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Lipoprotein(a) and the risk of diabetic retinopathy

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 August 2024 and was last updated on 24 August 2024.

INTRODUCTION

Review question / Objective The objective of this meta-analysis is to systematically evaluate and synthesize the existing evidence on the association between elevated serum lipoprotein(a) [Lp(a)] levels and the risk of developing diabetic retinopathy (DR) in patients with type 2 diabetes. The review aims to determine whether higher levels of Lp(a) serve as a potential risk factor for the onset and progression of DR, thereby contributing to a better understanding of the role of Lp(a) in the pathophysiology of diabetic microvascular complications. This meta-analysis will analyze data from observational studies to provide a comprehensive assessment of the strength and consistency of this association, which may have implications for risk stratification and management of patients with type 2diabetes.

Rationale Diabetic retinopathy (DR) is a leading cause of vision impairment and blindness among individuals with type 2 diabetes. While the pathogenesis of DR is multifactorial, emerging evidence suggests that dyslipidemia, particularly elevated levels of certain lipoproteins, may play a significant role in its development and progression. Lipoprotein(a) [Lp(a)] is a unique lipoprotein particle that has been associated with cardiovascular disease and other atherosclerotic conditions. However, its role in microvascular complications like DR is less clear.

The rationale for this study stems from the need to better understand the potential link between elevated Lp(a) levels and DR in type 2 diabetes. As Lp(a) is known to promote inflammatory processes and endothelial dysfunction, it may contribute to the vascular damage seen in DR. Several observational studies have explored this relationship, but their findings have been inconsistent, with some studies reporting a significant association while others have not.

Given the growing prevalence of type 2 diabetes and the substantial burden of DR on patients and healthcare systems, clarifying the role of Lp(a) as a risk factor for DR could have important clinical implications. If a strong association is established, Lp(a) could be considered in risk stratification

models and potentially targeted in preventive strategies to reduce the incidence and severity of DR in patients with type 2 diabetes. This meta-analysis aims to systematically review and synthesize the available evidence to provide a more definitive answer to this important clinical question.

Condition being studied Lipoprotein(a) and the risk of diabetic retinopathy.

METHODS

Search strategy Key search terms will include "Lipoprotein(a)" or "Lp(a)," "Diabetic Retinopathy" or "DR," "Type 2 Diabetes" or "T2DM," and terms related to "Risk Factor" and "Association." These terms will be used in various combinations to ensure an exhaustive search. The review will include studies published in English, with no date restrictions, to capture all relevant evidence.

Participant or population The review will focus on studies that include participants diagnosed with type 2 diabetes mellitus (T2DM), who have been assessed for diabetic retinopathy (DR) as an outcome. Participants may be of any age, gender, or ethnicity, and the studies may include those at various stages of DR, from mild non-proliferative diabetic retinopathy (NPDR) to severe proliferative diabetic retinopathy (PDR). The review will specifically target studies that have measured serum lipoprotein(a) [Lp(a)] levels in these participants to investigate the potential association between elevated Lp(a) levels and the risk of developing or worsening DR. Studies involving participants with type 1 diabetes, other forms of retinopathy, or secondary causes of elevated Lp(a) will be excluded from the review.

Intervention The review will evaluate studies that have quantified Lp(a) levels in participants with type 2 diabetes and assessed whether higher Lp(a) levels are associated with an increased risk of developing DR or its progression. No therapeutic interventions will be directly assessed, as the review's aim is to understand the potential role of Lp(a) as a risk factor for DR rather than the impact of any specific treatment.

Comparator In this review, the comparative intervention refers to the comparison between different levels of serum lipoprotein(a) [Lp(a)] in the target population of patients with type 2 diabetes. Specifically, studies that compare participants with elevated Lp(a) levels to those with normal or lower Lp(a) levels will be included. The primary comparison will involve assessing the difference in the risk of developing or progressing diabetic retinopathy (DR) between these groups. This comparison aims to determine whether higher Lp(a) levels are associated with an increased risk of DR compared to lower Lp(a) levels.

Study designs to be included To address the objective of this review, we will include observational study designs that investigate the relationship between serum lipoprotein(a) [Lp(a)] levels and the risk of diabetic retinopathy (DR) in patients with type 2 diabetes. Specifically, we will consider cohort studies (both prospective and retrospective) that track participants over time to assess DR incidence or progression relative to Lp(a) levels, case-control studies that compare Lp(a) levels between individuals with and without DR, and cross-sectional studies that examine Lp(a) levels and DR status at a single point in tim.

Eligibility criteria No additional criteria applied.

Information sources The review will include a comprehensive search of several electronic databases, including PubMed, Embase, and Web of Science. The search strategy will employ a combination of Medical Subject Headings (MeSH) and free-text terms to identify relevant studies.

Main outcome(s) The outcomes of the review will focus on evaluating the association between elevated serum lipoprotein(a) [Lp(a)] levels and diabetic retinopathy (DR) in patients with type 2 diabetes. The primary outcome will be the presence or severity of DR, assessed using diagnostic criteria or severity scales reported in the studies. We will measure this outcome using effect metrics such as odds ratios (OR) for observational studies.

Additional outcome(s) None.

Data management To manage records and data for the review, a systematic process will be employed. Searches will be conducted in selected electronic databases, and records will be exported into reference management software such as EndNote or Zotero for organization. Initial screening of titles and abstracts will be followed by full-text review to determine study inclusion. Data extraction will be conducted using a standardized form, with multiple reviewers involved to ensure accuracy. Extracted data will be entered into a database or spreadsheet, with regular backups to maintain data integrity.

Quality assessment / Risk of bias analysis The quality of included studies will be assessed using

appropriate tools like the Newcastle-Ottawa Scale (NOS). Data synthesis and analysis will be performed using statistical software to aggregate effect measures and assess the association between elevated lipoprotein(a) levels and diabetic retinopathy, including sensitivity and subgroup analyses to ensure robustfindings.

Strategy of data synthesis Data analysis will focus on aggregating odds ratios (OR) from case-control studies to evaluate the association between elevated serum lipoprotein(a) [Lp(a)] levels and the risk of diabetic retinopathy (DR). The odds ratios will be calculated to compare the likelihood of DR occurrence in individuals with high Lp(a) levels versus those with normal or lower levels. Meta-analysis will be performed using statistical software to pool ORs across studies, with a focus on assessing the overall effect size. Heterogeneity among studies will be evaluated to understand the variability in effect estimates. Sensitivity analyses will be conducted to test the robustness of the OR findings, and publication bias will be assessed to ensure that the results are not unduly influenced by selective reporting.

Subgroup analysis Subgroup analysis will be conducted to explore variations in the association between elevated serum lipoprotein(a) [Lp(a)] levels and diabetic retinopathy (DR) across different study characteristics and participant factors. Subgroups will be defined based on variables such as study design (e.g., case-control vs. cohort), demographic factors (e.g., age, gender, ethnicity), Lp(a) measurement methods, and the severity of DR. By examining these subgroups, we aim to identify potential sources of heterogeneity and better understand how different factors may influence the relationship between Lp(a) levels and DR. This analysis will help clarify whether specific groups of patients or methodological differences impact the observed association and provide insights into the generalizability and applicability of the findings.

Sensitivity analysis Sensitivity analysis will be conducted to assess the robustness of the findings regarding the association between elevated serum lipoprotein(a) [Lp(a)] levels and diabetic retinopathy (DR). This analysis will involve systematically evaluating the impact of various factors on the overall results. Key sensitivity analyses will include examining the influence of study quality by excluding lower-quality studies, assessing the effect of sample size by comparing results from large versus small studies, and testing different thresholds for defining high Lp(a) levels to determine if the results are consistent across different cut-offs. Additionally, sensitivity analysis will evaluate the impact of removing individual studies to check for any significant changes in the overall effect size. These analyses will help ensure that the conclusions drawn from the meta-analysis are reliable and not unduly influenced by specific study characteristics or methodological variations.

Language restriction English.

Country(ies) involved China.

Keywords Lipoprotein(a); Diabetic Retinopathy; Type 2 Diabetes; Risk Factor; Serum Biomarkers.

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