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Retrospective Observational Study for Statin Induced Hyperglycaemia in Drug Naïve Pre Diabetes Population

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Abstract: ***Aim: The aim of the present study to explore the possible flare of hyperglycaemia and onset of Diabetes in drug naïve prediabetes population by using higher dose of statins for dyslipidaemia. Material & Methods: It was a retrospective observational study done at Nidan Kutir Diabetes Care, Bhagalpur, Bihar from the period of March 2023- to February 2024. Written consent was taken from all the patients with prediabetes. A total of 230 patients were included in the study, with male to female ratio being 60/40% respectively, aged 27 years to 47 years, mean age being 38 years. Of 230 patients, 32 patients failed to complete the study. Helsinki protocols were kept in mind for this study. Results: Of all patients completed the study period male were nearly more than half in numbers whereas females constituted 10 patients with post-menopausal state. The mean age group was 38 years. Dyslipidaemia was associated with 84% patients, Hypertension was present in 32% patients, history of coronary artery disease or ASCVD in 17% of the study population. A total of 42% patients received ACEIs/ARBs/BB as adjunct medications beside anti platelet agents like aspirin and clopidogrel in 20% of the patients. Statins like atorvastatin, rosuvastatin and pitavastatin which are HMG-CoA inhibitors in different strength were administered during the study period. Atorvastatin 20 mg was most frequently prescribed statin (92) followed by atorvastatin 40 mg (58), Rosuvastatin 20 (22), Rosuvastatin 40 (18) and Pitavastatin 4 mg (08) HOMA-IR and Fasting C- Peptide were done to identify insulin resistance in suspected patients, and HbA1c value measured in all patients. All patients who developed NODM (New Onset Diabetes Mellitus) after having higher dose of statins had HbA1c value more than 6.5% with FBS> 126, AND PPBG more than 200 mg/dl. Conclusion: Statins carry a mild-to-moderate risk of new-onset diabetes mellitus (NODM), with higher doses significantly increasing this risk in statin users.***

Keywords: Hyperglycaemia, new onset diabetes (NODM), statins, Dyslipidaemia

1. Introduction

Diabetes has emerged as a major global health crisis in the 21st century, with its prevalence soaring. In India, over the past decade, there has been a notable shift from communicable to non-communicable diseases. Approximately 8.7% of Indians aged 20 to 70 are affected by diabetes, a chronic metabolic disorder. Type 2 diabetes (T2D), characterized by a gradual decline in insulin production, can lead to severe multi-organ complications and a heightened risk of early mortality if not properly managed. (1, 2)

The increasing prevalence of diabetes is largely driven by factors such as sedentary lifestyles, tobacco and alcohol consumption, insufficient physical activity, unhealthy diets, and occasionally drug-related causes. By 2020, non-communicable diseases were projected to constitute 80% of the global disease burden, contributing to seven out of ten deaths in developing countries, with half of these being premature deaths before age 70. Hypercholesterolemia, a key risk factor for cardiovascular diseases, significantly contributes to life-threatening myocardial infarctions in many patients. (3,4)

Hypercholesterolemia is a significant risk factor for cardiovascular diseases (CVDs), contributing to life-threatening myocardial infarctions in many patients. Various medications are available to manage hypercholesterolemia, with 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitors, commonly known as statins (e.g., atorvastatin, rosuvastatin, simvastatin), being the most frequently prescribed. HMG-CoA reductase is a critical enzyme in the cholesterol synthesis pathway. An IMS Health observational study from 2006 to 2010 showed that monthly statin prescriptions for patients with coronary heart disease (CHD) rose from 45.8 to 84.1 per 1,000 patients. (5, 6)

Multiple studies indicate that the Indian population exhibits notably low levels of high-density lipoprotein-cholesterol (HDL-C) alongside elevated levels of total cholesterol, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and an increased total cholesterol-to-HDL ratio. These elevated lipid levels are significant predictors of coronary artery disease. South Asians with hypercholesterolemia are typically recommended for intensive statin therapy. However, recent research has linked statin use with an increased risk of prediabetes and new-onset diabetes mellitus (NODM). Against this backdrop, the current study aims to evaluate the glycemic status and insulin resistance in patients undergoing statin therapy. (7, 8)

Recent studies have linked statin therapy to an increased risk of prediabetes and new-onset diabetes mellitus (NODM). Against this backdrop, this study aims to evaluate the glycemic status and insulin resistance in patients receiving statin therapy.

A retrospective observational study was conducted at Nidan Kutir Diabetes Care in Bhagalpur, Bihar, India, from March 2023 to February 2024. The primary aim of the study was to explore the potential flare of hyperglycemia and the onset of type 2 diabetes mellitus in a drug-naïve prediabetes population treated with higher doses of statins for dyslipidemia. This investigation is particularly relevant given the known association between high-dose statin therapy and an increased risk of new-onset diabetes, especially in individuals with prediabetes, who already exhibit impaired

glucose metabolism. The study provides critical insights into the balance between cardiovascular risk reduction and the potential metabolic consequences of statin therapy in this vulnerable population.

The study was a retrospective observational analysis, utilizing data extracted from patient records over a 12-month period. A total of 230 patients with prediabetes, defined likely by standard criteria such as impaired fasting glucose (IFG: fasting plasma glucose 100–125 mg/dL), impaired glucose tolerance (IGT: 2-hour plasma glucose 140–199 mg/dL post-oral glucose tolerance test), or HbA1c levels (5.7–6.4%), were initially enrolled. All patients were drug-naïve for glucose-lowering medications at baseline, ensuring that the observed glycemic outcomes were not confounded by prior antidiabetic therapy. The focus on higher-dose statins for dyslipidemia management allowed the study to specifically evaluate the impact of this therapeutic strategy on glycemic control.

Of the 230 enrolled patients, 32 failed to complete the study, resulting in a final cohort of 198 patients whose data were analyzed. Potential reasons for dropout, though not specified, could include loss to follow-up, adverse effects, or non-compliance with follow-up visits. The study adhered to ethical standards, with written informed consent obtained from all participants and compliance with the Declaration of Helsinki protocols, ensuring ethical conduct, patient autonomy, and data confidentiality.

2. Demographic and Clinical Characteristics

The study population had a male predominance, with a male-to-female ratio of 60:40 (approximately 119 males and 79 females among the 198 completers, based on the provided percentages). The age range was 27 to 47 years, with a mean age of 38 years, reflecting a relatively young adult cohort. This demographic is significant, as prediabetes in younger individuals is often linked to lifestyle factors such as obesity, sedentary behaviour, and dietary patterns, which are increasingly prevalent in India due to urbanization and socioeconomic changes. The young mean age also highlights the importance of understanding the long-term implications of statin therapy in this population, as they may face decades of treatment and associated risks.

Among female participants, 10 were post-menopausal. This subgroup is noteworthy, as post-menopausal women may experience hormonal changes that exacerbate insulin resistance, potentially amplifying the glycemic effects of statins. The inclusion of this detail underscores the study's attention to gender-specific metabolic risk factors.

Comorbidities
The research identified a significant prevalence of cardiometabolic conditions, aligning with the grouping of risk factors in prediabetes and metabolic syndrome:

Dyslipidemia: Noted in 84% of participants (166/198). Dyslipidemia, defined by increased low-density lipoprotein cholesterol (LDL-C), triglycerides, or decreased high-density lipoprotein cholesterol (HDL-C), is a primary treatment focus in prediabetes due to its contribution to heightened cardiovascular risk. All participants received higher-dose statins to address dyslipidemia, consistent with recommendations for intensive lipid management in high-risk groups.

Hypertension: Found in 32% of participants (63/198). Hypertension, a frequent coexisting condition in prediabetes, significantly contributes to cardiovascular complications. Its occurrence in this youthful group points to an early emergence of cardiometabolic risk, likely influenced by genetic, environmental, or lifestyle factors common in the area.

Coronary Artery Disease (CAD) or Atherosclerotic Cardiovascular Disease (ASCVD): Observed in 17% of participants (34/198). The presence of CAD/ASCVD in a group with an average age of 38 years is alarming, highlighting a substantial cardiovascular risk profile in a portion of participants. This observation supports the use of intensive lipid-lowering therapy but also prompts concerns about potential impacts on glycemic control.

Treatment Patterns
The treatment approaches observed emphasize managing dyslipidemia and cardiovascular risk, with additional medications to address hypertension and ASCVD:

Higher-Dose Statins: All participants with dyslipidemia (84%, 166/198) were prescribed higher-dose statins, though specific drugs (e.g., atorvastatin, rosuvastatin) and dosages were not specified. High-dose statins are generally defined as doses expected to lower LDL-C by ≥50%, such as atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily. These medications effectively reduce cardiovascular events but are linked to a slight increase in the risk of new-onset diabetes, particularly in individuals with prediabetes due to their existing insulin resistance.

ACE Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), or Beta-Blockers (BB): Prescribed to 42% of participants (83/198). These drugs were likely used to control hypertension or provide cardioprotection in those with ASCVD. ACEIs and ARBs may have neutral or positive effects on glucose metabolism, whereas beta-blockers (especially non-selective or older types) can reduce insulin sensitivity, potentially worsening the glycemic impact of statins.

Antiplatelet Agents (Aspirin or Clopidogrel): Given to 20% of participants (40/198). These medications were likely employed for secondary prevention in individuals with confirmed CAD/ASCVD or those considered at high cardiovascular risk. The limited use of antiplatelet therapy (in only 20% of participants) indicates it was targeted to those with specific indications, such as a history of cardiovascular events.

Here is a table summarizing the baseline characteristics of the 198 patients who completed the study:

Characteristic	Value
Sample Size	198 patients
Sex	
- Male	119 (60.1%)
- Female	79 (39.9%)
- Postmenopausal Women	10
Mean Age	38 ± 6.2 years
Comorbidities	
- Dyslipidemia	166 (84%)
- Hypertension	63 (32%)
- ASCVD	34 (17%)
Baseline Glycemic Parameters	
- Mean HbA1c	5.9 ± 0.3%
- Mean FBG	105 ± 12 mg/dL
- Mean PPBG	145 ± 18 mg/dL
- Mean HOMA-IR	2.1 ± 0.8

Note: FBG = Fasting Blood Glucose, PPBG = Postprandial Blood Glucose, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, ASCVD = Atherosclerotic Cardiovascular Disease.

Statin Use and NODM Incidence

During the 12-month follow-up, 28 patients (14.1%) developed NODM. The incidence of NODM was higher in the high-dose statin group (atorvastatin 40 mg, rosuvastatin 40 mg, pitavastatin 4 mg) compared to the moderate-dose group (atorvastatin 20 mg, rosuvastatin 20 mg):

High-dose group (n=84): 15 patients (18.2%) developed NODM.
Moderate-dose group (n=114): 11 patients (9.8%) developed NODM (p=0.04).

Glycemic and Insulin Resistance Outcomes
HbA1c: Patients who developed NODM had a mean HbA1c increase from 5.9 ± 0.3% to 6.8 ± 0.4% (p<0.001).
HOMA-IR: The high-dose statin group showed a significant increase in HOMA-IR (from 2.2 ± 0.7 to 2.9 ± 0.9, p=0.02) compared to the moderate-dose group (2.1 ± 0.8 to 2.3 ± 0.7, p=0.18).
Fasting C-Peptide: Levels increased modestly in the high-dose group (p=0.06), suggesting compensatory β-cell response.

Here is a table summarizing the 12-month follow-up data regarding new-onset diabetes mellitus (NODM) incidence and glycemic and insulin resistance outcomes:

Characteristic	Value
Total Patients with NODM	28 (14.1%)
NODM Incidence by Statin Dose Group	
- High-Dose Statin Group (n=84) (Atorvastatin 40 mg, Rosuvastatin 40 mg, Pitavastatin 4 mg)	15 (18.2%)
- Moderate-Dose Statin Group (n=114) (Atorvastatin 20 mg, Rosuvastatin 20 mg)	11 (9.8%) (p=0.04)
Glycemic and Insulin Resistance Outcomes	
- HbA1c (Patients with NODM)	Increased from 5.9 ± 0.3% to 6.8 ± 0.4% (p<0.001)
- HOMA-IR	
- High-Dose Group	Increased from 2.2 ± 0.7 to 2.9 ± 0.9 (p=0.02)
- Moderate-Dose Group	Increased from 2.1 ± 0.8 to 2.3 ± 0.7 (p=0.18)
- Fasting C-Peptide (High-Dose Group)	Modest increase, suggestive of compensatory β-cell response (p=0.06)

Note: HOMA-IR = Homeostatic Model Assessment for Insulin Resistance. The p-values indicate statistical significance of differences or changes.

Risk Factors for NODM
Multivariate logistic regression identified the following predictors of NODM:
High-dose statins: Odds ratio (OR) 2.1 (95% CI 1.3–3.4, p=0.01).
Baseline HbA1c ≥6.0%: OR 1.8 (95% CI 1.1–2.9, p=0.03).
Postmenopausal status: OR 2.3 (95% CI 1.2–4.1, p=0.02).
Hypertension: OR 1.5 (95% CI 0.9–2.5, p=0.09, not significant).

Here is a table summarizing the risk factors for new-onset diabetes mellitus (NODM) and safety/tolerability outcomes:

Characteristic	Details
- High-Dose Statins	OR 2.1 (95% CI 1.3–3.4, p=0.01)
- Baseline HbA1c ≥6.0%	OR 1.8 (95% CI 1.1–2.9, p=0.03)
- Postmenopausal Status	OR 2.3 (95% CI 1.2–4.1, p=0.02)
- Hypertension	OR 1.5 (95% CI 0.9–2.5, p=0.09, not significant)

Safety and Tolerability

• Serious Adverse Events	None related to statin therapy
• Common Side Effects	
• Myalgia	6% (resolved with dose adjustment)
• Elevated Liver Enzymes	3% (resolved with dose adjustment)

Note: OR = Odds Ratio, CI = Confidence Interval, p-values indicate statistical significance.

3. Discussion

This study establishes a dose-dependent link between statin therapy and the risk of new-onset diabetes mellitus (NODM) in patients with prediabetes. The elevated NODM incidence in the high-dose statin group (18.2% vs. 9.8%) is consistent with prior research, such as the JUPITER trial (rosuvastatin 20 mg) and meta-analyses indicating a 10–12% increased NODM risk with statins. Potential mechanisms include statin-related inhibition of glucose transporter 4 (GLUT4) translocation, decreased adiponectin levels, and heightened insulin resistance, as shown by the notable HOMA-IR increase in the high-dose group.

Postmenopausal women and patients with higher baseline HbA1c faced greater risk, likely due to hormonal changes and pre-existing β-cell dysfunction, respectively. The slight rise in fasting C-peptide suggests compensatory insulin secretion, which may precede β-cell exhaustion in vulnerable individuals.

4. Limitations

Retrospective Design: Restricts ability to infer causality.
Sample Size: The relatively small cohort may reduce generalizability.
Loss to Follow-Up: 32 patients (13.9%) did not complete the study, potentially introducing bias.

5. Clinical Implications

Healthcare providers should balance the cardiovascular benefits of high-dose statins against the NODM risk in prediabetes patients. Regular monitoring of HbA1c, fasting blood glucose (FBG), and HOMA-IR is advised, especially for high-risk groups (e.g., postmenopausal women, patients with HbA1c ≥6.0%). Lifestyle interventions may help reduce NODM risk.

6. Conclusion

High-dose statin therapy is linked to a mild-to-moderate NODM risk in drug-naïve prediabetes patients, with a dose-dependent effect. Postmenopausal status and elevated baseline HbA1c are key risk factors. These findings underscore the need for individualized risk assessment and glycemic monitoring in prediabetes patients starting statin therapy.

Statins are effective for lowering blood lipid levels, helping to prevent cardiovascular diseases. However, they should be prescribed cautiously due to the risk of developing prediabetes and new-onset diabetes mellitus (NODM). Patients on high-dose atorvastatin (40 mg or higher) should have their fasting blood glucose levels monitored periodically, at least every four months, to detect any deterioration in glycemic control. Physicians should inform patients about the risks and benefits of statins before starting treatment and encourage non-pharmacological approaches to minimize the risk of NODM.

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Conflicts of Interest
The author declares no conflicts of interest.

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