



Effect of high dose versus low dose of atorvastatin therapy on inflammation and coagulation factors in type 2 diabetic patients; a randomized clinical trial study

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Abstract

Introduction: Statins are one of the most widely used therapies in different groups of patients not only because of cholesterol-lowering properties but also due to their non-lipid related mechanisms. However, the effects of atorvastatin on inflammatory and coagulation markers in type 2 diabetic patients are not well examined.

Objectives: To evaluate, the effects of two different doses of atorvastatin on lipid profile, inflammatory coagulation markers, and liver enzymes in type 2 diabetic patients.

Patients and Methods: In a randomized double-blinded controlled trial, 150 diabetic patients were randomly assigned to get atorvastatin 10 mg/d (n = 74) or 40 mg/d (n = 76) for 12 weeks. The concentration of biomarkers was determined both at the onset of the study as well as at the completing time of the intervention.

Results: Significant differences between the mean levels of lipid profiles, fibrinogen, interleukin-1 (IL-1) and IL-6 were observed between two groups after three months treatment with atorvastatin 10 and 40 mg/d ($P < 0.05$). Furthermore, significant improvement in all blood values after atorvastatin 40 mg/d ingestion was observed ($P < 0.05$) except for homocysteine and creatine phosphokinase (CPK) levels ($P > 0.05$).

Conclusion: Atorvastatin therapy especially with higher dose was associated with inflammation and coagulation parameters improvement in diabetic individuals.

Trial Registration: Registration of randomized double-blinded clinical trial has been approved in Iranian registry of clinical trial (identifier: IRCT201502226710N5; <http://www.irct.ir/trial/7136>).

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Introduction

Type 2 diabetes mellitus as chronic metabolic disorder, is characterized by inappropriate hyperglycemia due to the deficiency in or resistance to insulin (1). It has gotten pandemic proportions and regarded as one of the causes of healthcare costs, incapability, and mortality (2). Diabetes incidence throughout the world is in a growing trend since 1980, going up from 4.7% to a double 8.5% in 2014 in adult individuals according to the World Health Organization (WHO) 2016 report (3). Insulin resistance can result in vasoconstriction, thrombosis, inflammation and increasing the risk of cardiovascular disease, including stroke and myocardial infarction (4). The best characterized and well standardized inflammation biomarker is C-reactive protein (CRP), while studies

Key point

Our data revealed a significant difference in the mean levels of lipid profiles, fibrinogen, interleukin-1 (IL-1) and interleukin-6 (IL-6) between two diabetic patients groups after three months treatment with atorvastatin 10 and 40 mg/d.

have approved its role as a precursor of the type 2 diabetes and metabolic syndrome (5). Furthermore, hyperglycemia can cause endothelial dysfunction in diabetes mellitus which is considered as a significant reason in the pathogenesis of diabetic micro-and macroangiopathy in different types of diabetes (6). Different glycol-oxidative products can decrease nitric oxide production, anticoagulant properties, raise the platelet aggregation,



the expression of the adhesion molecules, cytokines and chemokines, and the production of reactive oxygen species from the endothelium (6). Moreover, the blood levels of homocysteine (Hcy), a Sulphur-containing amino acid which is involved in the methionine metabolism, is also involved in diabetic vascular complications (7), while the elevated levels of this amino acid have been implicated with insulin resistance (7). However, lipid-lowering drugs especially statins (inhibitors of 3-hydroxy-3-methylglutaryl-CoA [HMG-CoA] reductase the main enzyme in the synthesis of cholesterol) are one of the most widely used therapies in different groups of patients not only because of cholesterol-lowering properties but also due to their “pleiotropic mechanisms” (8). The reduction in vascular inflammation and oxidative stress and improvement in atherosclerotic plaque stability, are some examples of statins pleiotropic effects (9). More recently, intensive lipid lowering with higher statin doses over regularly used doses have gained more attention because they might have significant therapeutic benefits (10). However, in a meta-analysis by Yicong et al, no significant decrease in low density lipoprotein-cholesterol (LDL-C) and CRP after treatment with low-dose versus high-dose statin plus ezetimibe was detected (11). Furthermore, the effects of different doses of atorvastatin on inflammatory and coagulation markers in type 2 diabetic patients are not well studied.

Objectives

The aim of this study was to examine the effects of high

dose versus low dose of atorvastatin on inflammatory and coagulation markers in type 2 diabetes mellitus at the same time.

Patients and Methods

Study design

This study was designed and carried out according to the instructions presented in the Declaration of Helsinki. Written informed consent was obtained from all participants. This randomized clinical trial study was conducted on 200 type 2 diabetic patients who were referred to endocrinology and diabetes unit of Imam Reza hospital (Tabriz, Iran). Sample size was computed according to the primary information attained from the Yicong et al, trial for high-sensitivity C-reactive protein (hs-CRP). Considering $\alpha = 0.05$ and a power of 80%, the sample size was calculated as 93 per group. This number was raised up to 100 per group to compensate for drop-outs. Previous history of diabetes or the American Diabetes Association (ADA) criteria were regarded as the diabetes diagnosis criterion. Study participants were aged >18 years old with a fasting triglyceride (TG) <500 mg/dl and LDL-C >70 mg/dL. Pregnancy or lactation, history of any metabolic disorder such as kidney and liver disease and also type 1 diabetes were considered as exclusion criteria (Figure 1).

Drug Intervention

When eligible, participants were randomly allocated to take either a low 10 mg daily dose of atorvastatin (group A) or high 40 mg daily dose (group B). Subjects were asked

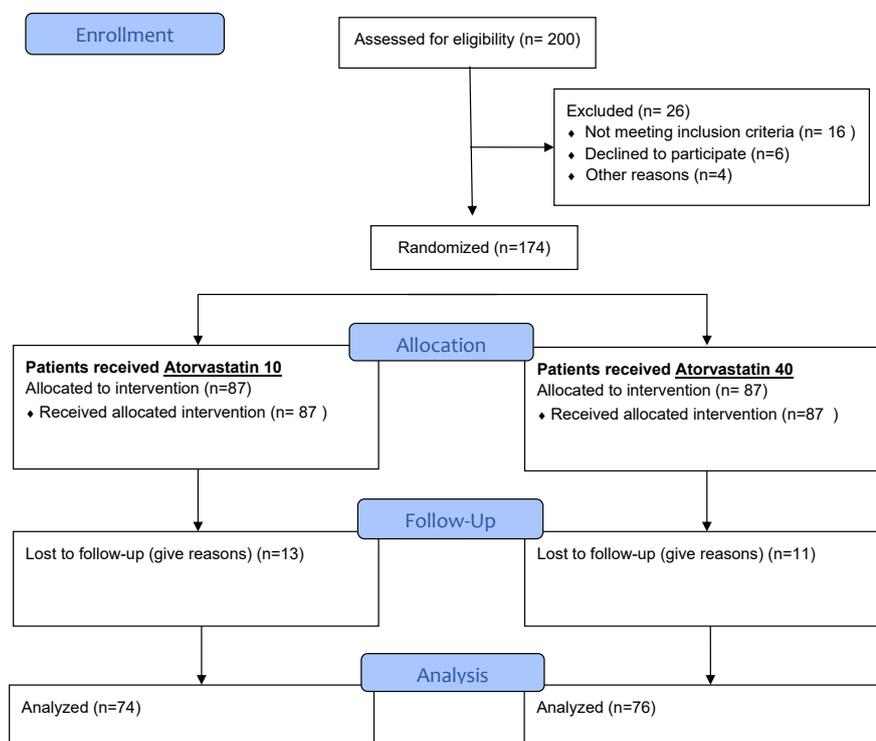


Figure 1. CONSORT flow diagram for the study.

to take 1 tablet per day for 12 weeks.

Clinical assessments and sample collection and analysis

Assessment of clinical parameters including body mass index (BMI), blood pressure (BP), and clinical data such as lipid profile, fasting blood sugar (FBS), HbA1C, interleukin-1 (IL-1), IL-6, CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fibrinogen, creatine phosphokinase (CPK) and homocysteine were evaluated at baseline and at the end of the study. BMI was calculated by dividing the body weight in kilograms into the square of the height in meters (kg/m^2). After 12-hour overnight fasting, the blood samples were collected and after the serum separation, samples were frozen at -70°C until analysis. Serum total cholesterol, HDL-C, LDL-C, and TG concentrations were determined by enzymatic procedures. Glucose levels were examined by an automated enzymatic/colorimetric assay. Serum IL-1, IL-6, HbA1C and CRP were analyzed with sandwich-type immunoassay methods, while, serum ALT and AST serum levels were also quantified using commercially available kits by automatic biochemistry analyzer. Total plasma fibrinogen was determined by a Fibri-Prest Automate method and homocysteine levels determined by homocysteine Elisa kits.

Ethical issues

This research was performed following the Declaration of Helsinki principles. Informed written consent was obtained from each patient. All information about individuals was coded and kept confidential. This study was approved by the Committee of Ethics in Human Research at Tabriz University of Medical Sciences with code Ir.rums.rec.1393168 dated 22/5/2015 and registered in Iranian Registry of Clinical Trials (IRCT) (identifier: IRCT201502226710N5; <http://www.irct.ir/trial/7136>).

Statistical analysis

SPSS software, version 21.0 was used to analyze the data using (IBM Corp., Armonk, NY, USA). Normality of the data distribution was checked by the Kolmogorov-Smirnov test. Parametric data were reported as the mean \pm standard deviation and nonparametric data were expressed as the median and interquartile range. Additionally, frequency and percentage were used to describe categorical ones. Paired *t* test was used to analyze between-group effects of atorvastatin from baseline. Independent samples *t* test and Mann Whitney U test were also used to compare differences between the two groups for parametric and nonparametric data, respectively. Accordingly, $P < 0.05$ was considered as statistically significant.

Results

Table 1 demonstrates the participants' baseline data. Around 150 individuals with a mean age of 53.77 ± 10.56

Table 1. General characteristics of individuals

	Group A	Group B	P
Age, years	52.78 \pm 11.41	54.73 \pm 9.65	0.25
Gender,% female	62.16	65.78	>0.05
BMI, kg/m^2	29.72 \pm 2.38	31.63 \pm 14.53	0.193

Variables are expressed as mean \pm SD (standard deviation) or percent. * Statistically significant ($P < 0.05$).

years (range 26-78 years) completed the study. Around, 64% of the participants were women. There were no significant differences between the two groups of patients' baseline characteristics as shown in Table 1 ($P > 0.05$). The mean levels of HbA1C (higher in group A), total cholesterol, LDL-C, and CPK (higher in group B) were significantly different between two groups before the intervention ($P < 0.05$; Table 2). The effects of two doses of atorvastatin on laboratory indices after 12 weeks of intervention are also presented in Table 2. Based on independent samples *t* test (Table 3), significant differences between the mean levels of total cholesterol, LDL-C, HDL-C, fibrinogen, IL-1 and IL-6 were observed between the groups ($P < 0.05$) while the reduction in the levels of mentioned parameters in group B was greater than group A. Furthermore, improvement in the serum FBS, HbA1C, AST, TG, total cholesterol, LDL-C, IL-1 and IL-6 values was achieved after treatment with atorvastatin 10 in group A according to paired *t* test results while, the difference was statistically significant in those markers before and after treatment ($P < 0.05$). Accordingly in group B, as paired *t* test revealed, significant differences in all blood values were evident after atorvastatin administration ($P < 0.05$) with the exception for serum homocysteine and CPK levels ($P > 0.05$).

Discussion

It seems that cardiovascular events and mortality in diabetic patients could be prevented partially by statins which are largely due to their lipid-lowering property (12). In our study, after intervention with atorvastatin, the total cholesterol and LDL-C levels were decreased specially in group B. It has been well recognized that statins decrease plasma LDL-C and cholesterol levels by inhibition of HMG-CoA reductase (9). Additionally, both doses of atorvastatin lowered TGs levels. It has been well recognized that statins, particularly atorvastatin can considerably decrease TG approximately ranging from 10% to 20% (13). Regulating very low-density lipoprotein (VLDL) secretion from the liver and improvement TG-rich lipoprotein clearance through induced LDL receptors from plasma appears to be the atorvastatin mechanism of action (8). Considering hsCRP levels, we found that atorvastatin 40 mg/d reduced CRP concentration by 40% which is approximately in line with previous studies. Comparable results were gained by the study of Vernagione et al (atorvastatin 10 mg/d orally for 6 months) (14). Furthermore, in a recent large population-based research,

Table 2. Serum biomarkers following atorvastatin 10 and 40 administration before and after interventions in each group

Parameter	Group A (Atorvastatin 10, mg/d)			Group B (Atorvastatin 40, mg/d)		
	Before	After	P	Before	After	P
	FBS (mg/dL)	184.11± 52.78	157.63± 46.02	<0.05*	165.47± 54.89	140.42± 35.21
HbA1C (%)	8.77± 1.15	8.01 ± 0.95	<0.05*	8.29± 1.33	7.71± 0.77	<0.05*
AST (IU/L)	20.94± 9.65	19.67± 6.94	<0.05*	21.92± 9.35	20.28± 5.83	<0.05*
ALT (IU/L)	25.81± 13.42	24.72± 9.06	0.1	29.77± 17.09	27.02± 11.45	<0.05*
TG (mg/dL)	200.6± 86.76	177.6± 75.53	<0.05*	185.53± 70.61	164.09± 78.28	<0.05*
Total cholesterol (mg/dL)	193.54± 36.94	158.75± 26.38	<0.05*	212.35± 41.1	145.47± 32.81	<0.05*
HDL-C (mg/dL)	42.68± 6.85	43.01± 6.2	0.3	45.32± 10.06	47.80± 9.09	<0.05*
LDL-C (mg/dL)	112.06± 35.28	80.72±23.93	<0.05*	129.91± 37.48	64.85± 32.8	<0.05*
hsCRP (mg/dL)	3.26± 2.58	4.01± 9.62	0.49	2.94± 2.32	1.74± 1.55	<0.05*
Fibrinogen (mg/dL)	370.64± 42.66	371.86± 46.14	0.79	374.26± 40.15	354.17± 39.47	<0.05*
Homocysteine (µmol/L)	14.24±6.06	14.47±6.03	0.59	16.3± 15.06	13.14± 5.88	0.064
CPK (IU)	74.97± 40.24	74.04± 46.7	0.83	91.32± 34.63	88.69± 29.8	0.36
IL-1 (pg/mL)	97.99± 23.47	94.29± 20.82	<0.05	102.81± 27.94	77.97± 21.04	<0.05*
IL-6 (pg/mL)	76.48± 31.01	72.36± 27.35	<0.05	81.43± 39.45	60.83± 28.03	<0.05*

Data are expressed as mean ± SD (standard deviation). * Statistically significant ($P<0.05$). FBS: fasting blood sugar; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; hsCRP: high sensitivity C-reactive protein; CPK: creatine phosphokinase; IL-1:interleukine 1; IL-6: interleukin 6.

Table 3. Serum biomarkers following atorvastatin 10 and 40 administration before and after interventions between groups

Parameter	Group A (Atorvastatin 10 mg/day)		Group B (Atorvastatin 40 mg/day)	P Value
	Before	After	After	
FBS (mg/dL)	Before	184.11 ± 52.78	165.47 ± 54.89	0.12
	After	157.63 ± 46.02	140.42 ± 35.21	0.12
HbA1C (%)	Before	8.77 ± 1.15	8.29 ± 1.33	<0.05*
	After	8.01 ± 0.95	7.71 ± 0.77	0.53
AST (IU/L)	Before	20.94 ± 9.65	21.92 ± 9.35	0.53
	After	19.67 ± 6.94	20.28 ± 5.83	0.91
ALT (IU/L)	Before	25.81 ± 13.42	29.77 ± 17.09	0.11
	After	24.72 ± 9.06	27.02 ± 11.45	0.84
TG (mg/dL)	Before	200.6 ± 86.76	185.53 ± 70.61	0.23
	After	177.6 ± 75.53	164.09 ± 78.28	0.69
Total cholesterol (mg/dL)	Before	193.54 ± 36.94	212.35 ± 41.1	<0.05*
	After	158.75 ± 26.38	145.47 ± 32.81	<0.05*
HDL-c (mg/dL)	Before	42.68 ± 6.85	45.32 ± 10.06	0.06
	After	43.01 ± 6.2	47.80 ± 9.09	<0.05*
LDL-c (mg/dL)	Before	112.06 ± 35.28	129.91 ± 37.48	<0.05*
	After	80.72 ± 23.93	64.85 ± 32.8	<0.05*
hsCRP (mg/dL)	Before	3.26 ± 2.58	2.94 ± 2.32	0.42
	After	4.01 ± 9.62	1.74 ± 1.55	0.06
Fibrinogen (mg/dL)	Before	370.64 ± 42.66	374.26 ± 40.15	0.59
	After	371.86 ± 46.14	354.17 ± 39.47	<0.05*
Homocysteine (µmol/L)	Before	14.24 ± 6.06	16.3 ± 15.06	0.27
	After	14.47 ± 6.03	13.14 ± 5.88	0.05
CPK (IU)	Before	74.97 ± 40.24	91.32 ± 34.63	<0.05*
	After	74.04 ± 46.7	88.69 ± 29.8	0.46
IL-1 (pg/mL)	Before	97.99 ± 23.47	102.81 ± 27.94	0.25
	After	94.29 ± 20.82	77.97 ± 21.04	<0.05*
IL-6 (pg/mL)	Before	76.48 ± 31.01	81.43 ± 39.45	0.39
	After	72.36 ± 27.35	60.83 ± 28.03	<0.05*

Data are expressed as mean ± SD (standard deviation). * Statistically significant ($P<0.05$). FBS: fasting blood sugar; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; hsCRP: high sensitivity C-reactive protein; CPK: creatine phosphokinase; IL-1:interleukine 1; IL-6: interleukin 6.

it was revealed that statins consumers had significant lower CRP concentrations than non-statin users (15). In addition, atorvastatin considerably diminished hs-CRP levels in subjects with or without diabetes or metabolic syndrome (16). The underlying mechanism might be the prevention of CRP production by statins through reduction of IL-1 β -inducible CRP expression in hepatocytes (16). In a study by Arnaud et al, statins lowered IL-6-induced CRP production at both the protein and mRNAs level in hepatocytes (17). On the other hand, it has been shown that systemic concentrations of several acute-phase proteins, cytokines, and chemokines such as IL-6 are raised in diabetic patients in comparison to healthy individuals (18). IL-6 probably interfere with insulin signaling in fat, liver, and muscle cells (19), while IL-1 β as a pro-inflammatory cytokine, prevents β -cell function and stimulates β -cell apoptosis (20). Consequently, diabetes development may stem from low-grade inflammation both due to induced insulin resistance and reduced insulin secretion. Additionally, statins have been shown to have anti-inflammatory effects (21). According to our results IL-1 and IL-6 levels improved after 12 weeks of atorvastatin therapy. Likewise, Tousoulis et al reported that levels of pro-inflammatory cytokines such as IL-6 decreased after administration of low dose atorvastatin in patients with heart failure (22). Similarly, Nawawi et al reported a significant reduction in IL-6 ($P < 0.0001$) and hs-CRP ($P < 0.01$) levels after three months intervention with atorvastatin 10 mg/d in patients with non-familial hypercholesterolemia (23). In another study, atorvastatin treatment (20-40 mg/d) attenuated pro-inflammatory markers of IL-1 and IL-6 in hypercholesterolemic patients (24). Anti-inflammatory effects of atorvastatin can be due to the lipid and lipid-derived substances reduction, such as lysolecithin, platelet activating factor and oxysterols which are considered as pro-inflammatory substances. Atorvastatin also diminishes the inflammatory response in tissues and inflammation factor in the arterial wall, respectively (25). Additionally, inhibition of primary redox sensitive transcription factors, mainly, NF- κ B, which in turn leads to suppression of cytokines, chemokines, as well as adhesion molecules synthesis, blocks pro-inflammatory activation in the vascular wall are other properties of atorvastatin (26). On the other hand, higher serum Hcy concentrations in diabetic patients were also associated with insulin resistance (7). In the present study, atorvastatin administration did not cause any significant changes in Hcy concentrations neither in group A nor in group B. Although, statins have reduced plasma tHcy levels in some studies (27,28), others have not reached the same conclusions (29–32). Parallel with our study, Miltiadous et al, reported that 40 mg/d atorvastatin for 10 weeks did not influence tHcy levels in 61 hyperlipidemia patients (30). Also, in another study carried out by Navarro et al, serum Hcy levels did not alter significantly in diabetic patients on hemodialysis, despite improvement in lipid profile

and hsCRP levels by atorvastatin administration (31). However, Van der Loo et al, revealed that administration of 80 mg/d of atorvastatin led to an increase in Hcy plasma levels in patients with peripheral arterial disease (33). The contradictories in different studies can be partly due to the dose of statins, the intervention duration, different types of diseases and patients' metabolic profiles.

Fibrinogen is an acute-phase reactant that has a key role in thrombogenesis, inflammation, immune responses, and atherogenesis (34). The level of fibrinogen was significantly lower after 12 weeks of atorvastatin treatment than before treatment only in group B. In a study by Min et al, receiving daily atorvastatin 20 mg/d for about four weeks reduced fibrinogen levels in patients with acute ischemic stroke (34). Krysiak et al also reported a decrease in fibrinogen levels after 90 days 40 mg/d atorvastatin therapy (35). As well, in another study reduction in fibrinogen level by statins was attributed to increased transcription of the endothelial nitric oxide synthase gene and increased production of endothelial nitric oxide synthase (36). Although statins are largely well accepted, they might have adverse effects on blood glucose levels, liver enzymes and also CPK (37). However, both FBS and HbA1C levels improved in both groups after 12 weeks treatment with atorvastatin which might be explained in part by the different medications which our patients received during the study. It is also possible that atorvastatin inhibits the 3T3-L1 pre-adipocytes differentiation and suppresses glucose transporter type 4 expression which in turn leads to impaired glucose uptake in adipocytes (38). It has been shown that continuous exposure of β - cells to high cholesterol concentrations can cause their dysfunction and death (39). As it was mentioned before, atorvastatin might cause hepatotoxicity, however, atorvastatin both doses lowered AST levels. However, ALT levels reduced only by atorvastatin 40 mg. In accordance with our study, Karpisek et al also presented that atorvastatin decreased AST values after three months; however, no changes in serum ALT levels was detected (37). In addition, Farsang et al revealed that the incidence of AST/ALT < 3 times of the higher limit of the average range in all patients was merely 0.8% without any rhabdomyolysis (38). Nevertheless, the atorvastatin hepatotoxicity and hepatic complications with 20 or 40 mg/d for 12 weeks are very unusual and hence it can be overlooked (38). Based on most clinical trials, creatine kinase (CK) concentration more than 10 times the upper limit of normal is regarded as myopathy induced by statins (39). Ballard et al showed that CK levels increased following atorvastatin 80 mg/d consumption from 132.3 ± 120.9 U/L at baseline to 159.7 ± 170.4 U/L and 153.1 ± 139.4 U/L at three and six months, respectively but changes in CK were not associated with changes in muscle function or the incidence of myalgia (40). However, at the present study a non-significant decrease in CPK levels was observed probably due to the low dose of atorvastatin or short duration of intervention.

Conclusion

Our finding shows that besides lipid lowering properties, atorvastatin can exert anti-inflammatory and anticoagulatory effects in type 2 diabetic patients, although effects of atorvastatin 10 mg/d seem to be milder. However, further randomized trial studies with larger population are required to clarify the exact effect of statins on inflammation, monitoring the adverse effects in higher doses or extended intervention durations.

Limitations of the study

The low number of patients may be a limitation for this study. Thus, designing a big study with more participants can be suggested.

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Conflicts of interest

We did not receive any support from atorvastatin manufactural company and we have no conflict of interest to declare.

Ethical considerations

Ethical issues (including plagiarism, double publication) have been completely observed by the authors. This article does not contain any studies with animals performed by any of the authors.

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