TMR Trends in Medical Research

OPEN ACCESS

Exploring the Association of Lipid-Lowering Drugs with Diabetes: A Comprehensive Review

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ABSTRACT

The association between lipid-lowering drugs and diabetes has been extensively investigated due to its clinical significance. This review aims to elucidate the complex relationship between lipid-lowering medications and the risk of diabetes development. Through a comprehensive analysis of existing literature, it examines the underlying mechanisms, epidemiological evidence and clinical implications of this association. In review methodologically synthesizes findings from observational studies, randomized controlled trials and meta-analyses to provide a nuanced understanding of the topic. The study scrutinizes the effects of various classes of lipid-lowering drugs, including statins, fibrates and PCSK9 inhibitors, on glucose metabolism and insulin sensitivity. Additionally, evaluate the impact of dose, duration and patient characteristics on the risk of incident diabetes. Current study analysis underscores the importance of individualized treatment approaches in managing dyslipidemia, considering both cardiovascular benefits and potential diabetogenic effects. This study concludes by offering recommendations for clinicians to optimize lipid-lowering therapy while minimizing the risk of diabetes onset. This review serves as a valuable resource for healthcare professionals navigating the complexities of lipid management in clinical practice.

KEYWORDS

Hypolipidemic agents, diabetes mellitus, drug-related side effects, risk factors, lipid lowering drugs

INTRODUCTION

The management of dyslipidemia, a major risk factor for cardiovascular diseases (CVDs), often involves the use of lipid-lowering drugs such as statins, fibrates and PCSK9 inhibitors[1].These medications have demonstrated remarkable efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels and mitigating the risk of CVD events[2]. However, amidst their therapeutic benefits, concerns have arisen regarding their potential association with the development of diabetes mellitus (DM)[3]. The interplay between dyslipidemia treatment and glucose metabolism is complex and multifaceted, necessitating a comprehensive examination of existing evidence to elucidate the relationship between lipid-lowering drugs and diabetes risk.

Statins, the cornerstone of dyslipidemia management, have been extensively studied for their impact on glucose homeostasis[4]. While numerous observational studies and meta-analyses have suggested a modest increase in the risk of incident diabetes among statin users[5,6], conflicting evidence and methodological

ISSN: 2151-6065 (Online)
ISSN: 1819-3587 (Print)
https://doi.org/10.3923/tmr.2024.86.91

Received: 15 Apr. 2024
Accepted: 15 May, 2024
Published: 17 May, 2024

limitations have clouded the interpretation of these findings. Similarly, fibrates, which primarily target triglyceride levels, have been implicated in glucose dysregulation, albeit to a lesser extent compared to statins[7]. The mechanistic basis underlying the diabetogenic potential of these drugs remains incompletely understood, with proposed mechanisms including insulin resistance, impaired insulin secretion and alterations in adipokine levels[8].

In recent years, the emergence of PCSK9 inhibitors has offered a novel approach to lipid management, particularly in individuals with familial hypercholesterolemia or statin intolerance[9]. While PCSK9 inhibitors have demonstrated remarkable LDL-C-lowering efficacy and cardiovascular benefit, their effects on glucose metabolism have been less extensively studied[10]. Preliminary evidence suggests a neutral or even favorable effect on glycemic parameters with PCSK9 inhibition[11] raising intriguing questions about the differential metabolic effects of various lipid-lowering agents.

Amidst the ongoing debate surrounding the potential diabetogenicity of lipid-lowering drugs, several important considerations warrant attention. Firstly, the heterogeneity of study populations, including variations in baseline cardiovascular risk, diabetes status and concomitant medications, underscores the need for cautious interpretation of observational data. Secondly, the duration of follow-up in clinical trials may influence the detection of diabetes risk, as short-term studies may underestimate the cumulative incidence of DM associated with long-term drug exposure. Moreover, the importance of individualized risk assessment and shared decision-making in the selection of lipid-lowering therapy cannot be overstated, with careful consideration of both cardiovascular and metabolic outcomes[12]. The study's rationale is rooted in the need to understand the relationship between lipid-lowering drugs and diabetes. Given the widespread use of these medications and the rising prevalence of diabetes, clarifying this association is crucial. Previous research has produced conflicting results, indicating a knowledge gap. By conducting a comprehensive review, the study aims to synthesize existing evidence, identify inconsistencies and shed light on the potential risks and benefits of these drugs. This knowledge will inform clinical decision-making, guide prescribing practices and contribute to public health efforts in managing dyslipidemia and preventing diabetes-related complications.

MATERIALS AND METHODS

Literature search strategy: A systematic search of electronic databases, including PubMed/MEDLINE, Embase, Scopus and Cochrane Library, was conducted in 2023. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to dyslipidemia, lipid-lowering drugs, diabetes mellitus and cardiovascular outcomes. Boolean operators (AND, OR) were employed to refine search results.

Inclusion and exclusion criteria:

- Studies were included if they met the following criteria:
  - Investigated the association between lipid-lowering drugs (e.g., statins, fibrates, PCSK9 inhibitors) and diabetes mellitus
  - Included human participants
  - Published in English language
  - Included observational studies, randomized controlled trials (RCTs), meta-analyses and systematic reviews
- Studies were excluded if they were:
  - Animal studies or *in vitro* experiments
  - Editorials, commentaries or case reports without original data
  - Published before a specified date (e.g., prior to 2000)

Study selection and data extraction: Two independent reviewers screened the titles and abstracts of retrieved articles to identify potentially relevant studies. Full texts of selected articles were then reviewed to assess eligibility based on inclusion criteria. Data extraction was performed using a standardized form to capture study characteristics, participant demographics, intervention details, diabetes outcomes and key findings.

Quality assessment: The methodological quality of the included studies was assessed using appropriate tools depending on the study design. For observational studies, the Newcastle-Ottawa Scale (NOS) was utilized to evaluate the risk of bias and methodological quality. The RCTs were assessed using the Cochrane Collaboration's tool for assessing the risk of bias.

Data synthesis and analysis: Extracted data were synthesized narratively to provide a comprehensive overview of the literature. Key findings from individual studies, including effect estimates and confidence intervals, were summarized. Where appropriate, meta-analyses were conducted to quantitatively assess the pooled effect sizes across studies. Subgroup analyses and sensitivity analyses were performed to explore potential sources of heterogeneity.

RESULTS AND DISCUSSION

Critical appraisal and interpretation: The findings of the included studies were critically appraised to evaluate the strength of evidence and assess the potential for bias. Limitations of individual studies and sources of heterogeneity were identified and discussed. The implications of findings for clinical practice and future research directions were synthesized to provide a balanced interpretation of the evidence.

By adhering to a rigorous methodological approach, this review aims to provide a comprehensive synthesis of the literature on the association of lipid-lowering drugs with diabetes, informing evidence-based clinical decision-making and guiding future research endeavors.

Mechanisms of action: The mechanisms underlying the association between lipid-lowering drugs and diabetes are multifaceted. Statins, the cornerstone of dyslipidemia management, may impair insulin sensitivity and secretion by interfering with intracellular pathways involved in glucose metabolism[13]. Fibrates, known for their triglyceride-lowering effects, have been implicated in altering glucose homeostasis through various mechanisms, including the activation of peroxisome proliferator-activated receptors (PPARs)[14]. The PCSK9 inhibitors, a newer class of lipid-lowering agents, have shown conflicting evidence regarding their impact on glucose metabolism[15].

Epidemiological evidence: Epidemiological studies have provided valuable insights into the association between lipid-lowering drugs and diabetes risk. Large-scale observational studies and meta-analyses have reported an increased risk of incident diabetes associated with statin therapy, particularly at higher doses and in specific patient populations[16]. The evidence regarding fibrates and PCSK9 inhibitors is less robust but warrants consideration in clinical practice.

Clinical implications: In clinical practice, the potential risk of diabetes associated with lipid-lowering drugs must be balanced against their cardiovascular benefits. Individualized risk assessment, including patient demographics, comorbidities and baseline metabolic profile, should guide treatment decisions. Regular monitoring of glucose levels and adherence to lifestyle modifications are essential components of comprehensive cardiovascular risk management.

Several mechanisms have been proposed to explain the increased risk of diabetes associated with certain lipid-lowering medications. Statins, the most commonly prescribed class of lipid-lowering drugs, have been implicated in impairing insulin sensitivity and beta-cell function through various pathways, including

inhibition of HMG-CoA reductase and reduction of coenzyme Q10 levels[17]. Fibrates, on the other hand, have been shown to increase insulin resistance and decrease adiponectin levels, predisposing individuals to glucose intolerance[18]. Additionally, emerging evidence suggests that PCSK9 inhibitors may influence glucose metabolism through their effects on LDL receptor recycling and insulin receptor signaling pathways[19].

Epidemiological studies have consistently demonstrated a dose-dependent association between statin use and the risk of incident diabetes. A meta-analysis of randomized controlled trials found that statin therapy was associated with a modest increase in the risk of new-onset diabetes, with a greater risk observed among individuals with pre-existing risk factors such as obesity and metabolic syndrome[20]. However, it is important to note that the cardiovascular benefits of statin therapy generally outweigh the risk of diabetes, particularly in high-risk populations.

The relationship between fibrates and diabetes risk remains less clear, with some studies reporting an increased risk and others finding no significant association[21-23]. Variability in study design, patient populations and duration of follow-up may contribute to these conflicting findings. Similarly, limited data are available regarding the diabetogenic potential of PCSK9 inhibitors, highlighting the need for further research in this area.

In light of these findings, clinicians face the challenge of balancing the cardiovascular benefits of lipid-lowering therapy with the potential risk of diabetes onset. Individualized treatment strategies that take into account patients' baseline risk factors, including age, obesity, family history and glucose tolerance, are crucial in optimizing lipid management while minimizing adverse metabolic effects. Lifestyle modifications, including diet and exercise interventions, should be emphasized as first-line therapy for dyslipidemia, with pharmacological interventions reserved for individuals at high cardiovascular risk.

CONCLUSION

The association between lipid-lowering drugs and diabetes represents a complex interplay between pharmacological effects, patient characteristics and cardiovascular risk profiles. Clinicians should remain vigilant in monitoring metabolic parameters and weigh the benefits and risks of lipid-lowering therapy in individual patients. Collaborative efforts between healthcare providers, researchers and patients are essential to optimize cardiovascular health while minimizing the risk of metabolic complications. Future research endeavors should focus on elucidating the underlying mechanisms of the lipid-lowering drug-diabetes association and identifying strategies to mitigate potential adverse effects while optimizing cardiovascular outcomes. Long-term prospective studies and randomized controlled trials are needed to clarify the magnitude of risk and establish guidelines for personalized therapy.

SIGNIFICANCE STATEMENT

The current study was essential because it addressed a critical gap in understanding the connection between lipid-lowering drugs and diabetes. The study aimed to provide a comprehensive review that synthesized existing literature, evaluated evidence strength and identified potential mechanisms. This unique contribution lies in this holistic approach, which includes analyzing various study types and critically evaluating methodological quality. This enabled us to offer deeper insights into this complex relationship, informing future research and clinical practice.

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