeks	187	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation did not have effect on TC and LDL-C when compared with placebo group.

RCT, randomized controlled trial; DN, diabetic nephropathy; TC, total cholesterol; TG, tryglicerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; WMD, weighted mean difference; CI, confidence interval.

Table 3. Validity Criteria

	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Mohammad, et al (2021)[8]	+	+	+	+	+	+	+	+	Moderate	1A-
Aghadavod, et al (2018)[9]	+	+	+	+	+	+	+	+	Moderate	1B
Dalan, et al (2020)[10]	+	+	+	+	+	+	+	+	Moderate	1B

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done? Not stated clearly
Systematic review and meta-analysis with troublesome heterogeneity

Table 4. Relevance Criteria

Article	Similarity Population	Similarity determinant/intervention/indicators	Similarity outcome
Mohammad, et al (2021)[8]	+	+	+
Aghadavod, et al (2018)[9]	+	+	+
Dalan, et al (2020)[10]	+	+	+

Discussion

Diabetes mellitus (DM) is closely associated with an abnormal lipid profile. In DM, the primary features are insulin resistance (IR) and dysfunction of β-cells. Insulin resistance, a fundamental aspect of diabetic dyslipidemia, plays a pivotal role in stimulating the production of Hepatic VLDL1. The liver primarily acquires triglycerides (TG) from three major sources: 1) free fatty acids (FFA) originating in adipose tissue, 2) fatty acids derived from remnants of TRL (Very Low-Density Lipoprotein and chylomicron), and 3) De Novo Lipogenesis (DNL). The newly synthesized TG effectively block the degradation of apoB within cells. In cases of insulin resistance, there is a reduced inhibition of hormone-sensitive lipase in adipose tissue, resulting in an increased influx of FFA into the portal system. The synthesis of TG from FFA, or even FFA itself, strongly impedes apoB degradation in the liver, thereby promoting the production of VLDL.[11]

While remnants of TG-rich lipoprotein TRL and De Novo Lipogenesis (DNL) do contribute triglycerides (TG) to the liver, their role in inhibiting apoB degradation is relatively minor. Insulin resistance diminishes the breakdown of apoB, which is regulated by phosphoinositide (PI) 3-kinase, and it enhances the activity of microsomal triglyceride transfer protein (MTP), a key factor in VLDL assembly. In a state of insulin resistance, the production of VLDL1 is specifically increased, with minimal impact on VLDL2 production. This excessive VLDL1 production is associated with an abundance of small, dense LDL particles and a reduction in large, cholesterol-rich HDL2, linking it metabolically. A lipid profile assessment in diabetic patients may be useful to reduce the risk of disease progression and also for early intervention. Related to atherogenic dyslipidemia, coronary artery disease, and myocardial

infarction, diabetic patients have increased risk of cardiovascular disease (CVD).[4,11,12]

Vitamin E is composed of eight compounds, including α-, β-, γ-, and δ-tocopherol, as well as α-, β-, γ-, and δ-tocotrienols, all of which are lipid-soluble. Among these, the α-forms of both tocopherols and tocotrienols are recognized as the most biologically active. However, α-tocopherol is the most efficiently absorbed, with up to 90% entering the bloodstream and body tissues, while the other types of vitamin E are metabolized and excreted.[13] As per the Recommended Dietary Allowance (RDA), the suggested daily intake of vitamin E for individuals aged 14 years and older, regardless of gender, is 15 mg (equivalent to 22 international units, IU), and this recommendation remains consistent for diabetic patients as well as the general adult population. Vitamin E can be found naturally in specific foods like seeds, nuts, certain vegetables, and fortified products. Alternatively, vitamin E supplements are available. Vitamin E plays multiple roles in the body, with its primary function being that of an antioxidant, protecting cells from oxidative damage by counteracting harmful substances called free radicals. Additionally, it is vital for maintaining a robust immune system and facilitating cellular communication. Patients with diabetes mellitus often have compromised immune systems, making the supplementation of vitamin E essential for bolstering their immunity.[14]

Vitamin E, being a fat-soluble vitamin with antioxidant and anti-inflammatory properties, has been demonstrated to function as a remover of peroxyl radicals, which aids in blocking the spread of free radicals and, as a result, prevents lipid oxidation. Within cells, vitamin E is present in the phospholipid layer of the cell membrane and in plasma lipoproteins, safeguarding polyunsaturated fatty acids (PUFA) from oxidation by peroxyl radicals, consequently, vitamin E could potentially play a role in preventing or postponing the onset of chronic diseases linked to reactive oxygen species molecules.[6]

In a systematic review and meta-analysis conducted by Mohammad et al.,[8] it was reported that the administration of oral vitamin E supplementation (specifically α-tocopherol) did not demonstrate a significant impact on various lipid parameters, specifically total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), when the supplementation duration exceeded 12 weeks. The reported mean differences (WMD) and associated confidence intervals (95% CI) were as follows: TC (WMD: -0.69 mg/dl; 95% CI: -15.03, 13.65; p = 0.93), TG (WMD: 1.33 mg/dl; 95% CI: -9.19, 11.85; p = 0.80), HDL-C (WMD: 0.68 mg/dl; 95% CI: -1.25, 2.61; p = 0.51), and LDL-C (WMD: -0.52 mg/dl; 95% CI: -8.30, 7.25; p = 0.90). It is suggested that vitamin E supplements may modulate the proliferator-activated-receptor-γ pathway, which activates genes related to fat synthesis and the differentiation of fat cells, leading to a reduction in cholesterol levels. Vitamin E is also believed to inhibit the signal protein kinase C pathway, which is associated with lipid metabolism. However, it's important to note some limitations of this study, including the sample sizes in certain included studies, a shortage of high-quality studies as assessed by the Jaded score, and the fact that the baseline vitamin E deficiency was not assessed in all the studies. This lack of assessment could potentially influence the results of the analyses.

The randomized controlled trial (RCT) conducted by Dalan et al,.[10] yielded a similar outcome, indicating that vitamin E supplementation had no discernible impact on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) when compared to the placebo group. This lack of effect may be attributed to the gene-dependent influence of vitamin E supplementation at the cellular level concerning the lipid profiles of diabetic patients. Notably, the study encompassed a diverse population comprising Chinese, Indian, and Malay ethnic groups, and it's conceivable that inherent disparities in lipid and metabolic profiles among these individuals may have contributed to the neutral results. Conversely, in a separate RCT led by Aghadavod et al., [9] the findings demonstrated a significant reduction in TC (-14.3 ± 29.9 mg/dL compared to -0.8 ± 13.1 mg/L, P =

.03), LDL-C (-16.4 ± 28.5 mg/dL compared to 0.1 ± 17.2 mg/L, P = .01), and the TC-HDL-C ratio (-0.5 ± 0.7 compared to 0.1 ± 0.5, P = .001) following vitamin E supplementation. The authors of this study concluded that high-dose vitamin E supplementation over a 12-week period had favorable effects on lipid profiles, except for triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C). The inhibition of signal transduction pathways, including protein kinase C, is one way in which vitamin E intake may operate. Additionally, vitamin E supplementation may activate the proliferator-activated-receptor-γ transduction pathway, subsequently leading to reduced cholesterol levels.

The study conducted by El-Aal et al,.[15] revealed significant alterations in metabolic markers following vitamin E supplementation, including improved glycemic control, increased levels of high-density lipoprotein cholesterol (HDL-C), and enhanced insulin function. Vitamin E was found to reduce lipid peroxidation and boost the activity of antioxidant enzymes in diabetic patients. In a systematic review and meta-analysis by Asbaghi et al., [16] the combined intake of omega-3 and vitamin E was associated with a significant reduction in triglycerides (TG) (WMD: -28.34 mg/dl, 95% CI: -37.44, -19.22, with an I2 of 59.6%) and low-density lipoprotein (LDL) (WMD: -8.07 mg/dl, 95% CI: -15.10, -1.05, with an I2 of 90.9%). However, this combination did not have a significant impact on total cholesterol (TC) and high-density lipoprotein (HDL) (WMD: -11.48 mg/dl, 95% CI: -24.15, 1.20, with an I2 of 92.8%; WMD: -0.52 mg/dl, 95% CI: -4.70, 3.66, with an I2 of 95.5%), respectively. Vitamin E is a powerful antioxidant that dissolves in fat, and its insufficiency is associated with a range of illnesses. Increased levels of reactive oxygen species (ROSs) have been implicated in the development of metabolic syndrome. Therefore, maintaining adequate levels of vitamin E appears crucial in such

patients. Conversely, elevated ROSs lead to excessive lipid peroxidation, causing damage to proteins and DNA. Vitamin E, as a key component of the nonenzymatic antioxidative defense, mitigates damage to polyunsaturated fatty acids, such as omega-3 fatty acids. Consequently, numerous studies have explored the synergistic effects of these compounds.

However, the research by Al-Ramadhan et al,.[5] did not find any correlation between vitamin E and triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL). The authors attempted to explain the discrepancies in results from other studies, suggesting that differences in population and the specific forms of oral vitamin E supplements used might be contributing factors. Furthermore, they discussed the limited oral bioavailability of certain vitamin E forms, such as tocotrienols, which did not yield significant results in lipid profiles.

Conclusions

Oral vitamin E supplements possess antioxidant and anti-inflammatory properties, making them a potential choice for reducing lipid profiles like total cholesterol and LDL in diabetic patients. However, after conducting critical reviews in this evidence-based case report, which included one systematic review and meta-analysis along with two randomized controlled trials (RCTs), it is evident that oral vitamin E supplementation does not lead to an improvement in the lipid profile of individuals with diabetes mellitus.

While the research did not demonstrate that vitamin E has a direct impact on reducing lipid profiles, it's worth noting that vitamin E can still be considered as a supplement for patients with chronic conditions such as diabetes mellitus. This is because it can help combat the increased presence of free radicals in the body due to the disease and serve as an antioxidant that supports overall immune system function.

Conflict of interest

The authors declare that no conflict of interest with another person or institution.

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