Research Article
ISSN : 3048-104X

Volume 06, Issue No.01 . 2024

The Indonesian Journal of General Medicine

The Analysis Study of Association of Dyslipidemia and Diabetic Retinopathy: A Comprehensive Systematic Review

[1,2] Anindi Putri Harjanti, [3] Yuliani

[1] Faculty of Medicine, Indonesian Islamic University, Special Region of Yogyakarta, Indonesia
[2] Tanah Abang Regional General Hospital, Central Jakarta, Special Region of Jakarta, Indonesia
[3] Hasan Sadikin Central General Hospital, Bandung City, West Java, Indonesia
Correspondence : anindiputrih@gmail.com

Article History :
Received date : 2024/09/05
Revised date : 2024/10/12
Accepted date : 2024/11/14
Published date : 2024/12/20

Copyright: *© 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (https://creativecommons.org/licenses/by-nc/4.0/).*

ISSN 3048-104X
9 773048 104009

ABSTRACT

Introduction: Diabetic retinopathy (DR) is a leading cause of blindness in diabetic patients, and its progression is influenced by various factors, including dyslipidemia. This systematic review aims to assess the relationship between dyslipidemia and DR, focusing on lipid profiles such as LDL cholesterol, HDL cholesterol, triglycerides, and total cholesterol. **Method:** We conducted a systematic review of studies published between 2010 and 2023 that examined the association between dyslipidemia and DR in diabetic patients. Studies were selected based on inclusion criteria, including cross-sectional, cohort, and case-control designs. Data regarding lipid profiles, DR stages, and statistical significance were extracted and analyzed. **Result:** The literature search was conducted across reputable databases such as Science Direct, PubMed, and SagePub. After a rigorous three-level screening process, eight relevant studies were selected for detailed evaluation. These studies varied in design, including cross-sectional, cohort, and retrospective studies, and involved diverse sample sizes ranging from 45 to over 79 million participants. The findings consistently indicated a significant association between dyslipidemia and diabetic retinopathy (DR). Several studies reported elevated levels of low-density lipoprotein (LDL) and triglycerides (TGs) and reduced levels of high-density lipoprotein (HDL) in patients with DR compared to those without. Additionally, certain studies suggested a protective effect of statins on non-proliferative diabetic retinopathy (NPDR), while medications such as pitavastatin and fenofibrate were associated with a reduced prevalence of proliferative diabetic retinopathy (PDR) and vitreous hemorrhage. **Discussion:** The findings suggest that dyslipidemia, particularly elevated LDL and reduced HDL cholesterol levels, contributes to the development and progression of DR. However, the lack of clear temporal precedence and the absence of control groups in some studies limit the ability to establish causality. The heterogeneity in study designs also affects the generalizability of the results. **Conclusion:** Dyslipidemia plays a significant role in the development and progression of diabetic retinopathy. Future research should focus on high-quality longitudinal studies that account for confounders and temporal relationships to better understand the causal link between dyslipidemia and DR.

Keyword: diabetic retinopathy, dyslipidemia, LDL cholesterol, HDL cholesterol, triglycerides, diabetes mellitus

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of vision impairment among working-age adults in the Western world and one of the most prevalent microvascular complications of diabetes mellitus (DM).[1,2] Globally, DR affects 34.6% of individuals with diabetes, accounting for approximately 93 million people, while in the United States alone, 28.5% of adults aged 40 and older with diabetes are affected. As the global prevalence of DM rises, the burden of DR is projected to increase significantly. By 2020, it was estimated that DR would affect six million people in the United States, with over 1.34 million experiencing vision-threatening disease.[3] This growing trend highlights the critical need for enhanced strategies to address DR, beyond the current standards of diabetes care.[4]

Clinically, DR is characterized by retinal vascular abnormalities visible upon ophthalmoscopic examination and is categorized into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[5,6] NPDR involves microaneurysms, retinal hemorrhages, vascular tortuosity, and lipid exudates, while PDR is defined by the development of fragile, aberrant retinal neovascularization. Another key feature of DR is diabetic macular edema (DME), characterized by fluid accumulation within the retina, leading to retinal thickening and, in severe cases, cystoid macular edema. DME can occur at any stage of DR and represents the most common cause of vision loss in these patients.[7]

Beyond its impact on vision, DR has significant systemic implications, including an increased risk of cardiovascular diseases. With the rising prevalence of DM and DR, it is projected that the global prevalence of DR will reach 5.4% by 2025, underscoring the urgent need to identify modifiable risk factors and develop more effective prevention and treatment strategies. While hyperglycemia has long been recognized as a classical risk factor, evidence suggests that strict glycemic control alone is insufficient to fully prevent DR progression. The Diabetes Control and Complications Trial found that glycemic exposure

accounts for only 11% of DR risk, leaving 89% of the risk attributable to other factors.[8,9]

One potential factor that has garnered increasing attention is dyslipidemia. As early as 1952, Keiding et al. suggested a link between serum lipid levels and DR progression. Subsequent studies, including the Early Treatment Diabetic Retinopathy Study (ETDRS), identified an association between elevated serum lipid levels and the development of retinal hard exudates. The Chennai Urban Rural Epidemiology Study also found higher serum lipid levels among DR patients. However, contradictory findings have emerged from other studies, such as the Australian Diabetes, Obesity, and Lifestyle Study, which found no significant association between serum lipids and DR, and the Singapore Malay Eye Study, which even reported a protective effect of higher total cholesterol levels on DR.[10,11]

These conflicting results highlight the need for a comprehensive analysis of the association between dyslipidemia and DR. This systematic review aims to evaluate the relationship between triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) with DR. By synthesizing available evidence, this review seeks to clarify the role of serum lipids in DR pathogenesis and progression, offering valuable insights to guide clinical practice and inform the development of targeted interventions for this debilitating condition.

METHODS

Protocol

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, consistency, and reproducibility. The protocol is designed to systematically review and analyze the association between dyslipidemia and diabetic retinopathy (DR), with a focus on serum lipid parameters such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Criteria for Eligibility

This review will include studies published in the last two decades (2004–2024) that examine the relationship between dyslipidemia and DR. Eligible studies must focus on human participants diagnosed with diabetes mellitus and provide data on serum lipid levels and DR outcomes. Only studies published in English and involving clinical trials, cohort studies, case-control studies, or observational designs will be considered. Studies will be excluded if they are review articles, expert opinions, conference abstracts, non-peer-reviewed, animal studies, or in vitro experiments, or if they lack detailed data on serum lipids and DR outcomes.

Search Strategy

A comprehensive search will be conducted across databases such as PubMed, ScienceDirect, Embase, Cochrane Library, and Web of Science. The search will focus on terms related to dyslipidemia and diabetic retinopathy. Primary search terms will include "Diabetic Retinopathy," "Dyslipidemia," "Triglycerides," "Cholesterol," "HDL-C," and "LDL-C." Secondary terms such as "Diabetes Mellitus," "Macular Edema," "Proliferative Diabetic Retinopathy," and "Non-Proliferative Diabetic Retinopathy" will also be used. Boolean operators (AND, OR) will help refine search results. Example search strings include: ("Diabetic Retinopathy" OR "Macular Edema") AND ("Dyslipidemia" OR "Cholesterol") AND ("Triglycerides" OR "LDL-C").

Data Retrieval

Titles and abstracts will be screened to assess their relevance to the topic of dyslipidemia and DR. Full-text articles meeting the inclusion criteria will be further assessed for details on study design, serum lipid measurements, DR classifications, and outcomes. Extracted data will include study characteristics, serum lipid parameters (TG, TC, HDL-C, LDL-C), and DR severity classifications (NPDR, PDR, DME). Studies that do not meet eligibility criteria will be excluded.

Quality Assessment and Data Synthesis

Two independent reviewers will evaluate the methodological quality of selected studies based on factors such as study design, sample

size, control of confounding variables, and reliability of outcome measures. Discrepancies will be resolved through discussion or consultation with a third reviewer. Only studies of robust methodological quality will be included in the final synthesis.

A qualitative analysis will summarize the findings on the relationship between serum lipids and DR progression. If sufficient homogeneous data are available, a meta-analysis will be conducted to quantify the association between specific lipid parameters and DR risk. Subgroup analyses will explore factors such as diabetes duration, glycemic control, and demographic variables (e.g., age, sex) to better understand their influence on the relationship between dyslipidemia and DR.

This systematic review adopts a structured approach to identify, evaluate, and synthesize current evidence on the association between dyslipidemia and DR, aiming to clarify this relationship and provide insights for clinical practice and future research.

Table 1. Search Strategy and Results

Database	Search Strategy	Hits
PubMed	("Diabetic Retinopathy" OR "Macular Edema") AND ("Dyslipidemia" OR "Triglycerides") AND "HDL-C"	420
ScienceDirect	"Diabetic Retinopathy" AND "Dyslipidemia" AND "LDL-C" AND "Macular Edema"	320
Embase	'Diabetic Retinopathy' OR 'Dyslipidemia' AND 'Cholesterol' OR 'Triglycerides'	275
Cochrane Library	"Diabetic Retinopathy" AND "Dyslipidemia" AND "Serum Lipids"	210
Web of Science	"Dyslipidemia" AND "Triglycerides" AND "Diabetic Retinopathy" AND "Macular Edema"	240

© The Indonesian Journal of General Medicine

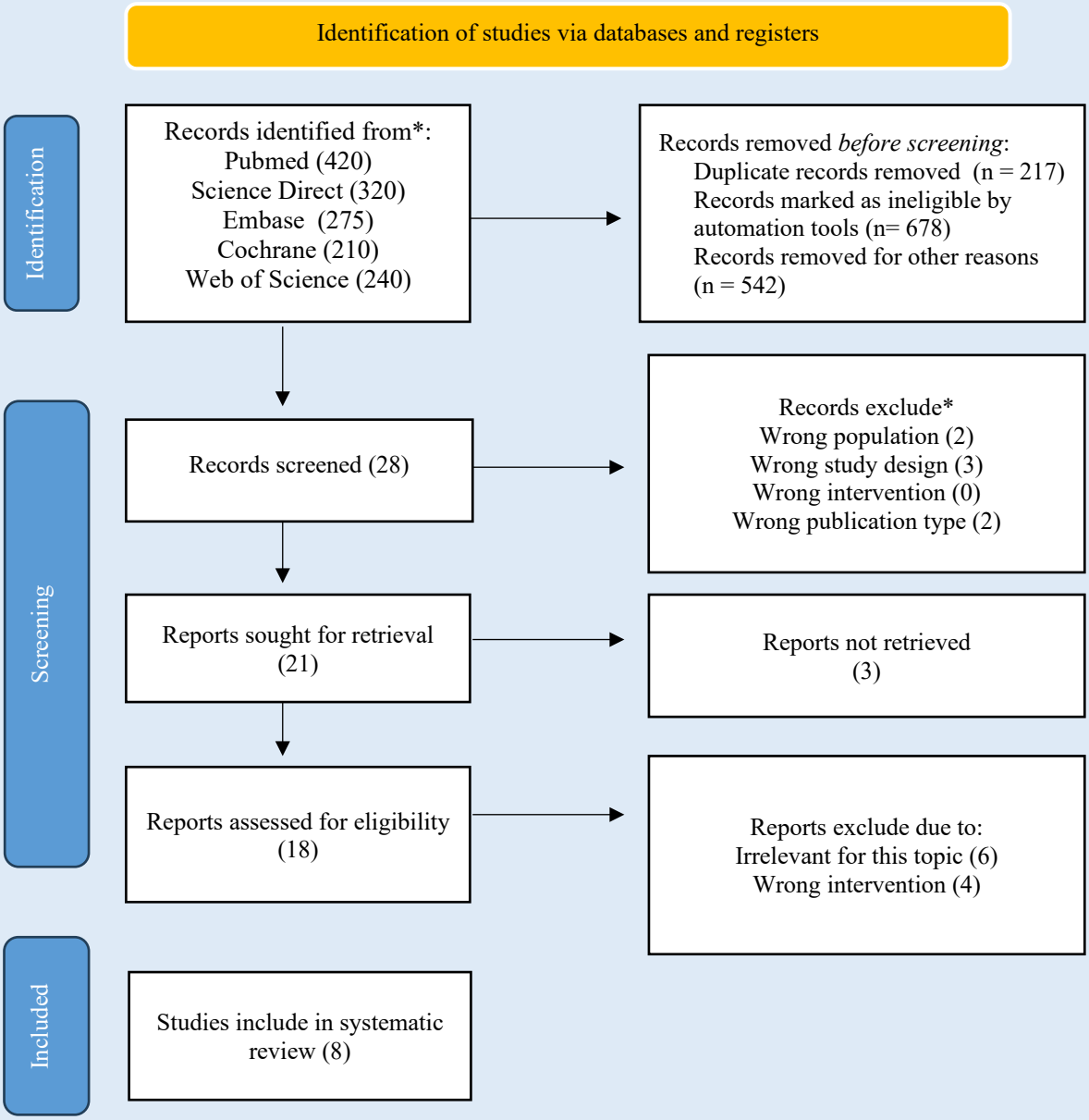


Figure 1. PRISMA Flowchart for Study Selection

RESULT

Our research team first gathered publications from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-level screening procedure, only eight papers were determined to be directly relevant to our ongoing systematic evaluation. Following that, these sections were picked for additional research and a close reading of the entire manuscript. The material that was evaluated for this analysis is compiled in Table 2 for ease of viewing.

Table 2. The literature included in this study

Author	Origin	Method	Sample Size	Result
Parveen N, Bukhari AAS, Khan Z, Mahmood R, Khan Q, Khan K, et al., 2018.[12]	Pakistan	Cross-sectional study	338 confirmed diabetic patients with or without retinopathy	Diabetic patients with or without retinopathy had no significant difference in plasma cholesterol concentration as compared to normal subjects (p=0.969). HDL levels were significantly lower in DNR, NPDR, and PDR patients compared to normal subjects (p<0.001). LDL and triglyceride levels were significantly elevated in DNR, NPDR, and PDR patients (p<0.001).
Ezhilvendhan K, Sathiyamoorthy A, Prakash BJ, Bhava BS, Shenoy A et al., 2021.[13]	India	Hospital-based cross-sectional study	200 patients	DR showed a significant association with raised LDL and TG levels, and lowered HDL on adjusted analysis. No significant association was found with total cholesterol, triglycerides, or LDL when adjusted for age, gender, diabetes duration, and glycemic control.
Elagamy A, Al Enazy BR, AL Zaaidi SE, et al., 2018.[14]	Saudi Arabia	Retrospective and cross-sectional study	800 patients	Significant differences in TC, LDL-C, and HDL-C levels between patients with and without diabetic macular edema (DME). LDL-C was higher and HDL-C was lower in patients with DME compared to those without (p<0.002 and p<0.003). No significant difference was found for triglycerides (p=0.5478).
Jeng, Chi-Juei et al., 2017.[15]	Taiwan	Prospective cohort study	23,867 patients in each group (dyslipidemia and nondyslipidemia)	The cumulative incidence of NPDR, DME, and PDR significantly increased in patients with dyslipidemia compared to those without (p<0.001). Adjusted hazard ratios for NPDR, DME, and PDR in patients with

				dyslipidemia were 1.77, 2.34, and 1.07 respectively. Statin use showed a protective effect against NPDR but had no effect on DME or PDR.
Srila Chadalavada et al., 2023.[16]	USA	Cross-sectional database study	79 million Americans	Patients on pitavastatin, fenofibrate, or evolocumab had a lower prevalence of proliferative DR compared to nonproliferative DR. Patients taking cholesterol medications had a lower prevalence of vitreous hemorrhage and, specifically, fibrates showed lower prevalence of neovascular glaucoma.
Liu Z et al., 2022.[17]	China	Case-control study	309 patients with DR, 186 with diabetes, 172 healthy controls	Increased levels of CHOL, TRIG, HDL-C, APOB, APOE, and SDLDL-C were associated with DR ($p<0.05$). Multivariable logistic regression analyses identified CHOL, TRIG, HDL-C, APOB, APOE, and SDLDL-C as risk factors for DR (OR values ranged from 1.269 to 14.719).
Fadhlan Hatta Agustian et al., 2024.[18]	Indonesia	Hospital-based cross-sectional study	45 patients	Prevalence of diabetic retinopathy was 37.8%, with 17.8% NPDR and 20% PDR. Significant differences in LDL categories ($p=0.007$) and total cholesterol ($p=0.038$) were observed between patients with and without diabetic retinopathy. No significant differences were found in HDL categories or triglycerides ($p=0.719$ and $p=1$).
Cetin EN, Bulgu Y, Ozdemir S et al., 2013.[19]	Turkey	Retrospective study	191 diabetic patients (61 NDR, 55 NPDR, 75 PDR)	No significant differences in mean levels of total cholesterol, triglycerides, LDL, HDL, or VLDL across different groups. However, blood glucose significantly correlated with total cholesterol and LDL levels

				(r=0.173, p=0.017; r=0.190, p=0.008).

Table 3. Critical appraisal of Study

Parameters	Parveen et al. (2018)	Ezhilvendhan et al. (2021)	Elagamy A et al. (2018)	Jeng et al. (2017)	Chadalavada et al. (2023)	Liu et al. (2022)	Agustian & Wardany (2024)	Cetin et al. (2013)
1. Bias related to temporal precedence								
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	No clear temporal precedence	Temporal precedence unclear	Temporal precedence unclear	Temporal precedence unclear	Temporal precedence unclear	Temporal precedence unclear	Temporal precedence unclear	Temporal precedence unclear
2. Bias related to selection and allocation								
Was there a control group?	No control group	No control group	No control group	Control group present	Control group present	Control group present	No control group	Control group present
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Unadjusted for confounders	Adjusted for factors like age, gender	Adjusted for factors like age, gender	Adjusted for underlying complications	Adjusted for confounders	Adjusted for HbA1c levels	Adjusted for confounders	Adjusted for confounders
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Similar treatment/care	Similar treatment/care	Similar treatment/care	Similar treatment/care	Similar treatment/care	Similar treatment/care	Similar treatment/care	Similar treatment/care
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Single measurement, no pre/post	Multiple measurements (pre/post)	Multiple measurements (pre/post)	Multiple measurements (pre/post)	Multiple measurements (pre/post)	Multiple measurements (pre/post)	Single measurement, no pre/post	Single measurement, no pre/post
Were the outcomes of	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

participants included in any comparisons measured in the same way?								Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Not mentioned	Follow-up not mentioned	Follow-up not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis	Appropriate statistical analysis

DISCUSSION

DISCUSSION

Diabetic retinopathy (DR) is a distinct and progressive complication of diabetes that threatens vision. It develops gradually through a series of changes in the retinal microvasculature, resulting in increased vascular permeability, reduced perfusion, and abnormal vascular proliferation. These pathophysiological processes have been extensively studied and elucidated. Clinically, DR is classified into two primary forms: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the earlier stage and is characterized by increased retinal vascular permeability, microaneurysm formation, exudates, hemorrhage, and subsequent retinal ischemia, leading to potential vision loss. As the condition progresses into PDR, it manifests with more severe features such as nerve fiber layer infarcts, neovascularization, vitreous hemorrhage, and tractional retinal detachment, all of which pose a significant risk for vision impairment.[8,20]

Diabetic macular edema (DME), a common complication of DR, occurs due to fluid or lipid accumulation in the macula—the central part of the retina—resulting in substantial vision impairment. Importantly, DME can develop at any stage of DR. Epidemiological data

from 2010 indicated that 34.6% of individuals with diabetes globally exhibited signs of DR, with 6.96% having PDR and 6.81% experiencing DME. In patients with type 1 diabetes (T1DM), DR is not present at the time of diagnosis but develops progressively, with nearly 99% exhibiting DR features after 20 years. Conversely, in type 2 diabetes (T2DM), DR can already be present at diagnosis, with 60% of patients showing retinopathy within two decades.[6-7,11]

Hyperlipidemia has increasingly been associated with the development and progression of diabetic retinopathy, particularly through complications like hard exudates and DME. Hard exudates are hypothesized to form due to lipid leakage from compromised retinal capillaries. Consequently, elevated levels of total cholesterol, LDL cholesterol (LDL-C), and triglycerides (TG) have been suggested as potential biomarkers for hard exudate development in diabetic patients. In the early stages of NPDR, strict glycemic control and adjustments in overall diabetes management are crucial.[9]

Cholesterol, a sterol found in all living organisms, is primarily synthesized endogenously in the liver, intestines, and skin, with the remainder obtained from dietary sources. Cholesterol exists in the form of lipoprotein complexes, which include chylomicrons, very low-density lipoproteins (VLDL-C), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL-C), and high-density lipoproteins (HDL-C). LDL-C accounts for 70–75% of total circulating cholesterol and is metabolized in hepatocytes via apolipoprotein B-100 (ApoB-100) binding to LDL receptors.[21]

Lipoproteins also contain various apolipoproteins, including ApoA1, ApoB, ApoC3, and ApoA5. Studies have shown an inverse relationship between ApoA1 levels and DR progression, while increased serum levels of ApoB and ApoC3, as well as the ApoA1/ApoB ratio, positively correlate with DR severity. ApoA1, a key component of HDL, exerts antioxidant and anti-inflammatory effects and has been found to protect against lipotoxicity in diabetic retinopathy. In contrast,

ApoB, the primary apolipoprotein in LDL and VLDL particles, plays a significant role in atherosclerosis and DR progression. Furthermore, HDL-bound ApoA1 and ApoB-containing particles (LDL and VLDL) have emerged as stronger predictors of DR compared to traditional lipid measures. [21-23]

Hyperlipidemia is characterized by reduced HDL-C levels and elevated LDL-C, VLDL-C, total cholesterol, or triglyceride levels. Evidence indicates that elevated circulating LDL-C contributes to atherosclerosis and is a key predictor of cardiovascular and metabolic disorders. Consequently, LDL-C has been identified as a primary target for lipid management in diabetic patients. Apolipoprotein B-100 (ApoB-100) is particularly recommended as a marker for cardiovascular risk in this population. Additionally, advanced glycation end-product modified LDL (AGE-LDL) and oxidized LDL (oxLDL) levels have been associated with DR progression, as demonstrated in longitudinal cohort studies.[23]

Cholesterol Metabolism and the Role of Protective Factors in the Retina

Cholesterol metabolism in the retina involves the uptake from the systemic circulation, clearance, and self-synthesis. The blood-retina barrier (BRB) plays a crucial role in regulating cholesterol homeostasis by controlling the pathways responsible for its entry and exit. The internal BRB, formed by retinal vascular endothelial cells, prevents cholesterol passage when intact, but this mechanism is disrupted under conditions like hyperglycemia. In studies using Akita mice, increased retinal vascular permeability was observed after 12 weeks of hyperglycemia. Later, morphological alterations were detected, including a reduction in the thickness of the inner plexiform and nuclear layers, a lower number of ganglion cell bodies, and the presence of acellular capillaries, morphologically altered astrocytes, and microglia after prolonged hyperglycemia. Breakdown of the internal BRB in diabetic patients leads to the passage of lipoprotein particles into the retina, increasing cholesterol levels and causing toxic

effects to surrounding cells. Cholesterol in the retina can be derived either from local biosynthesis or from lipoprotein particles taken up from the choroidal circulation by the external BRB. After uptake by retinal pigment epithelial (RPE) cells, cholesterol is exported either back to the choroidal circulation via reverse cholesterol transport or to the neural retina. The RPE and neural retina also metabolize cholesterol to oxysterols using cytochrome P450 enzymes, which activate liver X receptors (LXRs). LXR activation promotes reverse cholesterol transport and inhibits inflammatory gene expression mediated by NF-κB. The SIRT1-LXR axis, influenced by nutrient sensing and acetylation, is impaired in diabetes, leading to reduced cholesterol elimination, insufficient vascular repair, and activation of macrophages and microglia, contributing to retinal defects. Restoring LXR activity can reverse these processes, preventing acellular capillaries and inflammation caused by diabetes.[24]

Advanced Glycation End Products (AGEs)

In a healthy retina, plasma lipoproteins do not affect the retinal tissue, but when the BRB is compromised, as in diabetes, lipoproteins extravasate, becoming modified (oxidized or glycated) and toxic to retinal cells. Glycation, a nonenzymatic process where sugars react with amino groups, is accelerated in diabetes due to high glucose levels, leading to the formation of AGEs. These AGEs bind to proteins and disrupt cellular functions. They also bind to cell membrane receptors, causing oxidative stress and activation of transcription factors, ultimately damaging cells. Elevated AGE levels are found in the vessels and nerve cells of diabetic retinas. AGEs damage the vascular endothelium, leading to diabetic microangiopathy, which includes the development of microaneurysms and increased vascular permeability. AGEs also enhance inflammation, oxidative stress, blood clotting, fibrosis, and alter cell signaling pathways. Modified lipoproteins, such as oxidized LDL, are more pathogenic than unmodified forms and accumulate in the retinal vessels,

contributing to the pathogenesis of diabetic retinopathy. Studies have shown that glycated LDL and oxidized LDL are cytotoxic to retinal capillary endothelial cells, pericytes, and RPE cells, leading to changes in cell signaling, gene expression, apoptosis, and autophagy. Moreover, lipid β-oxidation, especially of very-long-chain fatty acids, may contribute to the increased oxidative stress in diabetes, exacerbating diabetic complications. [25]

The Role of Fibroblast Growth Factor 21 (FGF21) in Lipid Metabolism

FGF21, a cytokine from the FGF19 protein subfamily, plays an essential role in regulating carbohydrate and lipid metabolism. Its levels are elevated in several cardio-metabolic disorders, including diabetes. In type 2 diabetes (T2DM) patients, FGF21 has been shown to reduce body weight and alleviate hyperlipidemia. In obese and diabetic mice, FGF21 lowers serum triglyceride (TG) levels by regulating lipoprotein catabolism and maintaining phospholipid homeostasis in adipose tissue. Additionally, FGF21 promotes lipid utilization during amino acid starvation. FGF21 is also an agonist of PPAR-δ, a key regulator of metabolic disorders, and can modulate PPAR-α, affecting fat content in the body. In diabetic mice with insulin deficiency, FGF21 inhibits the secretion of proinflammatory cytokines, enhances antioxidant defenses in the retina, and improves retinal function. FGF21 also modulates adiponectin, which plays a crucial role in glucose and lipid metabolism. Furthermore, studies have shown that FGF21, mediated by adiponectin, can inhibit retinal neovascularization in diabetic mice.[26]

Protective Effects of Retinal PPARα Activation in Diabetic Retinopathy (DR)

Peroxisome proliferator-activated receptors (PPARs), particularly PPARα, play a significant role in regulating fatty acid oxidation by controlling the expression of proteins responsible for fatty acid uptake, such as the multifunctional fatty acid translocase CD36. In diabetes, PPAR signaling is disrupted in both animal and human models. CD36 is upregulated in the kidneys of diabetic individuals and participates

in mediating the apoptotic and oxidative effects of oxidized LDL immune complexes in retinal pericytes. PPARα is expressed in all layers of the retina and plays a protective role in diabetic retinopathy. Activation of PPARα by fenofibrate in animal and cell models has shown anti-inflammatory and antiapoptotic effects in endothelial cells, pericytes, and RPE cells. PPARα overexpression in diabetic rats significantly reduces retinal leakage, retinitis, neuroprotection, and prevents pericyte atrophy. Moreover, PPARα overexpression inhibits endothelial cell migration and proliferation, further protecting the retina from diabetes-induced damage.[27]

Prevention

Diet

To prevent and manage chronic diseases, it is essential to limit the consumption of total fat (<30% of total energy), saturated fatty acids (<10% of total energy), and trans fats. Epidemiological studies have shown that excessive consumption of these fats is associated with an increased risk of diabetes, ischemic heart disease, and cancer. Saturated and trans fatty acids contribute to atherosclerosis by raising total cholesterol and LDL-C levels and promoting inflammation and thrombosis. A significant source of cholesterol is animal fat, and its intake should be limited to 300 mg per day, with a recommendation of 200 mg per day for cardiovascular disease prevention. Foods high in cholesterol include egg yolks, organ meats, pate, and liver. Instead of animal fats, unsaturated fats from vegetable sources should be chosen. Both n-6 monounsaturated and polyunsaturated fatty acids reduce total and LDL-C levels while increasing HDL-C levels. Eating fish twice a week is recommended to obtain essential omega-3 polyunsaturated fatty acids, such as EPA and DHA, which help lower triglyceride levels.[9,20-22]

The relationship between fat intake and diabetic retinopathy is not entirely clear. Some studies found no direct correlation between fat consumption and retinopathy, while others suggested that monounsaturated fatty acids (MUFA) and oleic acid may reduce the risk of retinopathy. Some data indicate that

polyunsaturated fatty acids (PUFAs) may play a role in preventing retinopathy.[27]

Physical Activity

Regular physical activity is essential for reducing hyperlipidemia and the risk of diabetic complications. In type 1 diabetes (T1DM) patients, aerobic training improves cardiovascular and respiratory fitness, reduces insulin resistance, and enhances lipid profiles and endothelial function. In T2DM patients, regular exercise reduces A1C, triglyceride levels, blood pressure, and insulin resistance. The benefits of yoga and tai chi are less well studied, but yoga may improve glycemic control, lipid levels, and body composition in adults with T2DM. Physical activity helps reduce hyperglycemia, which can damage blood vessels and exacerbate oxidative stress, leading to advanced glycation end product formation. [27]

Stimulants

Moderate alcohol consumption has been linked to a lower risk of diabetic retinopathy in the general population. The beneficial effects of alcohol include increased HDL levels, reduced platelet aggregation, and decreased fibrinogen levels. Green tea has been shown to protect diabetic retinal neurons, reduce reactive oxygen species (ROS) generation, and enhance antioxidant defense. Green tea also restores intercellular connections and glutamine/glutamate circulation, helping to maintain retinal health. Furthermore, green tea may reduce inflammatory markers and prevent retinal membrane thickening. Smoking, however, is associated with higher cholesterol, triglyceride, and LDL levels and lower HDL levels, contributing to an increased risk of diabetic complications. [27]

Pharmacotherapy

Statins

Statins have been shown to have beneficial effects on diabetic retinopathy by lowering total cholesterol and LDL-C levels. Studies have demonstrated that statin therapy can reduce the incidence of diabetic retinopathy and prevent visual acuity deterioration. Statin treatment is also associated with a reduced need for intravitreal injections and vitrectomy in patients with diabetic retinopathy. Some studies, however, have failed to

© The Indonesian Journal of General Medicine

show a significant benefit of statins in preventing diabetic retinopathy, with some concluding that statins play a more significant role in reducing cardiovascular disease risk than in preventing retinopathy.[4]

Fenofibrate

The FIELD study, which evaluated fenofibrate in diabetic patients, showed that fenofibrate reduced the need for laser treatment of diabetic macular edema (DME) by 31%. Fenofibrate has been shown to improve lipid profiles and may help prevent complications associated with diabetic retinopathy.[4,7]

The association between dyslipidemia and diabetic retinopathy (DR) has been explored extensively across various studies, with findings often highlighting the role of lipid profile abnormalities in the development and progression of DR.

Ezhilvendhan et al. (2021) in India conducted a hospital-based cross-sectional study involving 200 patients and found a significant association between DR and raised LDL cholesterol, triglycerides (TGs), and lowered HDL cholesterol. Their results indicated that patients with DR had a longer duration of diabetes and a statistically significant older mean age compared to those without retinopathy. Notably, moderate nonproliferative diabetic retinopathy (NPDR) was the most prevalent form, while proliferative DR (PDR) was less common. However, the association of DR with total cholesterol, LDL, and TG levels was not observed when adjusted for age, gender, duration of diabetes, and glycemic control. Interestingly, only HDL levels remained significantly associated with the severity of DR.[12]

Similarly, Parveen et al. (2018) in a multicenter study in Pakistan demonstrated elevated LDL and serum triglyceride levels along with significantly reduced HDL levels in patients with DR compared to normal subjects. This emphasizes the consistent role of HDL as a protective factor, as its lower concentration was observed across DR subgroups (NPDR, PDR) compared to controls.[13] The study by Liu et al. (2022) in China further supports these findings. In a population-based case-control study involving 309 DR patients, lipid parameters such as cholesterol, TG,

HDL-C, APOB, APOE, and small dense LDL-C were significantly elevated in DR patients. Notably, multivariable logistic regression analyses identified cholesterol, TG, HDL-C, and APOB as independent risk factors for DR, highlighting the strong predictive role of lipid abnormalities.[17]

In contrast, Cetin et al. (2013) from Turkey did not observe a significant difference in lipid parameters between DR and non-DR groups. Although mean blood glucose and HbA1c levels correlated with total cholesterol and LDL, these findings suggest that glycemic control may play a more critical role than dyslipidemia in DR progression within this population.[19]

Notably, Jeng et al. (2017) in Taiwan conducted a large prospective cohort study and demonstrated a significant increase in the cumulative incidence of NPDR, diabetic macular edema (DME), and PDR in patients with dyslipidemia. Adjusted hazard ratios (HRs) revealed increased risks for NPDR and DME, while statin use was found to have a protective effect against NPDR. However, this effect was not observed for DME and PDR, suggesting that lipid-lowering medications may exert differential effects on DR subtypes.[15]

From a therapeutic perspective, Chadalavada et al. (2023) in a large US cohort highlighted the beneficial effects of lipid-lowering agents such as pitavastatin, fenofibrate, and evolocumab in reducing the prevalence of PDR and vitreous hemorrhage. This underscores the potential role of lipid management in mitigating DR progression.[16] Lastly, Fadhlan and Yulia (2024) in Indonesia found significant differences in LDL and total cholesterol levels in type 2 diabetes patients with DR compared to those without, further corroborating the importance of lipid abnormalities in DR pathogenesis.[18]

Collectively, these studies reveal a consistent association between lipid abnormalities, particularly low HDL cholesterol, elevated LDL cholesterol, and triglycerides, with the presence and severity of diabetic retinopathy. While glycemic control remains central to DR prevention, dyslipidemia plays an independent

role, particularly in advanced DR subtypes. The therapeutic benefits of lipid-lowering agents, such as statins and fenofibrate, further highlight the potential for integrated glycemic and lipid management strategies to reduce the burden of diabetic retinopathy. Future research should focus on the mechanisms linking lipid dysregulation to retinal microvascular damage and the long-term outcomes of lipid-targeted interventions in preventing DR progression.

CONCLUSION

This systematic review evaluated the association between dyslipidemia and diabetic retinopathy (DR) across various studies, including cross-sectional, cohort, and case-control designs. The studies consistently highlight the significant relationship between lipid profiles, particularly low HDL cholesterol and high LDL cholesterol, and the presence and progression of diabetic retinopathy in patients with diabetes mellitus. However, the risk of bias analysis revealed several limitations across the included studies. Many studies did not include control groups, which reduces the ability to draw strong causal conclusions. Furthermore, there was variability in the adjustment for potential confounding factors such as age, gender, diabetes duration, and glycemic control. In some cases, temporal precedence was not clearly established, limiting the strength of the findings regarding the directionality of the relationship between dyslipidemia and DR. Despite these limitations, the evidence suggests that dyslipidemia, particularly the imbalance in lipid profiles, may play a role in the development and progression of diabetic retinopathy. Future studies with more robust designs, including control groups, clearer temporal precedence, and better adjustment for confounders, are needed to confirm these findings and explore potential therapeutic strategies targeting lipid profiles to prevent or manage diabetic retinopathy in diabetic patients. Overall, while the studies reviewed provide valuable insights, the current body of evidence is not definitive, and further research is required to establish stronger causal relationships and improve the understanding of the role of dyslipidemia in diabetic retinopathy.

© The Indonesian Journal of General Medicine

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

REFERENCES

1. Bryl A, Mrugacz M, Falkowski M, Zorena K. The Effect of Hyperlipidemia on the Course of Diabetic Retinopathy—Literature Review. Journal of Clinical Medicine. 2022; 11(10):2761. DOI
2. Sacks, D.; Baxter, B.; Campbell, B.C.V.; Carpenter, J.S.; Cognard, C.; Dippel, D.; Eesa, M.; Fischer, U.; Hausegger, K.; Hirsch, J.A.; et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. Int. J. Stroke 2018, 13, 612–632.
3. Yau, J.W.Y.; Rogers, S.L.; Kawasaki, R.; Lamoureux, E.L.; Kowalski, J.W.; Bek, T.; Chen, S.-J.; Dekker, J.M.; Fletcher, A.; Grauslund, J.; et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care 2012, 35, 556–564.
4. Mozetic, V.; Freitas, C.G.; Riera, R.; Evans, J.; Ramachandran, S. Statins and Fibrates for Diabetic Retinopathy: Protocol for a Systematic Review. JMIR Res. Protoc. 2017, 6, e30.
5. Mrugacz, M.; Bryl, A.; Zorena, K. Retinal Vascular Endothelial Cell Dysfunction and Neuroretinal Degeneration in Diabetic Patients. J. Clin. Med. 2021, 10, 458.
6. Mrugacz, M.; Bryl, A.; Bossowski, A. Neuroretinal Apoptosis as a Vascular Dysfunction in Diabetic Patients. Curr. Neuropharmacol. 2016, 14, 826–830.
7. Knickelbein, J.E.; Abbott, A.B.; Chew, E.Y. Fenofibrate and Diabetic Retinopathy. Curr. Diabetes Rep. 2016, 16, 90.
8. Sasso, F.C.; Pafundi, P.C.; Gelso, A.; Bono, V.; Costagliola, C.; Marfella, R.; Sardu, C.; Rinaldi, L.; Galiero, R.; Acierno, C.; et al. High HDL cholesterol: A risk factor for diabetic retinopathy?

Findings from NO BLIND study. Diabetes Res. Clin. Pract. 2019, 150, 236–244.

9. Busik, J.V. Lipid metabolism dysregulation in diabetic retinopathy. J. Lipid Res. 2021, 62, 100017.
10. Barber, A.J.; Antonetti, D.A.; Kern, T.S.; Reiter, C.E.N.; Soans, R.S.; Krady, J.K.; Levison, S.W.; Gardner, T.W.; Bronson, S.K. The Ins2Akita Mouse as a Model of Early Retinal Complications in Diabetes. Investig. Ophthalmol. Vis. Sci. 2005, 46, 2210–2218.
11. Lin, J.B.; Mast, N.; Bederman, I.R.; Li, Y.; Brunengraber, H.; Björkhem, I.; Pikuleva, I.A. Cholesterol in mouse retina originates primarily from in situ de novo biosynthesis. J. Lipid Res.
12. Parveen N, Bukhari AAS, Khan Z, Mahmood R, Khan Q, Khan K, et al. Association of diabetic retinopathy with dyslipidemia: a multicenter study. J Rehman Med Inst. 2018;4(4):21-24.
13. Elagamy A, Al Enazy BR, AL Zaaidi SE (2018) Association between Dyslipidemia and Diabetic Retinopathy in Type 2 Diabetic Patients. J Ophthalmic Stud 1(1): dx.doi.org/10.16966/2639-152X.111
14. Ezhilvendhan K, Sathiyamoorthy A, Prakash BJ, Bhava BS, Shenoy A. Association of dyslipidemia with diabetic retinopathy in Type 2 diabetes mellitus patients: A hospital-based study. J Pharm Bioallied Sci. 2021;13(Suppl 2):S1062-S1067. doi:10.4103/jpbs.jpbs_164_21.
15. Jeng CJ, Hsieh YT, Yang CM, Yang CH, Lin CL, Wang IJ. Diabetic retinopathy in patients with dyslipidemia: development and progression. Ophthalmology Retina. 2017;doi:10.1016/j.oret.2017.05.010.
16. Chadalavada S, Shaia JK, Russell M, Talcott K, Singh R. Impact of dyslipidemia medications on the prevalence of diabetic retinopathy among a large US cohort. Invest Ophthalmol Vis Sci. 2023;64(8):2267.
17. Liu Z, Shao M, Ren J, Qiu Y, Li S, Cao W. Association between increased lipid profiles and risk of diabetic retinopathy in a

population-based case-control study. J Inflamm Res. 2022;15:3433-3446. doi:10.2147/JIR.S361613.

18. Agustian FH, Wardany Y. Lipid profile in type 2 diabetes mellitus patients with and without diabetic retinopathy. Sumat Med J. 2024;7(3):132-140. Available from: https://talenta.usu.ac.id/smj/article/view/15462.
19. Cetin EN, Bulgu Y, Ozdemir S, et al. Association of serum lipid levels with diabetic retinopathy. Int J Ophthalmol. 2013;6(3):346-349. doi:10.3980/j.issn.2222-3959.2013.03.17.
20. Pearsall, E.A.; Cheng, R.; Matsuzaki, S.; Zhou, K.; Ding, L.; Ahn, B.; Kinter, M.; Humphries, K.M.; Quiambao, A.B.; Farjo, R.A.; et al. Neuroprotective effects of PPARalpha in retinopathy of type 1 diabetes. PLoS ONE 2019, 14, e0208399.
21. Sasaki, M.; Kawasaki, R.; Rogers, S.; Man, R.E.K.; Itakura, K.; Xie, J.; Flood, V.M.; Tsubota, K.; Lamoureux, E.L.; Wang, J.J. The Associations of Dietary Intake of Polyunsaturated Fatty Acids with Diabetic Retinopathy in Well-Controlled Diabetes. Investig. Ophthalmol. Vis. Sci. 2015, 56, 7473–7479.
22. Alcubierre, N.; Navarrete-Muñoz, E.M.; Rubinat, E.; Falguera, M.; Valls, J.; Traveset, A.; Vilanova, M.-B.; Marsal, J.R.; Hernández, M.; Granado-Casas, M.; et al. Association of low oleic acid intake with diabetic retinopathy in type 2 diabetic patients: A case–control study. Nutr. Metab. 2016, 13, 40.
23. Colberg, S.R.; Sigal, R.J.; Yardley, J.E.; Riddell, M.C.; Dunstan, D.W.; Dempsey, P.C.; Horton, E.S.; Castorino, K.; Tate, D.F. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016, 39, 2065–2079.
24. Caturano, A.; Galiero, R.; Pafundi, P.C.; Cesaro, A.; Vetrano, E.; Palmiero, G.; Rinaldi, L.; Salvatore, T.; Marfella, R.; Sardu, C.; et al. Does a strict glycemic control during acute coronary syndrome play a cardioprotective role in type 2 diabetes mellitus? The importance

of the timely glucose control. Cardiovasc. Diabetol. 2020, 19, 1–8.

© The Indonesian Journal of General Medicine