Comparative efficacy and safety of atorvastatin, simvastatin and lovastatin in the management of dyslipidemic Type 2 diabetic patients

Molouk Hadjibabaie, Kheirollah Gholami, Hossain Khalili, Seyed Hamid Khoei, Manoochehr Nakhjavani, Kobra Rayati, Atefeh Tohidi, Roja Rahimi & Mohammad Abdollahi†

†Author for correspondence Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, PO Box 14155–6451, Iran Tel.: +98 216 695 9104 Fax: +98 216 695 9104 mohammad@tums.ac.ir

Background: Type 2 diabetic patients frequently have a lipid abnormality that is a major risk factor for cardiovascular diseases. Lipid-lowering agents, especially statins, are recommended for use in these patients. **Aim:** The aim of this open-label, randomized, parallel-group, comparative study was to evaluated the comparative efficacies of three statins – atorvastatin (10 mg), simvastatin (20 mg) and lovastatin (20 mg), once-daily over a period of 12 weeks. **Participants:** Considering inclusion and exclusion criteria, 53 patients completed the study. **Results:** In atorvastatin, simvastatin and lovastatin groups, total cholesterol (29, 18 and 21%, respectively), low-density lipoprotein cholesterol (37, 19 and 22%, respectively) and triglyceride (41, 26 and 24%, respectively) levels decreased, while high-density lipoprotein cholesterol (5, 7 and 5% respectively) increased after 12 weeks of treatment in comparison with baseline levels. The differences in high-density lipoprotein cholesterol between the three groups after treatment were not statistically significant (atorvastatin: 48 ± 11 mg/dl; simvasatin: 49 ± 9 mg/dl; and lovastatin: 47 ± 8 mg/dl). Low-density lipoprotein cholesterol levels for the atorvastatin group were significantly lower than that of the simvastatin group (96 ± 23 vs 126 ± 41 mg/dl, p = 0.02) after treatment. The levels of other parameters were also lower in the atorvastatin group, although the differences were not significant. **Conclusions:** The results of this study confirm that among statins, atorvastatin is a better choice for the control of hyperlipidemia in Type 2 diabetic patients.

Keywords: atorvastatin, dyslipidemia, lovastatin, simvastatin, Type 2 diabetic patients

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Type 2 diabetic patients have a marked increase in the risk of coronary artery disease (CAD) [1]. The management of dyslipidemia, a well-recognized and modifiable risk factor among patients with Type 2 diabetes, is an important factor in the multifactorial approach to preventing coronary heart disease (CHD). In diabetic patients, dyslipidemia typically consists of elevated triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) [2]. LDL-C is the strongest independent predictor of CHD followed by HDL-C [3]. Both the National Cholesterol Education Program (NCEP) and the American Diabetes Association (ADA) give first priority to achieving the LDL-C target. Both recommend treatment with a statin for all diabetic subjects with a LDL-C greater than 130 mg/dl [4]. According to current guidelines, the primary lipid target is a LDL-C of less than 100 mg/dl (<70 mg/dl in very high-risk patients) and, to this end, the agents of choice are statins [2]. The efficacy of statins in lowering LDL-C and having a favorable effect on the LDL:HDL ratio have been demonstrated in patients with Type 2 diabetic patients [5,6]. Generally, statins are initiated at starting doses, and then titrated as needed until the goal of therapy is achieved [7]. A number of factors that limit dose titration include the cost of therapy and the safety of high doses of statins. The choice of statin appears to be one of the important factors that influence the success of therapy. A statin with a greater LDL-C-lowering effect enables more patients to achieve LDL-C goals, and most patients can be effectively treated with starting doses of the more efficacious statins. The objective of this study is to compare the efficacy of low doses of three statins – atorvastatin, simvastatin and lovastatin – in Type 2 diabetic dyslipidemic patients.

Methods

This study was an open-label, randomized, parallel-group, 12-week comparative study that was performed in a central university hospital to evaluate the efficacy of once-daily atorvastatin 10 mg, simvastatin, 20 mg and lovastatin 20 mg. All Type 2 diabetes patients with hyperlipidemia who had the criteria for the trial entered the study. Patients' characteristics

Table 1. Baseline characteristics of patients with Type 2 diabetes with hyperlipidemia, treated by atorvastatin, simvastatin and lovastatin.

	Atorvastatin 10 mg/day	Simvastatin 20 mg/day	Lovastatin 20 mg/day
Patients (n)	19	18	16
Age (years)	53 ± 9	56 ± 6	52 ± 7
Sex (female/male)	17/2	16/2	15/1
Duration of diabetes (years)	8 ± 6	11 ± 4	9 ± 5
HbA1c (%)	7 ± 1	8 ± 1	6 ± 2
Fasting glucose (mg/dl)	148 ± 17	157 ± 36	152 ± 21
Body mass index (kg/m^2)	31 ± 5	29 ± 2	30 ± 4
Diabetes treatment (number of patients)			
Diet	1	2	1
Tablets	14	15	13
Insulin	2	0	1
Tablets + insulin	2	1	1

at baseline are detailed in Table 1. The study included 60 men and nonpregnant women aged between 18 and 70 years with Type 2 diabetes with a serum LDL-C concentration of 100 mg/dl or more, TG level of 400 mg/dl or less and a HbA1c value of 9% or under. Patients with hepatic and renal dysfunction, uncontrolled hypothyroidism, Type 1 diabetes mellitus, pregnancy, current use of lipid-lowering drugs, women on hormone-replacement therapy and uncontrolled hypertension were excluded. The study was conducted in accordance with the institutional review board for human study at Tehran University of Medical Sciences (Tehran, Iran). All patients gave written informed consent to participate in the study.

Before randomization, the patients who were recruited into the study were informed of the importance of compliance with diet and exercise, which were assessed regularly during the study period. Patients were then randomly assigned to one of three treatment groups, including atorvastatin 10 mg/day, simvastatin 20 mg/day and lovastatin 20 mg/day. The drugs were administered once daily after an evening meal for 12 weeks. After 12 weeks of treatment, total cholesterol (TC), LDL-C, HDL-C and TG were measured in all patients.

To monitor safety, adverse events were recorded at every visit to the clinic. Serum aminotransferase and creatinine phosphokinase concentrations were determined at the beginning and end of the treatment period. Blood glucose levels were checked regularly.

Differences between three groups were compared using two-way ANalysis Of VAriance (ANOVA). Data are presented as mean ± standard deviation (SD). A p value of less than 0.05 was considered statistically significant.

Results

In total, 53 out of 60 patients were randomized for treatment and completed the study. Seven patients discontinued treatment before the end of the study. Four patients withdrew owing to adverse effects and three patients were lost to follow-up. The clinical profile of 53 patients has been shown in Table 1. Before the start of treatment, the values of serum lipids and lipoprotein cholesterol were not significantly different between treatment groups ($p > 0.05$). After 3 months of therapy, serum TG, TC and LDL-C levels decreased and HDL-C levels increased significantly ($p < 0.05$) compared with their baselines in all groups (Table 2). LDL-C levels for the atorvastatin-treated group was significantly lower than LDL-C for the simvastatin group (96 ± 23 vs 126 ± 41 mg/dl, $p = 0.02$) after 3 months of treatment. The LDL-C value for the atorvastatin-treated group was not significantly lower than that of the lovastatin-treated group (96 ± 23 vs 113 ± 30 mg/dl, $p = 0.2$). The amounts of TC and TG were also lower in the atorvastatin group compared with other groups, although these differences were not significant. The differences in HDL-C levels between the three groups after treatment were

Table 2. Baseline and changes from baseline in TC, TGs, LDL-C and HDL-C after 3 months.

	Atorvastatin 10 mg/day	Simvastatin 20 mg/day	Lovastatin 20 mg/day	p*; p‡; p§; p¶
Baseline (before treatment)				
TC (mg/dl)	248 ± 41	248 ± 47	235 ± 38	NS; NS; NS; NS
TG (mg/dl)	269 ± 31	230 ± 47	217 ± 54	NS; NS; NS; NS
LDL-C (mg/dl)	151 ± 30	155 ± 37	144 ± 30	NS; NS; NS; NS
HDL-C (mg/dl)	45 ± 11	45 ± 12	44 ± 10	NS; NS; NS; NS
After treatment				
TC (mg/dl)	177 ± 35	203 ± 42	186 ± 45	NS; NS; NS; NS
TG (mg/dl)	156 ± 57	170 ± 89	164 ± 82	NS; NS; NS; NS
LDL-C (mg/dl)	96 ± 23	126 ± 41	113 ± 30	0.02;0.03;NS;NS
HDL-C (mg/dl)	48 ± 11	49 ± 9	47 ± 8	NS; NS; NS; NS

**p-value for the comparison among groups I, II and III.*

‡p-value for the comparison between groups I and II.

§p-value for the comparison between groups I and III.

¶p-value for the comparison between groups II and III.

All parameters tested (TC, TG, LDL-C, HDL-C) showed significant improvement ($p < 0.05$) from baseline for all three drugs.

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; NS: Non-signifcant; TC: Total cholesterol; TG: Triglyceride.

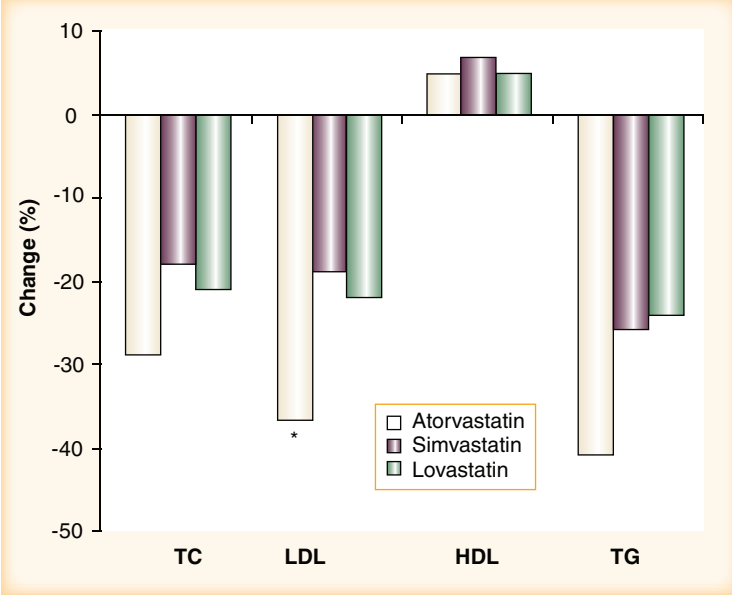
not statistically significant (atorvastatin: 48 ± 11 mg/dl; simvasatin: 49 ± 9 mg/dl; lovastatin: 47 ± 8 mg/dl). The percentage changes in serum lipids and lipoprotein cholesterol in treated groups are shown in **Figure 1**. As shown, atorvastatin 10 mg/day produced greater reductions from baseline in LDL-C (-37%) than simvastatin 20 mg/day (-19%) or lovastatin 20 mg/day (-22%), even though all the statins significantly reduced LDL-C levels from baseline.

The overall frequency of adverse events was similar between all treated groups. Reported adverse effects included urticaria, headache, nausea, rash and myalgia. There was no elevation of aminotransferase from normal levels and no report of myopathy in any treatment group.

Discussion & conclusion

Dyslipidemia is common in patients with Type 2 diabetes. Owing to the increased risk of CHD in these populations, the lipid abnormalities should be treated aggressively. Therefore, intensive lipid-lowering therapy should be used for primary and secondary preventive therapy against macrovascular complications in Type 2 diabetic patients [8]. Furthermore, after an acute coronary event, diabetic patients have a higher mortality rate compared with their nondiabetic counterparts [9,10]. Statins are useful adjuncts in the treatment of diabetes because, in addition to their lipid-lowering effect, they beneficially influence thrombogenic and fibrinolytic factors [11]. Collins and colleagues have demonstrated that allocation to simvastatin 40 mg daily reduces the rate of first major vascular events by approximately a quarter in diabetic patients [12]. Structurally, simvastatin is closely related to lovastatin and both are potent inhibitors of 3-hydroxy-3-methylgluatryl coenzyme A (HMG-CoA) reductase. Atorvastatin has a different structure, a longer half-life and greater hepatic selectivity [13]. The present study is one of the few trials to compare the efficacy of different statins in treating hypercholesterolemia in Type 2 diabetes patients. The effects of atorvastatin on the lowering of lipids in this study are consistent with previous results in diabetic patients [6,14] and in the general population [15]. A study in nondiabetic patients with hypercholesterolemia demonstrated that treatment with atorvastatin at a dose of 10 mg once daily for 4 weeks resulted in a 41% reduction in LDL-C [15]. A study in Type 2 diabetes patients with hypercholesterolemia showed a 37% reduction of LDL-C with the same dose of atorvastatin [14]. In this study, atorvastatin 10 mg/day produced greater reductions from baseline in LDL-C (-37%) than simvastatin 20 mg/day (-19%) or lovastatin 20 mg/day (-22%), even though all the statins reduced LDL-C levels from baseline significantly. These changes in LDL-C are consistent

Figure 1. 12-week percentage change from baseline in TC, LDL, HDL, and TG in three groups after administration of atorvastatin, simvastatin and lovastatin.



*p < 0.05 vs simvastatin.
HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

with other comparative trials and confirm the superior LDL-C-lowering potential of atorvastatin 10 mg/day compared with simvastatin and lovastatin at equivalent doses. In addition of high LDL-C levels, increased TG levels [16] and decreased HDL-C levels [17] are also shown to be independent risk factors for CHD. In the present study, patients treated with atorvastatin had a greater increase from baseline in HDL-C levels, comparable with those observed in the lovastatin-treated group; however, patients treated with simvastatin had favorable increases in HDL-C levels from baseline compared with atorvastatin. In addition, reductions in the levels of TG were greater with atorvastatin (-41%) than with simvastatin (-26%) or lovastatin (-24%), even though all statins decreased TG levels significantly from baseline. In other studies, atorvastatin 10 mg/day has been shown to provide more significant reductions in TG levels than simvastatin 10 mg/day or lovastatin 20 mg/day [18,19]. All the statins in this study had similar effects on TC and significantly reduced levels from baseline. In one study, atorvastatin provided significantly greater reductions in TC than simvastatin or lovastatin [14].

It was shown that atorvastatin has beneficial effects on oxidative stress in patients with hyperlipidemia – it reduces the urine 8-isoprostane, which is a biomarker of oxidative stress [20]. Regarding the role of oxidative stress in the pathogenesis of diabetes and hyprlipidemia, it appears that the antioxidant properties of atorvastatin potentiates its lipid-lowering capacities and, thus, might be responsible for reduction of TC, TG and LDL-C [21–25].

HMG-CoA reductase inhibitor agents are generally well-tolerated drugs [19]. Clinically important AEs of statins included increases in serum aminotransferase levels, which occur within the first months of treatment, and the duration of this study was long enough to detect such an AE [26]. In the present study, no patients experienced clinically significant elevations in serum aminotransferase. Severe elevations in

Highlights

- This study compares the efficacy of simvastatin, lovastatin and atorvastatin in treating hyperlipidemia in patients with Type 2 diabetes.
- After 3 months of therapy, all of the studied statins decreased serum total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels and increased high-density lipoprotein cholesterol (HDL-C) levels significantly ($p < 0.05$) compared with the baseline level prior to treatment.
- Atorvastatin produces a greater reduction in LDL-C from baseline when compared with simvastatin and lovastatin.
- The overall frequency of adverse events (AEs) was similar between all treatment groups. Reported AEs included urticaria, headache, nausea, rash and myalgia. There was no elevation of aminotransferase from normal levels and no report of myopathy in any treatment groups.
- The results of this study confirm that, among statins, atorvastatin is a better choice in controlling hyperlipidemia of Type 2 diabetes patients.
- Since oxidative stress plays an important role in the pathogenesis of diabetes and hyprlipidemia, it appears that the antioxidant properties of atorvastatin are responsible for its better lipid-lowering ability.

creatinine phosphokinase and myositis have been experienced with the use of statins [27]. However, in this study, no subjects experienced this AE The results of this study confirm the findings of previous clinical trials that compared the effects of statins in patients with Type 2 diabetes with hypercholesterolemia [14]. These drugs are very effective at reducing LDL-C and TG, are well tolerated and have no AEs on glycemic control in this patient population. However, further studies with larger sample sizes must be performed in this population to clarify the influence of factors, such as genetics, age and sex.

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Affiliations

Molouk Hadjibabaie, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Kheirollah Gholami, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Hossain Khalili, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy, T
ehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Seyed Hamid Khoei, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Manoochehr Nakhjavani, MD
Department of Endocrinology,
Faculty of Medicine,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Kobra Rayati, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Atefeh Tohidi, PharmD
Department of Clinical Pharmacy,
Faculty of Pharmacy,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran

Roja Rahimi, PharmD
Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran
Tel.: +98 216 695 9104
Fax: +98 216 695 9104
mohammad.abdollahi@utoronto.ca

Mohammad Abdollahi, PhD
Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences,
Tehran, PO Box 14155–6451, Iran
Tel.: +98 216 695 9104
Fax: +98 216 695 9104
mohammad.abdollahi@utoronto.ca