# RESEARCH

# Prevention of Adverse Outcomes among Adult Patients with Diabetes Comorbid with Dyslipidemia - A Narrative Review of the Existing Literature

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## ■ Abstract

**Introduction:** Globally, around 537 million individuals have diabetes, and this number is anticipated to increase consistently. Though even diabetes alone substantially increases one's risk of suffering several cardiovascular morbidities, dyslipidemia comorbid with diabetes substantially increases the risk of these morbidities. We did a narrative review to identify studies which have suggested interventions for preventing adverse outcomes among people with diabetes who have dyslipidemia. **Methods:** We identified literature from PubMed and Google Scholar using different relevant search terms to conduct this review. We included all the articles identified based on this search strategy without putting any limits on our search. **Results:** Different interventions that were identified in this review include triglyceride–HDL-C phenotyping, Apis mellifera L., eicosapentaenoic acid, evolocumab, alirocumab, Korean balanced diet, anthocyanins, Roux en Y gastric bypass and rosuvastatin. **Conclusion:** Though several of these interventions demonstrated efficacy and safety in effecting different outcomes indirectly related to cardiovascular morbidity, studies are required to check the effect of these interventions on morbidity and mortality outcomes among these patients.

**Keywords:** Diabetes, Dyslipidemia, Prevention, Adverse Outcomes, Comorbidity.

## 1. Introduction

Diabetes is one of the important risk factors for cardiovascular disease like myocardial infarction, stroke and other similar diseases [1]. Globally, around 537 million individuals have diabetes, and this number is anticipated to grow to 643 million in 2030 [2]. Through several cohort studies, it is found that patients with type2 diabetes mellitus have almost 3 to 4 times higher risk of suffering from different cardiovascular diseases [3]. Additionally, it is also reported that when patients have dyslipidemia comorbid with diabetes, the risk of getting different cardiovascular diseases increases even further. Dyslipidemia's key characteristics include increased concentration of small dense LDL-cholesterol particles, high triglycerides and low HDL cholesterol in the blood [4]. Some researchers have explained the interaction of dyslipidemia comorbid with diabetes as a triumvirate of atherosclerosis and described them as a major threat to the human species because of the substantial effect of these diseases together on morbidity and mortality [5]. Though there is a need to formulate personalised approaches to give drug therapy to patients with diabetes and dyslipidemia, the majority of these patients need statins combined with other newer agents like ezetimibe to control their lipids

and, therefore, prevent cardiovascular diseases [6]. Due to the increased risk of cardiovascular diseases among these patients, it is recommended that both the sugar and lipid levels be rigorously controlled to mitigate the risk of different cardiovascular diseases [7, 8].

Though there is extensive literature on the prevention of complications from diabetes or prevention of dyslipidemia and its complications, the number of studies which have tested the preventive approaches among patients having diabetes comorbid with dyslipidemia are limited in scope to testing a specific type of intervention mostly in a controlled environment. Most of the studies have reported preventive approaches for either diabetics or individuals with dyslipidemia. Despite this limitation in the literature, we do not have reason to believe that preventive strategies for patients from either morbidity cannot work together in patients with both morbidities. However, there is a need to analyse the individual interventions effectively and then suggest possible composite interventions for people with diabetes and dyslipidemia. The approach in analysing these different interventions can include assessing whether the interventions designed to prevent diabetes or complications related to diabetes work effectively or not when diabetes is comorbid with dyslipidemia [9]. With the same rationale, it is also

important to understand that interventions for preventing dyslipidemia or complications related to dyslipidemia work effectively when it is comorbid with diabetes [10]. There is also the need to know if any intervention can effectively prevent the combined effect of atherosclerosis caused by both these conditions. With this background and the identified gap in the literature, we intend to conduct a narrative review of the published literature to identify studies that have suggested interventions for preventing adverse outcomes among people with diabetes who have dyslipidemia.

## 2. Methodology

To conduct this review, a comprehensive literature search was performed using search engines such as PubMed and Google Scholar, using different relevant search terms. The search terms we used for diabetes included diabetes, hyperglycemia and "insulin resistance". Similarly, we used search terms like dyslipidemia, dyslipidemias, "lipid metabolism disorders", hyperlipidemias, hypercholesterolemia, "LDL Cholesterol", hypertriglyceridemia, triglyceride, lipoproteins, VLDL, "Mixed hyperlipidemia", hyperlipoproteinemia, "hyperlipoproteinemia Type II", "hyperlipoproteinemia Type III" and "Familial Hypercholesterolemia" for identifying studies that talked about dyslipidemia. Additionally, terms like prevention, "health promotion," and "disease prevention" were used to capture articles related to prevention. Finally, we formulated the search strategy by combining these search terms using the appropriate Boolean operators. All the articles found based on this search strategy from the specified search engines were included for subsequent screening, and no restriction was used to identify these articles. Through this search strategy, we identified a total of 4,223 articles, out of which we found 87 articles relevant to our discussion topic based on the titles and abstracts. Upon reading the full article, 12 articles were included in the final review (Table 1).

**Table 1:** Shows the Summary of the Included Studies.

| Study | Talked about Diabetes, Dyslipidemia or Both | Sample Size | Gender | Type of Study | Prevention Approach |
|---|---|---|---|---|---|
| Kaze et al. 2021 | Both | 4199 | Both | RCT | triglyceride–HDL-C phenotyping |
| Moayedi et al. 2023 | Both | 60 | Female | RCT | 500 mg propolis capsules + Exercise training |
| Takeshita et al. 2021 | Both | 20 | Both | RCT | Eicosapentaenoic acid |
| Müller-Wieland et al. 2017 | Both | 413 | Both | RCT | Alirocumab |
| Muhlestein et al. 2006 | Both | 300 | Both | RCT | Fenofibrate |
| Kim et al. 2022 | Dyslipidemia | 104 | Female | RCT | Balanced Korean diet |
| Li et al. 2015 | Both | 58 | Both | RCT | Anthocyanin |
| Ikramuddin et al. 2013 | Both | 120 | Both | RCT | Roux-en-Y gastric |
| Lorenzatti et al. 2019 | Both | 981 | Both | RCT | Evolocumab |
| Werida, Khairat, and Khedr 2021) | Both | 160 | Both | RCT | Atorvastatin |
| Li et al. 2015 | Both | 58 | Both | RCT | Anthocyanins |
| Liu et al. 2023 | dyslipidemia | 1019 | Both | Cross-sectional study | Deep Learning Prediction model to predict dyslipidemia |

## 3. Results

### 3.1 Findings from Randomized Controlled Trials

There is evidence of a strong relationship between dyslipidemia and adverse cardiovascular vascular outcomes among individuals with type 2 diabetes mellitus. Therefore, it is emphasised to do the risk stratification of these people with diabetes based on whether they have dyslipidemia or not [11]. Around 40% of the individuals with type 2 diabetes also have dyslipidemia. Additionally, HDL-C and metabolic dyslipidemia are related to deaths due to cardiovascular events among individuals with type 2 diabetes. Based on these findings, it is recommended that researchers explore ways to prevent adverse cardiovascular events among diabetes patients by considering triglyceride–HDL-C phenotyping.

One study studied the role of a natural resinous mixture named propolis made by Apis mellifera L. to improve dyslipidemia among diabetic women [12]. This interventional study had multiple arms, and women who received propolis with and without exercise training were compared to the control group, which did not receive either exercise training or propolis. It was found that when an exercise training program was combined with a propolis supplement, it decreased markers capturing inflammatory activity and enhanced women's antioxidants, resulting in improved defences for women against different cardiovascular morbidities. The outcomes of this study were different markers used to capture inflammatory activity. The important question is how well the reported reduction in inflammatory activity will translate into a reduction in morbidity and mortality from different adverse cardiovascular outcomes among these women, which is still required to be investigated through future studies.

Hepatokines are bioactive proteins that play an important role in glucose homeostasis [13]. One important hepatokine in preventing adverse outcomes among individuals with dyslipidemia comorbid with diabetes is selenoprotein P, as the increased expression of the genes

related to this protein increases the chances of different adverse outcomes among people with diabetes [14]. Therefore, decreasing the expression of genes involved in producing selenoprotein P is a therapeutic option. This can be done by eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid that reduces the expression of these genes. In a small study done on 20 individuals having diabetes along with dyslipidemia, they were randomly assigned to a group given 900 mg of EPA twice daily or a control group; the intervention group did not report a reduction in the level of selenoprotein P [14].

Evolocumab is a proprotein convertase subtilisin kexin-type inhibitor used alone or with other medicines to treat patients with heterozygous familial hypercholesterolemia [15]. In a study done in China, evolocumab 140 mg given every two weeks or evolocumab 420 mg given on a monthly in combination with atorvastatin was compared to placebo to check the effect of different dose regiments on evolocumab on the level of LDL cholesterol [16]. It was found that the arm that received 140 mg of evolocumab every two weeks, along with atorvastatin, resulted in a significant reduction in LDL cholesterol at week 12 of the follow-up. The study also showed that this effect was consistent in Chinese and non-Chinese populations.

Through other randomised controlled trials, proprotein convertase subtilisinkexin type 9 inhibitor alirocumab was compared to routine care among the individuals who had diabetes comorbid with dyslipidemia to see the effect of alirocumab on controlling non-HDL cholesterol [17]. Though this trial demonstrated a significant effect of alirocumab on reducing non-HDL cholesterol among the specified population, this study failed to demonstrate an effect on glycated haemoglobin. In double-blind, randomised controlled trials, simvastatin, fenofibrate and a combination of these two medicines were used to see their impact on high-sensitivity Creactive protein and lipoprotein-associated phospholipase among people with diabetes with dyslipidemia [18]. Though both arms demonstrated a reduction in the outcome, i.e., highsensitivity Creactive protein and lipoprotein-associated phospholipase, there was no statistically significant difference between the two arms. A Korean balanced diet is another possible intervention that has been tested for dyslipidemia in females. This diet reduced non-high-density lipoprotein cholesterol and triglyceride concentrations compared to the control diet. Still, it needs to be shown that the same effect remains if checked among people with diabetes who have dyslipidemia [19]. Another study investigated the effect of anthocyanins on oxidative stress and insulin sensitivity among people with diabetes with dyslipidemia [20]. This study found that anthocyanin substantially reduced LDL cholesterol, apolipoprotein, and apo C-III, as well as increased HDL cholesterol, compared to the placebo. Since the reduction was demonstrated as compared to placebo, it is also important to investigate the effect of anthocyanins on the specified outcomes compared to standard therapy to suggest superiority or possible

equivalence of anthocyanins in the standard treatment.

One study conducted in the United States and Taiwan compared the RouxenY gastric bypass as an intervention for diabetic individuals with dyslipidemia to check the effect of this surgical intervention in the specified group compared to lifestyleintensive medical management intervention [21]. It was found that adding lifestyle and medical management to gastric bypass surgery resulted in positive outcomes. However, it is recommended that while deciding to recommend such surgery to a patient, it is important to weigh the risk of adverse events because of surgery to the anticipated benefit.

Evolocumab, combined with atorvastatin, is another agent investigated and showed a reduction in LDL-C and other atherogenic lipids among people with diabetes with dyslipidemia [22]. Though statins are used as lipid-lowering drugs, there is a debate about which specific statins should be used in people with diabetes and dyslipidemia. To address some uncertainty around this issue, rosuvastatin was compared to atorvastatin to check its effect on reducing different atherogenic lipids in the blood [23]. It was found that rosuvastatin was more productive than atorvastatin in improving lipid profile and atherogenic index. It was also found that both rosuvastatin and atorvastatin are equivalent in terms of their cardioprotective ability among patients with diabetes and dyslipidemia. Anthocyanin is another therapeutic agent whose effect was checked among patients' diabetics comorbid with dyslipidemia. Anthocyanin was found to be efficacious in improving antioxidant capacity and improved insulin resistance [20].

### 3.2 Artificial Intelligence-based Interventions

Other than the study findings, with the recent advances in artificial intelligence (AI), the discussion of disease prevention is incomplete without mentioning the role of AI in preventing any disease, including diabetes and its complications [24]. Though a lot of emphasis is on the formulation of different algorithms for prevention or risk stratification of individuals with diabetes, it is important to understand that data plays a critical role in the formulation of such algorithms, and therefore, subsequently allowing clinicians and public health practitioners to make informed real-time decisions. At the level of the population, it is important to formulate data governance and data partnership frameworks to ensure that data is shared in an interoperable format so that such data through a well-designed pipeline can effectively contribute to an algorithm contributing to providing personalised care to individual patients who have diabetes comorbid with dyslipidemia and identifying individuals at increased risk of morbidities at the level of population [25]. Such data can contribute to the predictive models to predict different outcomes, as one study has formulated and subsequently reported deep learning models to predict dyslipidemia [26].

### 3.3 Genomic Approaches for Disease Prevention

Apart from the identified studies, we found some studies that have explored the genetic reasons for the

aggregation of some morbidities. One such study has suggested the existence of syndrome X, resulting in dyslipidemias becoming comorbid with diabetes [27]. Several genomic approaches have been proposed to reduce the risk of cardiovascular diseases among individuals having diabetes comorbid with dyslipidemia [28]. These studies use approaches like genome-wide association and Mendelian randomisation. One possible way is to risk stratify, which will help prevent cardiovascular diseases by calculating and reporting genetic risk scores, which will subsequently be a function of the probability of suffering from cardiovascular diseases [29]. Studies have shown that these risk scores improve the predictive ability of cardiovascular diseases among large cohorts [28]. Several genetic sequences are related to coronary artery disease and may also affect lipid metabolism [30]. This active area of research will enable health professionals to formulate personalised treatments for different patients and optimise treatment doses based on genetic information.

The major strength of this narrative review is that most studies included in this article were randomised controlled trials with large and multiethnic sample sizes. This research could give a framework for healthcare providers, diabetologists, endocrinologists, cardiologists, and decision-makers to establish guidelines and take required measures to reduce dyslipidemia in patients with diabetes.

## 4. Conclusion and Recommendations

Many studies have reported different pharmaceutical and other therapeutic approaches to reduce the vulnerability of people with diabetes and dyslipidemia to various adverse outcomes. Though many of these studies have shown efficacy for their specified outcome, we could not find studies that reported a reduction in outcomes like morbidity, mortality, cost of care or improving the quality of life for these individuals. Additionally, the emerging areas of artificial intelligence and personalised medicine are areas where further interventional studies must be designed. Tools formulated from these studies are required to be made part of composite interventions for different public health programs, which can reduce mortality and morbidity among people with diabetes having dyslipidemia.

## 5. Declaration

### 5.1 Ethics Approval and Consent to Participate
Not applicable.

### 5.2 Consent for Publication
Not applicable.

### 5.3 Data Availability
The data used in this study are all published articles, which are freely available online.

### 5.6 Author Contributions
A single author did all the research work related to this article.

### 5.7 Competing Interests
The author declares none.

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