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Original Research Article

Assessment of Insulin Resistance and Glycemic Changes among Hypercholesterolemic Patients Receiving Atorvastatin: A Retrospective Observational Study

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Abstract:

Background: Statins, particularly atorvastatin, are among the most prescribed lipid-lowering agents worldwide. While their cardiovascular benefits are well-established, growing evidence suggests that long-term atorvastatin use may adversely alter glycemic homeostasis, potentially accelerating the onset of new-onset diabetes mellitus (NODM) or worsening pre-existing glucose intolerance. Despite this pharmacological concern, data from tertiary care settings in India remain limited. Objectives: This study aimed to evaluate glycemic status, including fasting blood glucose (FBG), postprandial blood glucose (PPBG), glycated haemoglobin (HbA1c), and insulin resistance indices, among hypercholesterolemic patients receiving atorvastatin therapy in a tertiary care hospital.

Materials and Methods: A retrospective record-based study was conducted over 12 months at a tertiary care hospital. Medical records of 182 adult hypercholesterolemic patients on atorvastatin (10 mg to 40 mg daily) without baseline diabetes were analysed. Glycemic parameters were recorded at baseline, 6 months, and 12 months. Data were analysed using SPSS version 22.0 and statistical significance was set at $p < 0.05$.

Results: The mean age of patients was 51.4 ± 10.7 years with a male predominance (53.8%). Statistically significant increases in FBG (96.4 to 107.3 mg/dL), PPBG (128.7 to 143.5 mg/dL), HbA1c (5.3% to 5.9%), and HOMA-IR (1.94 to 2.73) were observed over 12 months ($p < 0.05$). New-onset diabetes was detected in 14 patients (7.7%) at 12 months, with higher incidence in those receiving 40 mg atorvastatin (10.9%) compared to 10–20 mg (4.4%). Impaired fasting glucose increased from 20.9% at baseline to 39.6% at 12 months.

Conclusion: Atorvastatin therapy is associated with progressive and dose-dependent worsening of glycemic parameters in hypercholesterolemic patients. Routine glycemic surveillance should be mandated in all patients receiving atorvastatin therapy, particularly those on higher doses or with pre-existing metabolic risk factors.

Keywords: Atorvastatin, Hypercholesterolemia, Glycemic status, New-onset diabetes mellitus, Fasting blood glucose, HbA1c.

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Introduction

Cardiovascular disease (CVD) remains one of the foremost causes of mortality across the globe. Among the modifiable risk factors for CVD, hypercholesterolaemia — particularly elevated low-density lipoprotein cholesterol (LDL-C) — occupies a central role in the pathogenesis of atherosclerosis. Statins, which are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are the cornerstone of pharmacological therapy for dyslipidaemia and have been shown to markedly reduce the risk of major adverse cardiovascular events. Atorvastatin, a synthetic, high-potency statin, is one of the most widely prescribed drugs globally due to its demonstrated efficacy in reducing LDL-C levels and cardiovascular event rates in both primary and secondary prevention settings. It is available in doses ranging from 10 mg to 80 mg, with higher doses providing greater lipid-lowering effects.

Despite their well-established cardiovascular benefits, statins have come under clinical scrutiny over the past decade for their potential diabetogenic effects. Several large-scale randomised controlled trials and meta-analyses have reported a modest but statistically significant increase in the risk of new-onset diabetes mellitus (NODM) among statin users. [1] The United States Food and Drug Administration (FDA) added a safety label revision to all statin drugs in 2012, indicating that increases in fasting blood glucose (FBG) and glycated haemoglobin (HbA1c) have been associated with statin use. [2] This raised significant concerns among clinicians managing hypercholesterolaemic patients who often present with pre-existing metabolic risk factors

including obesity, hypertension, and impaired fasting glucose.

The risk of statin-induced glycaemic alterations appears to be class-specific and dose-dependent. High-intensity statins such as atorvastatin 80 mg and rosuvastatin 20 mg have been associated with a higher excess risk of new-onset diabetes compared to moderate-intensity statins. [3] A network meta-analysis reported that high-dose atorvastatin increased the odds of developing diabetes even when compared with pravastatin, simvastatin, and low-dose atorvastatin. [4] Mechanistically, statins are believed to impair insulin sensitivity and compromise pancreatic β-cell secretory capacity, possibly through the inhibition of intracellular cholesterol synthesis and downstream effects on Ca^{2+} signalling, GLUT-4 downregulation, and altered adipocyte differentiation. [5]

Epidemiological data from large observational studies corroborate these findings. A retrospective cohort study using data from over 53,000 patients demonstrated that statin use was associated with a hazard ratio of 2.01 (99% CI: 1.74–2.33) for incident diabetes compared to non-users. [6] Similarly, a meta-analysis of 20 observational studies confirmed a pooled relative risk of 1.44 (95% CI: 1.31–1.58) for NODM among statin users versus non-users, reinforcing the existence of a class effect. [7] In the landmark METSIM observational study involving more than 8,000 men, simvastatin and atorvastatin were associated with dose-dependent increases in post-glucose load glycaemia, a mean decrease in insulin sensitivity by 24%, and a decline in insulin secretion by 12%. [8]

Despite this growing body of evidence, there remains a paucity of Indian hospital-based retrospective data specifically examining the glycaemic consequences of atorvastatin use among hypercholesterolaemic patients. Most existing studies are from Western populations and may not be directly applicable to Indian patients, who have inherently higher susceptibility to type 2 diabetes mellitus and insulin resistance due to genetic and lifestyle factors. Moreover, the majority of studies focus on mixed statin classes rather than atorvastatin specifically. There is, therefore, a compelling clinical need for hospital-based, patient-centric data from tertiary care centres in India to understand the magnitude and trajectory of glycaemic changes in this population.

In this context, the present retrospective study was designed to evaluate the glycaemic status of hypercholesterolaemic patients receiving atorvastatin therapy over a 12-month period at a tertiary care hospital. The study assessed changes in fasting blood glucose, postprandial blood glucose, HbA1c, and indices of insulin resistance (HOMA-IR) at baseline, 6 months, and 12 months of treatment. The findings are expected to provide clinically meaningful insights that can guide glycaemic monitoring protocols for patients initiated on atorvastatin therapy.

Materials and Methods

Study Design and Setting: This was a hospital-based, retrospective observational study conducted in the Department of Pharmacology and Medicine at a tertiary care teaching hospital. Medical records spanning a 12-month study period were retrieved and reviewed. The study was conducted following approval from the Institutional Ethics Committee (IEC) and adhered to the principles of the Declaration of Helsinki.

Inclusion Criteria: Adult patients (≥18 years) diagnosed with hypercholesterolaemia (total cholesterol ≥200 mg/dL or LDL-C ≥130 mg/dL), prescribed atorvastatin (10 mg, 20 mg, or 40 mg per day) for at least 12 months, and without a pre-existing diagnosis of diabetes mellitus at baseline (FBG <100 mg/dL and HbA1c <5.7%) were included in the study.

Exclusion Criteria: Patients with a history of type 1 or type 2 diabetes, those on insulin or oral hypoglycaemic agents, patients with secondary dyslipidaemia (hypothyroidism, nephrotic syndrome), hepatic or renal impairment, missing or incomplete laboratory records, and those on concurrent medications known to alter glycaemic status (corticosteroids, antipsychotics) were excluded.

Data Collection: Retrospective data were extracted from electronic health records and physical case files. The following data were collected: sociodemographic profile (age, sex, BMI), clinical details (blood pressure, duration of hypercholesterolaemia, concomitant conditions), lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides), and glycaemic parameters — fasting blood glucose (FBG), postprandial blood glucose (PPBG), HbA1c, fasting serum insulin, and HOMA-IR — recorded at baseline, 6 months, and 12 months of atorvastatin therapy. Atorvastatin dose was categorised as low-to-moderate intensity (10–20 mg/day) and moderate-to-high intensity (40 mg/day).

Outcome Measures: The primary outcome was change in glycaemic parameters (FBG, PPBG, HbA1c, HOMA-IR) from baseline to 12 months. The secondary outcome was the incidence of new-onset diabetes mellitus (NODM), defined as FBG ≥126 mg/dL on two separate occasions, HbA1c ≥6.5%, or initiation of antidiabetic treatment during the study period.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using SPSS version 22.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Paired t-test was used to compare glycaemic

parameters at baseline, 6 months, and 12 months within the same group. Chi-square test was used for comparison of categorical variables between groups. Differences were considered statistically significant at $p < 0.05$.

Results

A total of 182 patients satisfied the inclusion criteria and were included in this analysis. The age distribution is depicted in Figure 1. The majority of patients belonged to the 51–60 year age group (n=58, 31.9%), followed by the 41–50 year age group (n=45, 24.7%). Only 8 patients (4.4%) were in the younger 21–30 year cohort, while 12 patients (6.6%) were aged above 70 years. This distribution suggests a preponderance of middle-aged and older adults among hypercholesterolaemic patients seeking care at the tertiary centre, which is consistent with the known epidemiology of dyslipidaemia.

Table 1 presents the baseline demographic and clinical characteristics of the 182 enrolled patients. A total of 98 patients (53.8%) were male and 84 (46.2%) were female. The overall mean age was 51.4 ± 10.7 years. Hypertension was the most common comorbidity, present in 74 patients (40.7%). Obesity (BMI ≥30 kg/m²) was recorded in 61 patients (33.5%). Smoking was significantly more prevalent in males (36.7% vs 14.3%; p=0.001). The mean baseline LDL-C was 178.3 ± 29.5 mg/dL and mean total cholesterol was 241.6 ± 34.2 mg/dL, confirming a hypercholesterolaemic cohort at baseline.

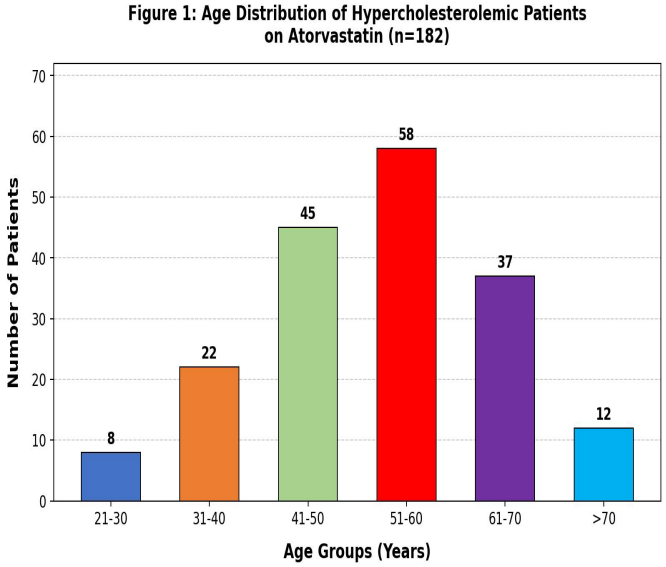

Figure 1: Age Distribution of Hypercholesterolemic Patients on Atorvastatin (n=182)

Table 1: Demographic and Baseline Clinical Characteristics of Study Patients (n=182)

Parameter	n (%)	Male n (%)	Female n (%)	p-value
Total Patients	182 (100)	98 (53.8)	84 (46.2)	-
Mean Age (years ± SD)	51.4 ± 10.7	52.1 ± 11.3	50.6 ± 10.0	0.38
Hypertension	74 (40.7)	42 (42.9)	32 (38.1)	0.51
Obesity (BMI ≥ 30)	61 (33.5)	31 (31.6)	30 (35.7)	0.56
Smoking	48 (26.4)	36 (36.7)	12 (14.3)	0.001
Family History of DM	55 (30.2)	28 (28.6)	27 (32.1)	0.61
Mean LDL-C (mg/dL ± SD)	178.3 ± 29.5	181.2 ± 30.4	175.1 ± 28.3	0.14
Mean Total Cholesterol (mg/dL ± SD)	241.6 ± 34.2	244.0 ± 35.1	238.8 ± 33.0	0.29

Table 2: Changes in Glycemic Parameters at Baseline, 6 Months, and 12 Months of Atorvastatin Therapy

Glycemic Parameter	Baseline (Mean ± SD)	After 6 Months (Mean ± SD)	After 12 Months (Mean ± SD)	p-value
FBG (mg/dL)	96.4 ± 10.2	101.8 ± 11.7	107.3 ± 13.4	0.003
PPBG (mg/dL)	128.7 ± 18.4	136.9 ± 19.8	143.5 ± 21.2	0.002
HbA1c (%)	5.3 ± 0.6	5.6 ± 0.7	5.9 ± 0.8	0.001
Fasting Insulin (µIU/mL)	8.1 ± 2.4	9.3 ± 2.7	10.2 ± 3.1	0.009
HOMA-IR	1.94 ± 0.58	2.37 ± 0.61	2.73 ± 0.74	0.004

Table 2 summarises the trend in key glycaemic parameters across the three time points. All glycaemic indices showed a progressive and statistically significant rise over the study period. Mean FBG increased from 96.4 ± 10.2 mg/dL at baseline to 107.3 ± 13.4 mg/dL at 12 months (p=0.003). Similarly, HbA1c rose from 5.3 ± 0.6% to 5.9 ± 0.8% (p=0.001) and HOMA-IR from 1.94 ± 0.58 to 2.73 ± 0.74 (p=0.004). These findings collectively indicate a meaningful deterioration in glycaemic homeostasis over the 12-month treatment period, with even moderate-dose atorvastatin producing measurable metabolic changes.

Table 3 classifies patients by glycaemic category at each time point. At baseline, 142 patients (78.0%) were normoglycaemic; this proportion declined to 52.7% at 12 months. The proportion with impaired fasting glucose (IFG) rose sharply from 20.9% to 39.6% over the same period. New-onset diabetes was identified in 14 patients (7.7%) by the end of 12 months. A dose-dependent pattern was evident: patients on atorvastatin 40 mg had a higher rate of NODM (10.9%) compared to those on 10–20 mg (4.4%), suggesting that the diabetogenic risk is intensity-dependent and necessitates dose-stratified monitoring strategies.

Table 3: Classification of Glycemic Outcomes and New-Onset Diabetes at Baseline, 6 Months, and 12 Months

Glycemic Category	Baseline n (%)	6 Months n (%)	12 Months n (%)	p-value
Normoglycemia (FBG <100 mg/dL)	142 (78.0)	118 (64.8)	96 (52.7)	0.001
Impaired Fasting Glucose (100–125 mg/dL)	38 (20.9)	57 (31.3)	72 (39.6)	0.001
New-Onset Diabetes (FBG ≥126 mg/dL)	2 (1.1)	7 (3.8)	14 (7.7)	0.003
HbA1c ≥ 6.5% (Diabetic Range)	0 (0)	4 (2.2)	11 (6.0)	0.002
Dose: 40 mg – New-Onset DM	—	5/92 (5.4)	10/92 (10.9)	0.04
Dose: 10–20 mg – New-Onset DM	—	2/90 (2.2)	4/90 (4.4)	0.21

Discussion

The present retrospective study evaluated the glycaemic impact of atorvastatin therapy over 12 months in 182 hypercholesterolaemic patients without baseline diabetes. The key findings demonstrate a progressive, statistically significant elevation in fasting blood glucose, postprandial blood glucose, HbA1c, and HOMA-IR across the study period, culminating in a new-onset diabetes rate of 7.7% by 12 months. These results are consistent with and add to the growing body of evidence linking atorvastatin use to adverse glycaemic outcomes, particularly in metabolically susceptible individuals.

Several landmark trials and meta-analyses have documented the diabetogenic potential of statins as a class. In the JUPITER trial, rosuvastatin was associated with a 26% increase in physician-reported incident diabetes compared to placebo. [9] Similarly, a meta-analysis by Sattar et al., encompassing 13 statin trials and over 91,000 participants, reported a 9% increase in incident diabetes associated with statin use, with higher-potency statins carrying greater risk. [10] Our findings further corroborate these observations with atorvastatin demonstrating a clear dose-response relationship: NODM was documented in 10.9% of patients receiving 40 mg compared to only 4.4% in those receiving 10–20 mg, a pattern consistent with prior pharmacoepidemiological evidence. [11]

The mechanistic basis for atorvastatin-induced glycaemic dysregulation is multifactorial. Statins are known to inhibit the mevalonate pathway, thereby reducing intracellular cholesterol synthesis. This, in turn, affects pancreatic β-cell membrane integrity and impairs calcium-mediated insulin exocytosis. [12] Additionally, downregulation of GLUT-4 glucose transporter expression in adipocytes contributes to peripheral insulin resistance, reflected in the significantly elevated HOMA-IR values observed in our cohort. A retrospective cohort study using data from 53,212 statin users reported a hazard ratio of 2.01 for incident diabetes compared to non-users, with atorvastatin ranking among the highest-risk agents. [13] These mechanistic and epidemiological findings align with the pattern of glycaemic deterioration observed in our study.

The association between statins and worsening glycaemic control in patients with pre-existing risk factors is particularly concerning. In our cohort, 40.7% of patients had hypertension, 33.5% had obesity, and 30.2% had a family history of diabetes — all established risk factors for the metabolic progression of impaired fasting glucose to frank diabetes. [14] A study by Zaharan et al., which reviewed medical records from a primary care setting, demonstrated that statin users had significantly higher HbA1c values compared to non-users even after adjustment for confounders, with differences persisting among those with known diabetes. [15,16] This is echoed in our finding that IFG prevalence more than doubled from baseline (20.9%) to 12 months (39.6%).

Importantly, the cardiovascular benefits of atorvastatin must not be overshadowed by its metabolic risk profile. Clinical guidelines continue to recommend high-intensity statins for patients with established

CVD and high-risk primary prevention populations, given the substantial reduction in major adverse cardiovascular events. The clinical imperative, therefore, is not to discontinue statin therapy but to integrate systematic glycaemic monitoring into the management framework for all patients initiated on atorvastatin. Regular assessment of FBG, postprandial glucose, and HbA1c — particularly at 6-month intervals — and lifestyle counselling should be considered mandatory components of care. [17,18]

The findings of this study carry important implications for pharmacovigilance and clinical pharmacy practice in tertiary care hospitals in India. Given the high prevalence of pre-diabetic states in the Indian population and the wide-scale prescription of atorvastatin for dyslipidaemia, the absolute risk of atorvastatin-related NODM in this setting may be higher than in Western populations. Clinicians should exercise heightened vigilance in patients aged above 50 years, those with obesity, hypertension, or a family history of diabetes, and those receiving atorvastatin 40 mg or above. In such patients, consideration should be given to using a less diabetogenic statin such as pravastatin or pitavastatin when cardiovascular risk management goals can still be achieved.

This study has several limitations inherent to its retrospective design. Firstly, data depended on the accuracy of existing medical records, which may have incomplete documentation of confounding variables such as dietary habits, physical activity, and concurrent medications. Secondly, the study was conducted at a single tertiary care centre, limiting the generalisability of findings to broader populations. Thirdly, the absence of a non-atorvastatin control group precludes causal inference. Fourthly, genetic polymorphisms influencing statin metabolism and glycaemic susceptibility were not assessed. Finally, medication adherence and actual drug consumption levels could not be verified, potentially introducing misclassification bias.

Conclusion

This retrospective study demonstrates that atorvastatin therapy is associated with a clinically significant and dose-dependent deterioration in glycaemic parameters over 12 months in hypercholesterolaemic patients. Fasting blood glucose, postprandial glucose, HbA1c, and insulin resistance indices all showed progressive increases, with new-onset diabetes observed in 7.7% of patients. These findings underline the critical importance of routine glycaemic monitoring in all patients receiving atorvastatin, particularly those at higher metabolic risk. A multidisciplinary approach integrating pharmacological management, lifestyle modification, and periodic glycaemic surveillance is essential to ensure safe and effective statin therapy.

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