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ORIGINAL RESEARCH

To study the impact of Atorvastatin on glycemic parameters in individuals with normal blood sugar levels and those with prediabetes

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ABSTRACT

Aim: To study the impact of Atorvastatin on glycemic parameters in individuals with normal blood sugar levels and those with prediabetes. **Materials and Methods:** 150 participants were consecutively recruited according to their glycemic status until 50 participants were included in each group:Group A (50 participants): Normoglycemic with normal baseline blood glucose levels.Group B (50 participants): Impaired fasting glucose (IFG) with normal glucose tolerance test (GTT); baseline fasting blood glucose levels between 100-125 mg/dL.Group C (50 participants): Impaired glucose tolerance (IGT); baseline 2-hour post-glucose blood sugar levels between 140-199 mg/dL.HbA1c levels were determined using the ion-exchange HPLC method.Serum glucose levels were measured using the glucose oxidase-peroxidase method in an autoanalyzer.Following a 75g glucose load in 150 ml of water, blood samples were drawn 2 hours later. The blood sample was collected in a sodium fluoride tube, promptly centrifuged, and the plasma was frozen until glucose measurement.Lipid levels were measured using routine enzymatic methods following the protocols of the Lipid Research Clinics. **Results:** The consistent p-value of <0.001 across all timepoints indicates that these changes were statistically significant, suggesting that higher doses of Atorvastatin might be associated with a greater increase in HbA1c, particularly in participants with pre-existing glucose intolerance.The p-values remained <0.001 across all timepoints, indicating that the increases in FBG were statistically significant, particularly with higher doses of Atorvastatin. This suggests a dose-dependent relationship between Atorvastatin and worsening glycemic control over time. The lipid-lowering efficacy of Atorvastatin, particularly at higher doses, which are associated with greater reductions in Total Cholesterol, LDL-C, and Triglycerides, and a modest increase in HDL-C.The regression analysis presented in this table assesses the relationship between Atorvastatin dose and changes in HbA1c levels. The regression coefficient (β) of -0.034 indicates a statistically significant inverse relationship between Atorvastatin dose and HbA1c change (p=0.002). **Conclusion:** The study's findings highlight the dual effects of Atorvastatin on lipid and glycemic control. While higher doses of Atorvastatin are more effective in lowering lipid parameters, they are also associated with a greater increase in HbA1c and fasting blood glucose levels, particularly in individuals with impaired glucose metabolism.

Keywords: Atorvastatin, glycemic parameters, Normal blood sugar, prediabetes

INTRODUCTION

Atorvastatin, a widely prescribed statin, is primarily used to manage hyperlipidemia and reduce cardiovascular events. It functions by inhibiting HMG-CoA reductase, an enzyme crucial for cholesterol synthesis in the liver. While its benefits in lowering LDL cholesterol and reducing cardiovascular risk are well-established, recent studies have highlighted potential adverse effects on glycemic control, particularly in individuals with pre-existing glucose intolerance or diabetes.[1]Glycemic control is a critical component in managing patients with diabetes and prediabetes. The progression from normoglycemia to prediabetes and eventually to diabetes is a complex process influenced by various metabolic and lifestyle factors. Prediabetes, characterized by elevated blood glucose levels that are not high enough to qualify as diabetes, poses a significant risk for the development of type 2 diabetes. Managing these intermediate states effectively is crucial for preventing the progression to diabetes and associated complications.[2]The impact of statins on glucose metabolism and diabetes risk has garnered attention due to the widespread use of these

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medications. Statins, including atorvastatin, have been shown to have a dose-dependent effect on glucose levels. The relationship between statin use and increased risk of new-onset diabetes is a topic of ongoing research. While statins are effective in reducing cardiovascular events, the potential for these drugs to exacerbate or induce glucose dysregulation raises important questions about their use in different patient populations.[3]Understanding the effects of atorvastatin on glycemic parameters in both normoglycemic and prediabetic subjects is essential for optimizing patient management strategies. Normoglycemic individuals, who maintain normal blood glucose levels, and prediabetic individuals, who have impaired glucose tolerance but not yet diabetes, represent two distinct populations with differing risks and needs. Evaluating how atorvastatin influences glucose levels and the risk of progression from prediabetes to diabetes in these groups can provide valuable insights into the overall impact of statin therapy on metabolic health.[4]

Several mechanisms have been proposed to explain the potential link between statin use and impaired glucose metabolism. Statins may affect glucose homeostasis through various pathways, including alterations in insulin sensitivity, beta-cell function, and changes in glucose production. Statin-induced changes in muscle and liver metabolism could also contribute to increased blood glucose levels. The net effect of these mechanisms could lead to an increase in HbA1c levels and fasting blood glucose, potentially exacerbating glucose intolerance in susceptible individuals.[5]The evidence regarding the impact of atorvastatin on glycemic control is mixed. Some studies suggest that statin use is associated with a modest increase in HbA1c and fasting blood glucose levels. In contrast, other research indicates that the increase in glucose levels is relatively small and may not outweigh the cardiovascular benefits provided by statin therapy. The variability in study outcomes can be attributed to differences in study design, patient populations, and atorvastatin dosing regimens.[6]Given the potential for atorvastatin to affect glycemic control, it is important to carefully monitor glucose levels in patients receiving high-dose statin therapy. This is particularly relevant for individuals with prediabetes, who are at a higher risk of developing type 2 diabetes. Balancing the benefits of atorvastatin in reducing cardiovascular risk with the potential risk of worsening glucose control requires a nuanced approach. Clinicians must consider individual patient characteristics, including baseline glycemic status, when prescribing statins and adjusting treatment plans.[7]Furthermore, the dose-dependent effects of atorvastatin on glucose metabolism warrant attention. Higher doses of atorvastatin may be associated with a greater impact on glycemic parameters, which could have implications for managing patients with prediabetes or those at high risk for diabetes. Understanding how different doses of atorvastatin influence glycemic control can inform dosing strategies and help mitigate potential adverse effects.[8]Research into the effects of atorvastatin on glycemic parameters in normoglycemic and prediabetic subjects is crucial for providing evidence-based recommendations for clinical practice. Investigating how atorvastatin affects glucose levels, both in individuals with normal glucose metabolism and those with prediabetes, can offer insights into the drug's overall impact on metabolic health. Such research can also help identify strategies for managing the potential risks associated with statin therapy, ensuring that patients receive optimal care while minimizing adverse outcomes.[9,10]

MATERIALS AND METHODS

This study is an observational, prospective panel study conducted to evaluate the effects of Atorvastatin on glycemic control among different groups of patients. The study population included subjects aged 18 to 70 years, of both genders, who had been on Atorvastatin for one month or less for dyslipidemia or the primary/secondary prevention of cardiovascular disease.

Inclusion and Exclusion Criteria

Participants included in the study were either normoglycemic or prediabetic and had voluntarily agreed to participate by signing an informed consent form. The diagnosis of diabetes mellitus and prediabetes was made according to the American Diabetes Association (ADA) guidelines. Prediabetes was defined as having a fasting plasma glucose (FPG) level of 100-125 mg/dL (5.6-6.9 mmol/L) for Impaired Fasting Glucose (IFG), a 2-hour plasma glucose level of 140-199 mg/dL (7.8-11.0 mmol/L) in the 75g Oral Glucose Tolerance Test (OGTT) for Impaired Glucose Tolerance (IGT), or an HbA1c level between 5.7% and 6.4%.

Patients who were diagnosed with diabetes mellitus (both type 1 and 2) and were on different anti-diabetic regimens, as well as those on β-blockers, thiazide diuretics, or corticosteroids, were excluded from the study. Pregnant and lactating women, along with patients with co-existing cardiovascular, renal, or hepatic diseases, were also excluded.The study was approved by the Institute Ethics Committee. Written informed consent was obtained from all participants after explaining the nature and purpose of the study, potential risks and benefits, alternative treatments, and the specific use of Atorvastatin.

Methodology

The study was conducted at the Outpatient Departments of Cardiology and Medicine, where 150 subjects were screened and recruited based on the inclusion and exclusion criteria. Subjects were consecutively recruited according to their glycemic status until 50 participants were included in each group:

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- **Group A (50 participants)**: Normoglycemic with normal baseline blood glucose levels.
- **Group B (50 participants)**: Impaired fasting glucose (IFG) with normal glucose tolerance test (GTT); baseline fasting blood glucose levels between 100-125 mg/dL.
- **Group C (50 participants)**: Impaired glucose tolerance (IGT); baseline 2-hour post-glucose blood sugar levels between 140-199 mg/dL.

At baseline, demographic and clinical data were collected for all participants. As all subjects were on Atorvastatin therapy, Alanine Aminotransferase (ALT) levels were measured to exclude existing hepatotoxicity. Non-directive questions were asked to identify any other side effects related to Atorvastatin. Participants were on varying doses of Atorvastatin: 10-20 mg/day (low dose) or 40-80 mg/day (high dose).All subjects were followed up at 4, 8, and 12 months. At each follow-up visit, glycemic parameters were evaluated, and adherence to statin therapy and dosing schedules were assessed. Progression from prediabetes to diabetes was considered the study endpoint.During follow-up visits, participants were asked non-directive questions to detect any adverse effects. They were also instructed to report any adverse effects to the investigators. If any symptoms of myopathy or hepatotoxicity were reported, ALT and creatine kinase tests were performed.

Primary Outcome Measures:

- **Glycosylated Hemoglobin (HbA1c%)**: HbA1c levels were determined using the ion-exchange HPLC method.
- **Fasting Blood Glucose**: Serum glucose levels were measured using the glucose oxidase-peroxidase method in an autoanalyzer.
- **Two-Hour Post-Prandial Blood Glucose**: Following a 75g glucose load in 150 ml of water, blood samples were drawn 2 hours later. The blood sample was collected in a sodium fluoride tube, promptly centrifuged, and the plasma was frozen until glucose measurement.

Secondary Outcome Measures:

- **Lipid Profile**: Lipid levels were measured using routine enzymatic methods following the protocols of the Lipid Research Clinics.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). A significance level of $p < 0.05$ (two-tailed) was set for all statistical tests. Baseline demographic and clinical variables between groups were compared using one-way ANOVA followed by the Tukey-Kramer multiple comparison post-test and the chi-square test. Changes in parameters over time were analyzed using repeated measures analysis of variance (RM-ANOVA) followed by Dunnett's multiple comparison post-test. Sphericity was assessed using Mauchly's test, and corrections were made using Huynh-Feldt or Greenhouse-Geisser methods as appropriate. Sub-group analysis was conducted based on the Atorvastatin dose (10-20 mg for the low-dose group and 40-80 mg for the high-dose group), and regression analysis was performed with Atorvastatin dose as the independent variable and change in HbA1c% as the dependent variable.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics

The baseline characteristics of the participants in the study were evaluated across three groups: Normoglycemic (Group A), Impaired Fasting Glucose (IFG, Group B), and Impaired Glucose Tolerance (IGT, Group C). The average age of participants was similar across all groups (Group A: 52.3 years, Group B: 54.1 years, Group C: 53.4 years), with no significant difference observed ($p=0.674$). Gender distribution was also comparable, with a slight male predominance in all groups, but this difference was not statistically significant ($p=0.910$). The Body Mass Index (BMI) of participants was marginally higher in Group B and Group C compared to Group A, but these differences were not statistically significant ($p=0.384$). However, significant differences were observed in fasting blood glucose levels and HbA1c percentages across the groups, with Group B and Group C showing higher values compared to Group A ($p<0.001$ for both parameters), indicating worse glycemic control in the IFG and IGT groups. The liver enzyme ALT showed no significant differences across the groups ($p=0.749$), suggesting that hepatic function was similar among participants at baseline.

Table 2: Changes in HbA1c (%)

At baseline, Group A (Normoglycemic) had the lowest HbA1c values, while Groups B (IFG) and C (IGT) had progressively higher values, consistent with their glycemic status. Over the 12-month period, both low-dose and high-dose groups showed a gradual increase in HbA1c levels across all groups. However, the increase was more pronounced in the high-dose Atorvastatin group. For example, in Group C (IGT), the HbA1c rose from $5.9 \pm 0.6\%$ at baseline to $6.5 \pm 0.8\%$ at 12 months in the high-dose group, compared to $6.3 \pm 0.8\%$ in the low-dose group. The consistent p-value of <0.001 across all timepoints indicates that these changes were statistically significant, suggesting that higher doses of Atorvastatin might be associated with a greater increase in HbA1c, particularly in participants with pre-existing glucose intolerance.

Table 3: Changes in Fasting Blood Glucose (mg/dL)

The changes in fasting blood glucose (FBG) are presented for low-dose and high-dose Atorvastatin groups across the three participant groups. At baseline, Group A (Normoglycemic) had the lowest FBG levels, while Groups B (IFG) and C (IGT) exhibited higher levels. Similar to the HbA1c findings, FBG levels increased over time in all

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groups, with the increase being more pronounced in the high-dose Atorvastatin group. For instance, in Group C (IGT), FBG increased from 99.3 ± 6.8 mg/dL at baseline to 102.3 ± 7.8 mg/dL at 12 months in the low-dose group, and to 103.8 ± 8.0 mg/dL in the high-dose group. The p-values remained <0.001 across all timepoints, indicating that the increases in FBG were statistically significant, particularly with higher doses of Atorvastatin. This suggests a dose-dependent relationship between Atorvastatin and worsening glycemic control over time.

Table 4: Lipid Profile Changes Based on Atorvastatin Dose

At baseline, the lipid parameters (Total Cholesterol, LDL-C, HDL-C, and Triglycerides) were similar between the low-dose and high-dose groups. Over time, significant reductions were observed in Total Cholesterol and LDL-C levels, with the high-dose group showing a more pronounced decrease. For example, Total Cholesterol decreased from 212.5 ± 31.0 mg/dL at baseline to 160.5 ± 22.4 mg/dL at 12 months in the high-dose group, compared to 180.4 ± 25.7 mg/dL in the low-dose group (p<0.001). LDL-C followed a similar pattern, indicating the efficacy of Atorvastatin in lowering these lipid parameters, particularly at higher doses. HDL-C levels slightly increased over time, with a statistically significant difference observed at 12 months (p=0.027), favoring the high-dose group. Triglyceride levels also showed a significant reduction, with the high-dose group experiencing a greater decrease (p=0.049). These findings confirm the lipid-lowering efficacy of Atorvastatin, particularly at higher doses, which are associated with greater reductions in Total Cholesterol, LDL-C, and Triglycerides, and a modest increase in HDL-C.

Table 5: Regression Analysis of Atorvastatin Dose and Change in HbA1c%

The regression analysis presented in this table assesses the relationship between Atorvastatin dose and changes in HbA1c levels. The regression coefficient (β) of -0.034 indicates a statistically significant inverse relationship between Atorvastatin dose and HbA1c change (p=0.002). This suggests that higher doses of Atorvastatin are associated with a greater increase in HbA1c, after adjusting for other factors. The negative β value aligns with the observations in Tables 2 and 3, where higher doses of Atorvastatin were linked to worsening glycemic control.

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Group A: Normoglycemic (n=50)	Group B: IFG (n=50)	Group C: IGT (n=50)	p-value
Age (years)	52.3 ± 10.2	54.1 ± 9.8	53.4 ± 10.5	0.674
Gender (M/F)	28/22	30/20	29/21	0.910
BMI (kg/m²)	26.1 ± 3.5	27.4 ± 3.2	26.9 ± 3.7	0.384
Fasting Blood Glucose (mg/dL)	90.2 ± 5.6	112.4 ± 7.1	99.3 ± 6.8	<0.001**
HbA1c (%)	5.2 ± 0.4	5.8 ± 0.5	5.9 ± 0.6	<0.001**
ALT (U/L)	25.3 ± 6.2	26.7 ± 7.3	26.2 ± 7.0	0.749

Notes: Data presented as mean ± SD for continuous variables. Statistical significance determined by one-way ANOVA.

Table 2: Changes in HbA1c (%)

Timepoint	Group A: Normoglycemic (n=50)	Group B: IFG (n=50)	Group C: IGT (n=50)	p-value (RM-ANOVA)
Low Dose				
Baseline	5.2 ± 0.4	5.8 ± 0.5	5.9 ± 0.6	<0.001**
4 Months	5.3 ± 0.5	5.9 ± 0.6	6.0 ± 0.7	<0.001**
8 Months	5.3 ± 0.4	6.0 ± 0.6	6.1 ± 0.7	<0.001**
12 Months	5.4 ± 0.5	6.1 ± 0.7	6.3 ± 0.8	<0.001**
High Dose				
Baseline	5.3 ± 0.4	5.9 ± 0.5	6.0 ± 0.6	<0.001**
4 Months	5.4 ± 0.5	6.0 ± 0.6	6.2 ± 0.7	<0.001**
8 Months	5.5 ± 0.5	6.2 ± 0.7	6.4 ± 0.8	<0.001**
12 Months	5.6 ± 0.5	6.3 ± 0.7	6.5 ± 0.8	<0.001**

Notes: Data presented as mean ± SD. RM-ANOVA used for analysis. **Significant at p < 0.05.**

Table 3: Changes in Fasting Blood Glucose (mg/dL)

Timepoint	Group A: Normoglycemic (n=50)	Group B: IFG (n=50)	Group C: IGT (n=50)	p-value (RM-ANOVA)
Low Dose				
Baseline	90.2 ± 5.6	112.4 ± 7.1	99.3 ± 6.8	<0.001**

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4 Months	91.0 ± 5.9	113.2 ± 7.5	100.5 ± 7.3	<0.001**
8 Months	91.3 ± 6.1	114.0 ± 7.7	101.0 ± 7.5	<0.001**
12 Months	91.7 ± 6.2	114.8 ± 8.0	102.3 ± 7.8	<0.001**
High Dose				
Baseline	91.0 ± 5.7	113.3 ± 7.2	100.1 ± 7.0	<0.001**
4 Months	92.1 ± 6.0	114.5 ± 7.6	101.7 ± 7.4	<0.001**
8 Months	92.5 ± 6.2	115.2 ± 7.8	102.5 ± 7.7	<0.001**
12 Months	93.0 ± 6.4	116.0 ± 8.1	103.8 ± 8.0	<0.001**

Notes: Data presented as mean ± SD. RM-ANOVA used for analysis. **Significant at p < 0.05.**

Table 4: Lipid Profile Changes

Parameter	Timepoint	Low Dose (10-20 mg) (n=75)	High Dose (40-80 mg) (n=75)	p-value (t-test)
Total Cholesterol (mg/dL)	Baseline	210.8 ± 30.2	212.5 ± 31.0	0.642
	4 Months	195.3 ± 27.1	175.4 ± 24.8	<0.001**
	8 Months	187.6 ± 26.2	165.3 ± 23.7	<0.001**
	12 Months	180.4 ± 25.7	160.5 ± 22.4	<0.001**
LDL-C (mg/dL)	Baseline	130.5 ± 22.4	132.3 ± 23.0	0.589
	4 Months	115.7 ± 20.1	98.2 ± 18.5	<0.001**
	8 Months	110.3 ± 19.2	94.7 ± 17.4	<0.001**
	12 Months	105.6 ± 18.3	90.3 ± 15.9	<0.001**
HDL-C (mg/dL)	Baseline	42.9 ± 5.8	42.3 ± 6.1	0.607
	4 Months	44.3 ± 6.1	45.5 ± 6.4	0.291
	8 Months	45.2 ± 6.3	46.8 ± 6.8	0.149
	12 Months	45.7 ± 6.4	47.8 ± 7.2	0.027*
Triglycerides (mg/dL)	Baseline	170.6 ± 32.9	172.3 ± 33.7	0.708
	4 Months	160.7 ± 31.8	150.5 ± 29.4	0.046*
	8 Months	155.1 ± 30.7	144.9 ± 28.2	0.037*
	12 Months	150.2 ± 30.5	140.6 ± 28.7	0.049*

Notes: Data presented as mean ± SD. Independent t-test used for analysis. **Significant at p < 0.05.**

Table 5: Regression Analysis of Atorvastatin Dose and Change in HbA1c%

Variable	Coefficient (β)	SE	t-value	p-value
Atorvastatin Dose	-0.034	0.011	-3.09	0.002**

Notes: Regression analysis was performed with Atorvastatin dose as the independent variable and change in HbA1c% as the dependent variable. SE: Standard Error.

DISCUSSION

In this study, the baseline characteristics of the three groups—Normoglycemic (Group A), Impaired Fasting Glucose (IFG, Group B), and Impaired Glucose Tolerance (IGT, Group C)—were comparable in terms of age, gender distribution, and BMI, with no significant differences (p>0.05). These findings align with the literature, where demographic variables like age and gender often do not show significant differences across groups with varying glycemic statuses in similar studies (Ford et al., 2010).[11] The significant differences in fasting blood glucose and HbA1c levels between the groups (p<0.001) reflect the distinct glycemic control statuses in the study population, consistent with findings from previous research (American Diabetes Association, 2021).[12]The progressive increase in HbA1c levels over the 12-month study period, particularly in groups receiving high-dose Atorvastatin, suggests that higher doses of Atorvastatin may be associated with worsening glycemic control. The findings are consistent with a body of evidence suggesting that statins, including Atorvastatin, may slightly increase HbA1c levels, especially in patients with pre-existing glucose intolerance (Sattar et al., 2010).[13] The significant increase in HbA1c in the high-dose group, particularly in those with IFG and IGT, could indicate a dose-dependent adverse effect of Atorvastatin on glycemic control, which has been observed in other studies (Ridker et al., 2012).[14]This highlights the importance of monitoring glycemic parameters in patients on high-dose statins, especially those at risk of diabetes.Similar to HbA1c, fasting blood glucose (FBG) levels also increased significantly over time in all groups, with a more pronounced increase in the high-dose Atorvastatin group. This dose-dependent effect of Atorvastatin on FBG corroborates findings from previous studies, which suggest that statin therapy can lead to an increase in blood glucose levels (Cederberg et al., 2015).[15] The consistent p-value of <0.001 across all timepoints underscores the significant impact of Atorvastatin on glycemic control, emphasizing the need for caution when

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prescribing higher doses, particularly in individuals with existing glucose metabolism disorders.

Atorvastatin's efficacy in lowering lipid parameters was evident in the significant reductions observed in Total Cholesterol, LDL-C, and Triglycerides, particularly in the high-dose group. These findings are consistent with the well-established lipid-lowering effects of Atorvastatin, as documented in numerous studies (Baigent et al., 2010).[16] The modest increase in HDL-C levels, although statistically significant only at 12 months, also aligns with existing literature suggesting that statins can slightly raise HDL-C levels (Barter et al., 2007).[17] The greater reduction in Total Cholesterol and LDL-C in the high-dose group supports the use of higher doses of Atorvastatin for more aggressive lipid management, particularly in patients at high cardiovascular risk (JUPITER Study Group, 2008).[18]The regression analysis revealed a significant inverse relationship between Atorvastatin dose and HbA1c change, indicating that higher doses of Atorvastatin were associated with a greater increase in HbA1c levels ($p=0.002$). This finding supports the dose-dependent adverse effect of Atorvastatin on glycemic control, as observed in other studies (Preiss et al., 2011).[19] The negative β value underscores the potential risk of worsening glycemic control with higher statin doses, a critical consideration for clinicians managing patients with or at risk for diabetes. This aligns with the recommendations from recent guidelines that suggest close monitoring of glucose levels in patients receiving high-dose statin therapy (Stone et al., 2014).[20]

CONCLUSION

The study's findings highlight the dual effects of Atorvastatin on lipid and glycemic control. While higher doses of Atorvastatin are more effective in lowering lipid parameters, they are also associated with a greater increase in HbA1c and fasting blood glucose levels, particularly in individuals with impaired glucose metabolism. These results are consistent with existing literature and underscore the importance of individualized patient management, balancing the cardiovascular benefits of Atorvastatin with its potential impact on glycemic control.

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