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Original Article

Chronotherapeutic Effects of Atorvastatin Administration on Lipid Profile in Patients with Type 2 Diabetes Mellitus: A Randomized Clinical Trial

Running Title: Morning Versus Evening Atorvastatin in Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is commonly associated with dyslipidemia and increased cardiovascular risk. Atorvastatin, a widely used statin, effectively improves lipid profiles. This study aimed to compare the effects of morning versus evening administration of atorvastatin on lipid parameters in patients with T2DM.
Materials and Methods: This randomized controlled trial enrolled 76 patients with T2DM, randomly assigned to receive Atorvastatin 40 mg either in the morning (n=38) or evening (n=38) for 4 weeks. Fasting serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured at baseline and post-treatment. Baseline lipid values were included as covariates in ANCOVA to compare post-treatment levels between groups.
Results: Atorvastatin significantly improved lipid profiles in both groups: LDL-C, TG, and TC decreased ($P<0.05$), while HDL-C increased ($P<0.001$) compared to baseline. After adjusting for baseline values, no significant differences were observed between morning and evening groups in LDL-C, HDL-C, TG, or TC ($P>0.05$).
Conclusion: Four weeks of Atorvastatin therapy significantly improved lipid profiles in patients with T2DM, irrespective of administration time. These findings suggest that dosing flexibility may enhance patient adherence without compromising efficacy.

Keywords: Type 2 diabetes mellitus, Atorvastatin, Lipid profile, Statin, Morning vs evening administration, Randomized clinical trial.

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Introduction

Diabetes mellitus prevalence is rising globally, with an estimated 643 million people worldwide projected to have diabetes by 2030, increasing to 783 million by 2045 (1). Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, in which insulin resistance and increased glucose entry into pancreatic beta cells lead to enhanced compensatory insulin secretion and progressive decline in the secretory function of these cells (2). In patients diagnosed with T2DM, serum concentrations of triglycerides (TGs), total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C) are elevated. In contrast, the level of high-density lipoprotein cholesterol (HDL-C) is often reduced. The lipid profile abnormalities in T2DM patients enhance the risk of cardiovascular diseases (CVDs) (3, 4). CVDs are the primary cause of mortality in patients with T2DM (5). An abundance of triglycerides prevents the intrahepatic degradation of Apo B-100, thereby increasing the formation and secretion of VLDL-C and ultimately elevating blood LDL-C concentrations (6). LDL-C is the strongest predictor of coronary artery disease (7). When the biochemical pathways for TG formation are activated, their synthesis increases. Metabolites from the TG synthesis pathway, such as diacylglycerol (DAG) and free fatty acids (FFAs), inhibit insulin signaling. Since cholesterol is a component of the plasma membrane, a rise of its intracellular level impairs insulin receptor (IR) function, therefore, elevated levels of TGs, LDL-C, and cholesterol can indicate insulin resistance (8). Furthermore, the rising global prevalence of type 2 diabetes has drawn much attention to the need for fundamental management strategies, particularly for cardiovascular health (9). Statins primarily inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), thereby hindering cholesterol synthesis (4, 10). Atorvastatin, a lipophilic statin, is more effective than other statins at lowering LDL-C and mitigating vascular complications. Atorvastatin also affects other lipid markers (8). According to the guidelines, statin therapy is recommended for all diabetic patients aged over 40 to prevent CVDs (11). Statins are often prescribed in the evening, as cholesterol biosynthesis peaks at night. However, flexibility in the timing of drug administration can enhance patient compliance and adherence. Patients on statins often take multiple concurrent medications, which may reduce drug tolerance and treatment efficacy.

Given the increasing global prevalence of T2DM and its strong association with CVDs, along with the importance of prescribing statins in these individuals, considering that flexible dosing timing can improve patient tolerance, this study aimed to investigate the effects of morning versus evening administration of Atorvastatin on the lipid profile of patients with T2 DM at Ayatollah Rouhani Hospital.

Materials and methods

Study design

This study was a randomized controlled trial (IRCT Code: 20211211053359N1). The study population comprised patients with T2DM referred to the Endocrine Clinic of Ayatollah Rouhani Hospital in

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Babol. Inclusion criteria were patients with type 2 diabetes mellitus aged over 40 years who had an indication for statin therapy. Exclusion criteria included a history of statin intolerance, active liver disease, severe renal impairment, pregnancy or breastfeeding, and use of lipid-lowering medications other than Atorvastatin during the study. 76 patients with T2DM were included in the study. The minimum sample size was calculated by the statistical consultant of the project. Based on data from similar studies, a total of 76 participants (38 per group) was determined. Demographic information of the patients, including age, gender, education level, employment status, body mass index (BMI), physical activity, underlying diseases, smoking, and alcohol consumption, was collected. To examine the patients' lipid profile, a 5cc blood sample was taken after a 12-hour fast at the study baseline. Baseline was defined as the initial measurement of lipid profile parameters obtained before the initiation of atorvastatin therapy. Samples were collected at the laboratory of Ayatollah Rouhani Hospital. Serum TG, TC, LDL-C, and HDL-C concentrations were measured using a fully automatic autoanalyzer with Pars Azmoun kits. After initial assessment and obtaining informed consent, participants were randomly assigned to either the morning or evening administration group. All patients received atorvastatin 40 mg/day. The dose of atorvastatin (40 mg/day) was selected based on current clinical guidelines recommending moderate- to high-intensity statin therapy for patients with type 2 diabetes mellitus over 40 years of age to reduce cardiovascular risk. Randomization was performed using a permuted block design. To hide group assignment, identical envelopes with unique three-digit codes were prepared for all participants. After enrollment, one of these envelopes was given to that subject in a specific order by the secretary to allocate his or her treatment time, and the code on the envelope was recorded in the patient file. At the end of the study, the codes were revealed. After four weeks of treatment, lipid profiles were remeasured in the same laboratory using the same kit. Adherence to the assigned dosing time was assessed by patient self-reports at follow-up visits and reinforced by regular telephone reminders throughout the study period. Patients received clear instructions on the exact timing of medication intake at enrollment **(figure 1).**

Ethical approval

The study was approved by the Ethics Committee of Babol University of Medical Sciences (Code: IR.MUBABOL.HEL.REC.1400.176). Written informed consent was obtained from all participants.

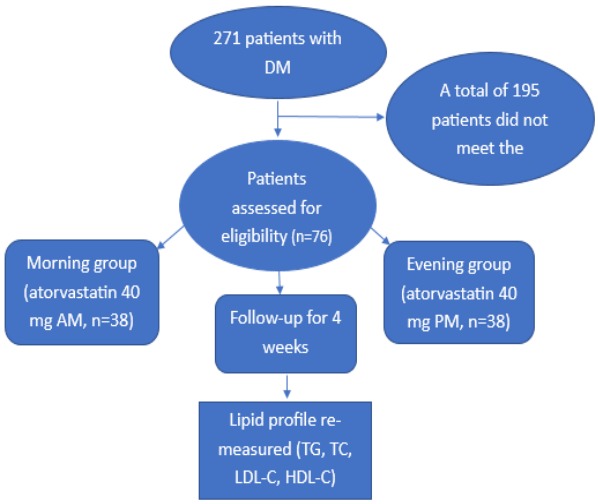

Figure 1. Summary of the study's methodology

Statistical analysis

Data were analyzed using SPSS version 26. T-test and Chi-square test were used to examine the variables at the beginning of the study between the two groups. Analysis of covariance (ANCOVA) was used to examine the effect of drug administration time on blood lipid and lipoprotein levels during the study. Baseline lipid values were included as covariates in the ANCOVA analysis. Fisher's exact test was used to compare study groups based on the ercentage of LDL reduction. Statistical significance was considered at p-value < 0.05.

Results

Seventy-six patients with T2DM were randomized into a morning atorvastatin group (n = 38) and an evening group (n = 38). The groups were comparable in age, BMI, employment, education, physical activity, underlying diseases, smoking, and alcohol consumption (P > 0.05), except for gender distribution (morning: 11 males/27 females; evening: 20 males/18 females; P < 0.05).

At baseline, HDL-C was higher in the morning group (42.7 ± 7 vs. 39.6 ± 7 mg/dL, P <0.05), while LDL-C, TG, and TC were similar between groups (P > 0.05) (**Table 1**).

After four weeks of atorvastatin therapy, both groups showed significant improvements from baseline in all lipid parameters: LDL-C, TG, and TC decreased, and HDL-C increased (P < 0.001 for TG, TC, HDL-C; P <0.05 for LDL-C) (Table 2, Figure 2). Post-treatment comparisons between morning and evening groups, adjusted for baseline values using ANCOVA, revealed no significant differences in LDL-C, HDL-C, TG, or TC (P > 0.05). Similarly, the distribution of patients by percentage LDL-C reduction (<30%, 30–49%, ≥50%) did not differ between groups (P >0.05) **(Table 3).**

In summary, four weeks of atorvastatin therapy significantly improved the lipid profile of T2DM patients, irrespective of administration timing.

Table 1. Study groups based on lipid profile at baseline

Parameters	Morning Group (n=38)	Evening Group (n=38)	P-value
LDL (mean ± SD) mg/dl	122.9 ± 36	116.3 ± 59	0.56
HDL (mean ± SD) mg/dl	42.7 ± 7	39.6 ± 7	0.01*
TG (mean ± SD) mg/dl	191.9 ± 135	185.2 ± 77	0.79
TC (mean ± SD) mg/dl	217.5 ± 51	200.1 ± 66	0.2

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, TC: Total cholesterol. *: P-value < 0.05.

Table 2. Lipid profile of patients before and after four weeks of atorvastatin treatment

Parameter	Morning Group (n=38)	Evening Group (n=38)	Between-group P-value*
	Baseline	After 4 weeks	Baseline
LDL-C (mg/dL)	122.9 ± 36	80.4 ± 21	116.3 ± 59
HDL-C (mg/dL)	42.7 ± 7	**47.7 ± 7**	39.6 ± 7
TG (mg/dL)	191.9 ± 135	141.3 ± 72	185.2 ± 77
TC (mg/dL)	217.5 ± 51	155.5 ± 29	200.1 ± 66

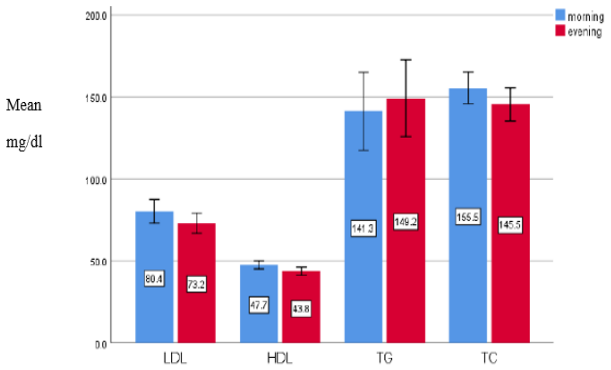

Figure 2. Diagram of study groups based on patients' lipid profile after four weeks of treatment

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LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride, TC: total cholesterol

Fisher's exact test was used to compare the two groups in terms of the percentage reduction in LDL. Based on this test, there was no statistically significant difference between the study groups in LDL percentage reduction (p>0.05) **(Table 3).**

Table 3. Comparison of study groups based on percentage of LDL reduction

Percentage of LDL reduction	Morning group (n=38)	Evening group (n=38)	P value
Less than 30 percent	20 patients (52.6%)	18 patients (47.4%)	0.48
Between 30 and 49 percent	9 patients (23.7%)	13 patients (34.2%)	
More than 50 percent	9 patients (23.7%)	7 patients (18.4%)	

Discussion

Increased blood sugar levels (hyperglycemia) lead to T2DM development (13). It is estimated that 30–60% of patients with T2DM have dyslipidemia (14). Specifically, patients with T2DM often demonstrated elevated serum levels of TG, TC, and LDL-C, and lower levels of HDL-C, which was consistent with the study by Andevari et al (15). Hyperglycemia-induced reactions elevate acetyl-CoA production, a major precursor for TG and cholesterol synthesis. Consequently, hyperglycemia upregulates levels of TG, TC, and LDL-C (16-18).

Since most patients with T2DM are obese, it is not surprising that many also develop insulin resistance and dyslipidemia (19). Dyslipidemia and hyperglycemia lead to cardiovascular, cerebral, neurological, ocular, and renal complications (20, 21). Statins are drugs that improve hyperglycemia and dyslipidemia, thereby reducing the development of such complications (3, 8). Some beneficial effects of statins in diabetic complications are due to their anti-inflammatory and antioxidant effects, which extend beyond the blocking of cholesterol synthesis. These additional properties are known as pleiotropic effects (22). Atorvastatin underlies these antioxidant and anti-inflammatory benefits due to its lipophilic properties and potent cholesterol-lowering effect.(3, 8).

Since endogenous cholesterol synthesis peaks during the night, statins are typically administered in the evening (23). This study had a short follow-up period. However, our study showed that four weeks of atorvastatin treatment significantly improved lipid profiles in diabetic patients, regardless of the time of intake. In a study published by Andevari et al., atorvastatin 40 mg per day for three months reduced LDL-C, TG, and TC, while significantly elevating HDL-C levels(8). This study aimed to compare the differences in patients' lipid profiles as a result of taking atorvastatin 40 mg in the morning and evening. No substantial difference was observed in the effectiveness of atorvastatin between morning and evening groups. The short follow-up period could be one reason for the lack of significant difference between the two groups. Plakogiannis et al. reported no statistically significant lipid profile variations between morning and evening groups after four weeks of treatment with 40 mg atorvastatin in patients with hyperlipidemia (24). In a study by Yi et al., patients with chronic kidney disease and dyslipidemia were divided into two groups to receive 20 mg of simvastatin either in the morning or evening for 8 weeks. There were no substantial differences between

the two groups in the percentage changes of TG, TC, and HDL-C (25). In a study published by Heng et al., hypercholesterolemic patients were given simvastatin at three time points (morning, evening, and before bedtime) for 16 weeks. The percentage reduction in LDL-C was significantly different between the three groups. The greatest reduction in LDL-C was observed when simvastatin was taken before bedtime (26). It is likely that a longer follow-up period is to be associated with greater changes in lipid profiles attributable to statin therapy. A study by Ozaydin et al. demonstrated this effect with atorvastatin. In this study, patients with coronary artery disease were treated with atorvastatin for 6 months, and as a result, the evening dose of atorvastatin mitigated LDL-C levels significantly more than the morning dose (27). Beyond the biochemical outcomes observed in this trial, the absence of a significant difference between morning and evening administration of atorvastatin may have important clinical implications. Allowing flexibility in dosing time could improve medication adherence, particularly in patients with type 2 diabetes mellitus who often require multiple daily medications and may have variable daily routines. Improved adherence may enhance the real-world effectiveness of statin therapy without compromising its lipid-lowering efficacy.

Nevertheless, the findings of this study should be interpreted with caution. The conclusions are limited to short-term lipid profile outcomes following a four-week intervention, and longer follow-up studies are needed to determine whether chronotherapeutic flexibility influences long-term cardiovascular outcomes. In addition, a statistically significant imbalance in gender distribution between the morning and evening groups was observed at baseline, which may have affected the results and should be considered as a limitation of the present study.

Conclusion

Atorvastatin significantly improved the lipid profile of patients with type 2 diabetes mellitus after four weeks of treatment, regardless of the timing of administration. No significant difference was observed between morning and evening dosing groups.

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Conflict of interests: The authors declare no conflict of interest.

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