Incidence of New-Onset Diabetes Mellitus (NODM) Among Patients Using Statins: A Systematic review.

Mohsen Huraybi Matar Alshammari[1], Dr Sabariah N. Harun[2], Dr. Baharudin Bin Ibrahim[3]

[1] *Discipline Of Clinical Pharmacy, School Of Pharmaceutical Sciences, University Sains Malaysia*
[2] *Discipline Of Clinical Pharmacy, School Of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia*
[3] *Faculty Of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
Corresponding author: Mohsen Huraybi Matar Alshammari

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Statins, New-Onset Diabetes Mellitus, Cardiovascular Risk, High-Potency Statins, Systematic Review, Metabolic Risk.

ABSTRACT
Background: The utilization of statins is essential for managing dyslipidemia and reducing cardiovascular risk. However, recent studies suggest a potential correlation between statin treatment and new-onset diabetes mellitus (NODM). Understanding the extent of this risk is critical for guiding clinical decision-making and patient care.
Objectives: To systematically review the incidence of NODM among patients using statins and explore the factors influencing this risk, such as statin potency and dosage.
Materials and methods: A systematic search has been performed across Google scholar, PubMed, and Web of Science for studies published between 2010 and 2023. Eligible studies included retrospective and prospective cohort investigations, observational investigations, and case-control investigations that reported the frequency of new-onset diabetes mellitus in adult cases without prior diabetes giving statin treatment. Data on sample size, statin types, follow-up duration, and NODM incidence were extracted and analyzed.
Results: Six investigations with a combined sample size exceeding 143,000 cases have been involved. The incidence of NODM ranged from 6.4% to 10% across studies. High-potency and high-intensity statins were correlated with a higher risk of new-onset diabetes mellitus compared to moderate-intensity statins. In one study, the adjusted hazard ratio for NODM was 2.18 (95% confidence interval, 1.10–4.51) for patients having high-intensity statins than moderate-intensity statins. However, another study found insignificant variance in the incidence of NODM among high-dose atorvastatin and rosuvastatin groups (P = 0.550).
Conclusion: Statin use, particularly at high intensity or potency, is correlated with an elevated risk of NODM. In spite of this risk, the cardiovascular benefits of statins outweigh the potential metabolic side effects for most patients. Personalized treatment strategies, including dose adjustments and regular glucose monitoring, are recommended for high-risk individuals.

Introduction

Statins, defined as 3-hydroxy-3-methyl-glutaryl coenzyme-A reductase inhibitors, are essential medications for managing dyslipidemia, a significant risk factor for cardiovascular disease **(1).** Besides their capacity to reduce serum cholesterol concentrations, various advantageous pleiotropic effects were also recognized, including enhanced stabilization of atherosclerotic plaques, anti-inflammatory properties and endothelial function with the efficacy of statins for both primary and secondary prevention of cardiovascular illness being established. **(2,3)**.

While statins are considered safe and are typically well tolerated by the majority of cases, several significant negative consequences, primarily myopathy and increased liver enzymes, can happen **(4).** A newly identified risk is the heightened occurrence of NODM correlated with statin therapy, leading the United States FDA for addition information to statin labels to include warnings about the elevated risk for NODM. **(5,6)**.

An important investigation by Culver et al. involving 153,840 females without DM revealed that baseline statin usage correlates with an elevated risk of new-onset diabetes mellitus (95% confidence interval 1.61–1.83, hazard ratio (HR) 1.71) **(7)**. The correlation between statin treatment and new-onset diabetes mellitus in cases prior to the onset of diabetes mellitus is significant **(8)**.

Several further investigations have demonstrated that the diabetogenic impact of statins is dosage-dependent, with the risk of new-onset diabetes mellitus rising at greater dosage **(9, 10).** The diabetogenic impact of statins may additionally be influenced by the period of their administration, as well as the dosage. Population-based control research has demonstrated that the probability of new-onset diabetes mellitus is elevated among new station users **(8).** An investigation by Dormuth et al. reported that a considerable probability of NODM within the first two years of treatment, with greater potency statins presenting the greatest probability during the

first four months of treatment. **(11)**.

This systematic review aimed to identify the frequency of new-onset diabetes mellitus correlated with utilization statin.

Materials and Methods

Search strategy: We carried out a thorough search on Google Scholar, Embase, PubMed, & Cochrane Library. The investigation utilized both textual terms and medical subject titles, such as statins, new-onset diabetes mellitus, cardiovascular disease, high-potency statins, and metabolic risk. In addition, we conducted a thorough search on ClinicalTrials.gov and examined the references cited in selected publications and reviews to discover more relevant observational research.

Inclusion criteria: Investigations have been involved when they met the following standards: Prospective and retrospective cohort investigations, observational studies, and case-control studies of adult patients without pre-existing diabetes at the start of statin therapy, use of any type or dose of statins, including high-intensity and moderate-intensity statin treatment, and reporting the frequency of NODM during or after statin use.

Exclusion criteria: Studies were excluded if they were reviews, meta-analyses, editorials, and case reports without original patient data; studies involving patients with pre-existing diabetes mellitus or gestational diabetes; studies without clear information on statin usage or dosage; and studies that did not report NODM incidence as an outcome measure.

Data extraction: Two researchers conducted separate assessments of the abstracts and titles of all the papers generated to determine their relevance. We thoroughly examined each trial that was discovered and decided whether to include it or not. Researchers also independently extracted the information into a standardized data extraction form. The two reviewers established a consensus on decisions about the inclusion of research and data extraction. The 3rd researcher would have the final authority to determine trial eligibility and extract data where discrepancies have been discovered.

Results:

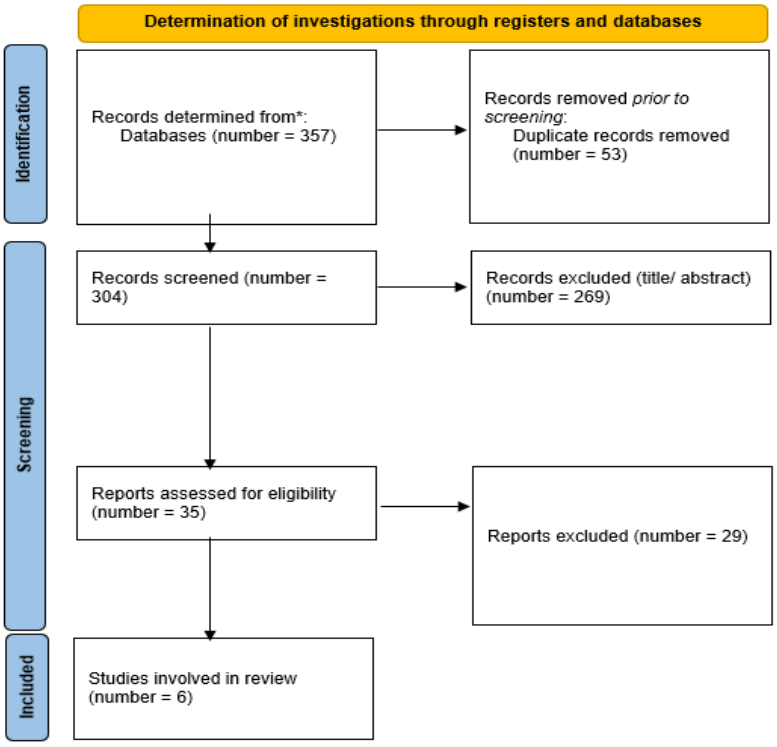

Figure (1): PRISMA flow diagram for research selection:

Table (1): Study Characteristics:

Study ID	Study year	Study design	Sample size	Age	Sex
Chung J et al., (12)	2023	Retrospective, observational, single-center study	1013	66.1±11.9 years	68.3% were men
Choi JY et al., (13)	2021	Prospective, multicenter, nationwide database study	2221	Mean age in the Atorvastatin group was 61.0 ± 12.5, and 61.0 ± 12.6 in the Rosuvastatin group.	1105 (81.9%) were men in the atorvastatin group and 720 (82.6%) in the rosuvastatin group.
Kim DW et al., (8)	2019	case–control study	38,502	51.1±13.1 years	26,050 (67.7%) males
Kato S et al., (14)	2018	Retrospective cohort study	2554	The patient mean age range was 59.8-69.2 years,	35.9%-55.9% were male
Lee J et al., (15)	2016	Retrospective cohort study	94,370	60.84 ± 11.63	Male patients represented 44.8%
Castro MR et al., (16)	2016	Observational cohort study	4460	60.12±13.60	2198 (49 %) males

Table (2): Frequency of NODM Among Statin Users: Intervention, Follow-up, and Key Findings:

Study ID	Intervention	Follow-up duration	Incidence of NODM	Key findings
Chung J et al., (12)	All research participants were administered either moderate-intensity statins (692 [68.3%]) or high-intensity statins (321 [31.7%]).	Median monitoring of 36.7 months	34 patients (6.4%)	The frequency rate of NODM was markedly elevated in cases receiving high-intensity statins compared to those on moderate-intensity statins (8.3% versus 4.5%, log-rank P-value = 0.026). The administration of high-intensity statins correlated with new-onset diabetes mellitus following the adjustment for various risk factors (adjusted hazard ratio, 2.18, P-value = 0.025, ninety-five percent CL 1.10–4.51). High-intensity statin treatment correlates with a greater frequency of new-onset diabetes mellitus. A novel intensity-based strategy for lowering cholesterol, as opposed to the traditional statin intensity-based method, can benefit high-risk cases without diabetes mellitus by maximizing therapy efficacy while mitigating the safety concerns associated with new-onset diabetes mellitus.
Choi JY et al., (13)	Cases without diabetes were given high-intensity atorvastatin (forty to eighty milligrams) and rosuvastatin (twenty milligrams).	During a three-year monitoring duration	New onset diabetes mellitus in 99 (7.5%) Atorvastatin group and 70	The event-free survival rate of NODM didn't differ significantly among the atorvastatin and rosuvastatin groups (92.5% versus 90.8%, correspondingly; log-rank P-value =

			(9.2%) in Rosuvastatin group	0.550). Multivariate Cox analysis indicated that statin type was not a prognostic determinant in the onset of new-onset diabetes mellitus. Furthermore, the giving of high-intensity atorvastatin and rosuvastatin in cases with acute MI yielded similar impacts on new-onset diabetes mellitus and clinical results, indicating their clinical equivalence in 2^{ry} prevention.
Kim DW et al., (8)	statin	for 3 years	6417 patients	The risk of NODM wasn't correlated with a rise in the total period of statin administration or with non-recent usage. Current short-term utilization of statins was correlated with an elevated risk of new-onset diabetes mellitus. Diabetes screening is necessary at the commencement of statin treatment.
Kato S et al., (14)	Statin: Cases have been categorized into high-potency and low-potency statin groups. 6 different statins have been administered as follows: atorvastatin (five or ten milligrams per day), pitavastatin (two milligrams per day), rosuvastatin (2.5 milligrams per day), fluvastatin (twenty milligrams per day), pravastatin (five or ten milligrams per day), and simvastatin (five milligrams per day).	A maximum of 5 years	The frequency rate of new-onset diabetes mellitus in the cohort was 7.4% (number = 190).	Kaplan-Meier survival curves indicated a markedly elevated incidence of new-onset diabetes mellitus in cases administered high-potency statins relative to cases receiving low-potency statins (P-value < .001, log-rank test). Baseline fasting plasma glucose concentrations, the utilization of high-potency statins, man sex, and combination therapy with immunosuppressants, ca channel blockers, or steroids have been recognized as significant risk factors for new-onset diabetes mellitus through Cox proportional hazard regression analysis. The administration of high-potency statins at a low standard daily dosage significantly elevated the probability of NOMD in cases than low-potency statins. Moreover, clinicians must exercise caution if prescribing statins alongside steroids or immunosuppressants because of the heightened risk of NOMD.
Lee J et al., (15)	Statins; Among the station users, 61.5% utilized simvastatin, 4.3% rosuvastatin, 13.8% atorvastatin, 12.6% pitavastatin, 2.9% pravastatin, & 2.7% engaged in complex treatment. 93.8% of users utilized moderate-intensity statins, while 4.0% and 2.2% utilized high- & low-intensity statins, correspondingly.	for more than one year	The frequency rates of NODM were 7.8%.	The risk of new-onset diabetes mellitus was elevated in statin users (crude hazard ratio 2.01, 95% confidence interval 1.93–2.10; adjusted hazard ratio 1.84, 95% confidence interval 1.63–2.09). Pravastatin demonstrated the least risk (adjusted hazard ratio 1.54, 95% confidence interval 1.32–1.81), whereas individuals exposed to

				multiple statins faced the greatest risk of NODM (adjusted hazard ratio 2.17, 95% CI 1.93–2.37). All statins are correlated with the risk of new-onset diabetes mellitus in cases with ischemic heart disease (IHD). Our research aims to enhance the understanding of the correlation among statins & NODM by examining statin usage in a real-world context.
Castro MR et al., (16)	33 % taking statins	The mean of six years of monitoring	1182 new diabetes diagnoses (ten percent)	The use of statins was discovered to be correlated with an elevated probability of incident diabetes in the normoglycemic group following a mean of six years of monitoring (HR 1.19; 95% confidence interval, 1.05 to 1.35; p-value = 0.007).Generally, the recommendation for the use of statins shouldn't be overly influenced by concerns regarding an elevated probability of developing diabetes, as the advantage of decreased death rates obviously outweighs this minor risk (19–24%).

Discussion

Our review found that the frequency of NODM among statin users varied from 6.4% to 10%, with high-potency and high-intensity statins showing a stronger association with NODM. For instance, **Chung J et al. (12)** demonstrated a significantly higher incidence with high-intensity statins (8.3%) compared to moderate-intensity (4.5%).

Similar to our findings, **Kato S et al. (14)** and Castro MR et al. (16) highlighted the dose-dependent impact of statins on NODM risk. Conversely, **Choi JY et al. (13)** found insignificant variance between high-intensity rosuvastatin and atorvastatin, suggesting clinical equivalence.

The association between statins and NODM may be attributed to their impact on insulin resistance and β-cell function, as previously suggested by several mechanistic studies (17, 18).

In comparison with similar prior systematic reviews and meta-analyses, it was found that **Coleman et al. (19)** carried out a meta-analysis of RCTs. The study (number = 39,791, monitoring range 2.7–6.0 years) determined that the progression of DM was insignificantly influenced by statins (95% confidence interval 0.89–1.19, risk ratio [RR] 1.03).

Additionally, **Sattar et al. (20)** carried out a meta-analysis of RCTs in which 2,226 cases who were administered statins and 2,052 cases who were administered the control therapy advanced diabetes mellitus over a mean of four years. The probability of developed diabetes mellitus was greatest in older subjects, and statin treatment resulted in a nine percent rise in the risk of incident diabetes (odds ratio [OR] 1.09, 95% CI 1.02–1.17), as demonstrated by a meta-regression.

The meta-analysis conducted by **Preiss et al. (21)** comprised five statin randomized controlled trials, which enrolled 32,752 subjects without diabetes at baseline. Of these, 2,749 advanced new-onset diabetes mellitus (moderate-dose group: number = 1,300; intensive-dose group: number = 1,449). The mean monitoring was 4.9 years (95% confidence interval 1.04–1.22; I2 = 0%, OR 1.12).

Within the meta-analysis carried out by **Cai et al. (22), 14** randomized controlled trials were involved, including 95,102 non-diabetic participants. The intensified target low-density lipoprotein-cholesterol concentrations of ≤1.8 millimole per liter & 1.8–2.59 millimole per liter have been shown to elevate the NODM risks by 33.0% (OR 1.33, 95% confidence interval 1.14–1.56; I2 = 7.7%) and 16.0% (odds ratio 1.16, 95% confidence interval 1.06–1.28; I2 = 0.0%), correspondingly. NODM wasn't correlated with an increased risk if

the target low-density lipoprotein-cholesterol concentration was qual or more than 2.59 millimole per liter (odds ratio 1.01, 95% confidence interval, 0.92–1.10; I2 = 0.0%).

The findings of this systematic review have important implications for clinical practice. While statins remain essential for reducing cardiovascular risk, clinicians should be aware of the potential for new-onset diabetes mellitus, particularly with high-potency or high-intensity statins. Careful patient selection and risk stratification are recommended, with particular attention to individuals with pre-existing metabolic risk factors. Regular monitoring of fasting glucose levels during statin therapy may help in early detection and management of hyperglycemia. Personalized treatment strategies, including considering moderate-intensity statins where appropriate, may help balance the benefits and risks associated with statin use.

Points of strength

This systematic review provides comprehensive data by including multiple studies with large sample sizes, enhancing the robustness and reliability of the results according to the correlation among the frequency of new-onset diabetes mellitus and utilization of statins. The inclusion of diverse study designs, such as retrospective and prospective cohort studies, allowed for a broader understanding of the association and strengthened the evidence base. The focus on comparing high-intensity and moderate-intensity statins adds valuable clinical insight, helping healthcare professionals tailor treatment plans based on patient risk profiles.

Limitations

In spite of its strengths, this review faces several limits. One of the primary challenges is the heterogeneity among the involved investigations, such as differences in study design, follow-up durations, and patient characteristics, which may introduce variability in the findings. Additionally, many studies didn't sufficiently control for confounding factors involved in body mass index, lifestyle behaviors, and concurrent medications, all of which can impact the development of diabetes. The review also lacked detailed information on the biological mechanisms linking statin use to NODM, limiting the ability to explain the underlying causes. Finally, the reliance on published literature can have introduced publication bias, as investigations with negative or inconclusive results might have been underrepresented.

Conclusion

This systematic review highlights a significant correlation among utilization of statins and the incidence of new-NODM, particularly with high-potency and high-intensity statins. The results recommend that statins remain essential for reducing cardiovascular disease risk; their potential metabolic side effects warrant careful consideration. Despite the observed risk of NODM, the cardiovascular benefits of statin therapy continue to outweigh these risks for most patients. Personalized treatment approaches, including dose adjustments and the use of moderate-intensity statins when appropriate, can help balance the benefits and risks. Routine glucose monitoring during statin therapy is recommended, especially for patients with predisposing metabolic factors, to facilitate early detection and management of hyperglycemia. Future research should explore the underlying mechanisms of statin-induced diabetes and investigate protective strategies to mitigate this adverse effect.

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