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Metabolic Changes with Atorvastatin in Type 2 Diabetic Jordanian Patients

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Abstract: Atorvastatin, potent lipid lowering agent has beneficial effects in enhancing insulin sensitivity. Its role in improving liver enzymes is controversial. This study aimed to investigate the effects of atorvastatin in improving liver enzymes. The study included 62 patients with diabetes type 2. They were assigned into two groups: Experimental group of 33 patients who received atorvastatin treatment for 2 months and control group of 29 patients. Blood samples were obtained before and after the experiment. Lipid profile, glucose and liver function test profile were observed. The results showed that both cholesterol and triglycerides levels decreased significantly ($p = 0.019$ and 0.025, respectively). No significant changes in glucose level were observed ($p>0.05$). Of liver enzyme profile, AST decreased significantly ($p = 0.05$). ALP, CKNAC, total proteins and total bilirubin did not show significant changes ($p >0.05$). Atorvastatin treatment decreased cholesterol and triglycerides and improved liver enzymes in diabetic type 2 patients.

Key words: Atorvastatin, cholesterol, triglycerides, glucose, liver, AST, ALP, CKNAC, protein, bilirubin

INTRODUCTION

Statins have been widely implicated clinically as lipid lowering agents to reduce morbidity and mortality from coronary artery disease. Statins work as inhibitors of the rate-limiting enzyme, 3 -hydro xy-3-me thylglutaryl-CoA (HMG-CoA) reductase, in cholesterol biosynthesis (Yousef *et al*., 2011). Statins's beneficial effects on atherosclerosis are mediated by decreased Low-Density Lipoprotein (LDL) cholesterol and improving endothelial function (Koh *et al*., 2010).

Several researchers indicated that lipophilic statins have pleiotropic actions that might cause unfavorable metabolic effects such as reduction of insulin secretion and exacerbation of insulin resistance (Kanda *et al*., 2003; Nakata *et al*., 2006). Furthermore, other studies pointed out the possibility that lipophilic statins might increase the rate of new onset diabetes (Sever *et al*., 2003; Ridker *et al*., 2008).

In a study conducted by Eliasson *et al*. (2011), it was found that blood lipid levels were lowered due to use of atorvastatin among patients with type 2 diabetes while Athyros *et al*. (2010) demonstrated that atorvastatin significantly improved liver functions by decreasing liver enzymes in patients with already abnormal liver test.

MATERIALS AND METHODS

Study design: The study design is an observational clinical study at Prince Rashed Military Hospital.

Clinical setting: Sample recruitment was in the period between July, 2010 and December, 2010. The study was conducted at healthcare facility in the Northern of Jordan; Prince Rashed Military Hospital.

Subject description: The study included 62 diabetic patients who were randomly recruited from the Medical Clinics of the PRH. Sample population was recruited depending on the following inclusion and exclusion criteria:

Inclusion criteria: Adult patients aged 18 years or more, diagnosed with type 2 diabetes.

Exclusion criteria:

- Presence of liver disease
- Type 1 diabetes
- Elevation of transaminase levels >1.5 times the upper normal limit at baseline
- Elevation of Creatine Kinase (CK) level >1.5 times the upper normal limit at baseline
- Presence of a condition of atrioventricular block and/or sinus bradycardia
- Presence of acute or chronic renal failure
- Evidence of electrolyte disturbances
- Cases of acute cerebrovascular disease or myocardial infarction within the preceding 3 months
- Evidence of alcohol abuse
- A condition of hypothyroidism
- Evidence of myopathy
- Pregnant patients
- Patients who had any medication changes during the 2 months preceding participation
- Previous treatment with anti-hyperlipidemia drugs during the 4 weeks before conducting the study

Data collection and patient interviews: A previously validated questionnaire was utilized for appropriate data collection and further statistical analysis. Each patient's medical profile of the medical clinic was reviewed.

Statistical analysis: Data were analyzed using SPSS version 15. Frequencies means and standard deviations were used to describe data wherever appropriate. Chi-square (χ^2) cross tabs were used to investigate the significance of difference between study and control groups. Binary logistic regression was used to determine factors associated with glycemic control $p \leq 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Clinical variables associated with diabetes among study and control groups: The study included 62 diabetic patients distributed into two groups: Control group (n = 29 (46.8%)) and study group (n = 33 (53.8%)). Among the variables investigated, 2 variables were significant glaucoma (p = 0.005) and family history of cardiac disease (p = 0.048). The other variables were not significant (p>0.05) (Table 1).

Personal parameters a mong study and control groups: Table 2 shows a comparison between study group and control group for the following factors: Age, BMI, WC, SBP and DBP. WC was the only variable with significance between study and control groups (p = 0.033) while the other variables were not significant (p>0.05) (Table 2).

Chemical parameters between study and control group: The following biochemical parameters were investigated among study and control groups and showed no significance (p>0.05): Glucose, total protein and AST. Cholesterol, triglyceride, HDLC2, LDLC2 and total bilirubin. The following variables were significant: ALP (0.019), CK-NAC (0.048) and amylase (0.043) (Table 3).

The effects of atorvastatin on chemical parameters after the end of experiment: After the end of the experiment, atorvastatin was able to decrease significantly the level of cholesterol (p = 0.019), triglycerides (p = 0.025). There was no significant reduction in the level of HDLC and LDLC (p>0.05). The glucose level was also reduced in significantly (p>0.05). The profile of liver enzymes showed significant decrease in the level of AST (p = 0.05) while there was insignificant decrease in the level of ALP (p>0.05) and insignificant increase in the level of CK NAC (p>0.05). Both of total protein and total bilirubin were decreased insignificantly (p>0.05) (Table 4).

Table 1: Clinical variables associated with diabetes and their significance

	Study group		
Variables	Control	Study	p-value
FHTD			
Yes	5	3	0.282
No	24	30	
Glaucoma			
Yes	11	20	0.005
No	18	13	
HD			
Yes	3	0	0.144
No	26	33	
ED			
Yes	9	4	0.162
No	20	29	
PNP			
Yes	1	0	0.468
No	28	33	
FHDM			
Yes	18	23	0.357
No	11	10	
FHTD			
Yes	6	2	0.091
No	23	31	
FHCD			
Yes	2	9	0.048
No	27	24	
HEPATIC			
Yes	6	7	1.000
No	23	26	
PNP			
Yes	21	25	0.780
No	8	8	
BP			
Yes	16	20	0.797
No	13	13	
DFU			
Yes	2	3	1.000
No	27	30	
Dyslipidemia			
Yes	1	0	0.480
No	28	33	

Table 2: Personal parameters among study and control groups

	Study group (n = 33)	Control group (n = 29)	
Variables	Mean±SD	Mean±SD	p-value
Age	56.6333±12.63679	57.3333±11.32082	0.849
WC	100.5500±4.96000	97.2060±6.07000	0.033
BMI	35.3294±29.19011	27.8111±8.15858	0.189
SBP	136.4286±21.80966	134.2857±15.01322	0.692
DBP	84.4828±14.03725	83.2759±8.89180	0.705

The present study is an observational study. It was conducted among diabetic groups. The data demonstrated that treatment with atorvastatin, as a lipid lowering agent, reduced the blood concentration of cholesterol significantly after the end of 2 months treatment (p = 0.019). Triglyceride level was also decreased significantly (p = 0.025). The levels of HDLC2 do not increase significantly (p = 0.325) and the levels of LDLC do not decrease significantly (p = 0.349). The findings for cholesterol and triglycerides indicate that

Table 3: Chemical parameters between study and control group

	Study group (n = 33)	Control group (n = 29)	
Variables	Mean±SD	Mean±SD	p-value
Glucose	229.79±73.57	245.81±94.18	0.413
ALP	88.12±24.69	103.28±25.57	0.019
TP	8.22±0.440	8.37±0.39	0.372
AST	20.96±12.10	26.34±16.50	0.194
CKNAC	105.33±59.75	76.47±46.64	0.048
Amylase	38.73±21.03	59.63±28.63	0.043
Cholesterol	219.89±60.96	217.24±44.18	0.837
TG	231.65±126.14	263.75±217.9	0.466
HDLC2	51.13±16.82	43.08±7.660	0.064
LDLC2	120.90±48.24	118.20±41.03	0.829
LDH	334.73±85.93	322.13±75.42	0.619
Total bilirubin	0.38±0.192	0.44±0.199	0.290

Table 4: The effects of atorvastatin on chemical parameters after experiment

	Before study	After study	
Variables	Mean±SD	Mean±SD	p-value
Cholesterol	220.757±55.40	201.909±53.63	0.019
Triglyceride	265.018±210.41	223.000±178.67	0.025
HDLC2	44.750±9.48	47.410±11.71	0.352
LDLC	121.630±42.011	112.510±37.82	0.349
Glucose	229.790±76.87	221.780±82.36	0.571
ALP	88.120±24.69	93.000±33.38	0.638
TP	8.220±0.44	7.980±0.32	0.319
AST	20.690±12.10	14.970±7.86	0.050
CKNAC	105.330±59.75	92.790±54.93	0.663
Total bilirubin	0.380±0.192	0.3048±0.18	0.290

statins in general are working as inhibitors for 3-hydro xy-3-me thylglutaryl-CoA (HMG-CoA) reductase, in cholesterol biosynthesis and cholesterol is more sensitive for statin treatment (Yousef *et al*., 2011; Koh *et al*., 2010). The findings are consistent results reported by Eliasson *et al*. (2011). Furthermore, non significant changes in the levels of HDLC2 and LDLC are explained by the need for long term treatment of atorvastatin as indicated by Athyros *et al*. (2010).

Treatment by atorvastatin reduced glucose level insignificantly ($p = 0.571$). In the study, glucose level decreased but not significantly while, a study reported by Anagnostis *et al*. (2011) showed increased level after statin therapy. The results showed decreased level of AST significantly ($p = 0.05$). This finding showed improvement of liver enzymes and consistent with reported findings of Athyros *et al*. (2010). It was also found no significant decrease in liver ALP, total proteins, CKNAC and total bilirubin ($p>0.05$ for all). These findings can be attributed to the fact that most participants were not hepatic patients, according to Athyros *et al*. (2010), patients with moderate hepatic disease has get more benefit from statin treatment.

CONCLUSION

Treatment by atorvastatin decreased cholesterol, triglycerides and improved liver enzymes in type 2 diabetic patients and long term study is needed to assess metabolic changes.

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