

## **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. Our 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 value 0.019 and 0.025 respectively). No significant changes in glucose level were observed (p value >0.05). Of liver enzyme profile, AST decreased significantly (p value 0.05). ALP, CK-NAC, total proteins and total bilirubin did not show significant changes (p value >0.05).

Conclusion: Atorvastatin treatment decreased cholesterol and triglycerides, and improved liver enzymes in diabetic type 2 patients.

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**Keywords:** Atorvastatin, cholesterol, triglycerides, glucose, liver, AST, ALP, CK-NAC, total protein and total 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-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, in cholesterol biosynthesis (Doustar Yousef, 2011).

Statins's beneficial effects on atherosclerosis are mediated by decreased low-density lipoprotein (LDL) cholesterol and improving endothelial function (Kwang Kon Koh, 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 M, 2006; Nakata M, 2006). Furthermore, other studies pointed out the possibility that lipophilic statins might increase the rate of new onset diabetes (Sever PS, 2003; Ridker PM, 2008).

In a study conducted by Eliasson B (2011), it was found that blood lipid levels were lowered due to use of atorvastatin among patients with type 2 diabetes, while Athyros VG (2011) 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***

1. Presence of liver disease.
2. Type 1 diabetes.
3. Elevation of transaminase levels >1.5 times the upper normal limit at baseline.
4. Elevation of creatine kinase (CK) level >1.5 times the upper normal limit at baseline.
5. Presence of a condition of atrioventricular block and/or sinus bradycardia.
6. Presence of acute or chronic renal failure.
7. Evidence of electrolyte disturbances.
8. Cases of acute cerebrovascular disease or myocardial infarction within the preceding three months.
9. Evidence of alcohol abuse.
10. A condition of hypothyroidism.
11. Evidence of myopathy.
12. Pregnant patients.

13. Patients who had any medication changes during the two months preceding participation.

14. 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 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 –value of  $\leq 0.05$  was considered statistically significant.

### Results

#### 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, two variables were significant glaucoma (p value 0.005) and family history of cardiac disease (p value 0.048). The other variables were not significant (p value  $> 0.05$ ) (table 1).

**Table 1:** Clinical variables associated with diabetes and their significance

Variable	Study group		P value
	Control	Study	
<b>FHTD</b>			
YES	5	3	0.282
NO	24	30	
<b>Glaucoma</b>			
YES	11	20	0.005
NO	18	13	
<b>HD</b>			
YES	3	0	0.144
NO	26	33	
<b>ED</b>			
YES	9	4	0.162
NO	20	29	
<b>PNP</b>			
YES	1	0	0.468
NO	28	33	
<b>FHDM</b>			
YES	18	23	0.357
NO	11	10	
<b>FHTD</b>			
YES	6	2	0.091
NO	23	31	

<b>FHCD</b>			
YES	2	9	0.048
NO	27	24	
<b>HEPATIC</b>			
YES	6	7	1.000
NO	23	26	
<b>PNP</b>			
YES	21	25	0.780
NO	8	8	
<b>BP</b>			
YES	16	20	0.797
NO	13	13	
<b>DFU</b>			
YES	2	3	1.000
NO	27	30	
<b>Dyslipidemia</b>			
YES	1	0	0.48
NO	28	33	

### Personal parameters among 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 value 0.033) while the other variables were not significant (p value > 0.05) (table 2).

**Table 2:** Personal parameters among study and control groups

Variable	Study group		Control group		P value
	Mean (N =33)	+/- SD	Mean (N= 29)	+/- SD	
Age	56.6333	12.63679	57.3333	11.32082	0.849
WC	100.55	4.96	97.206	6.07	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

### Chemical parameters between study and control group

The following biochemical parameters were investigated among study and control groups and showed no significance (p value >0.05): glucose, total protein, 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).

**Table 3:** Chemical parameters between study and control group

Variable	Study group		Control group		P value
	Mean (N =33)	+/- SD	Mean (N= 29)	+/- SD	
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	0.44	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	217.90	0.466
HDLC2	51.13	16.82	43.08	7.66	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

### 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 value 0.019), triglycerides (p value 0.025). There was no significant reduction in the level of HDLC and LDLC (P value > 0.05). The glucose level was also reduced insignificantly (P value > 0.05). The profile of liver enzymes showed significant decrease in the level of AST (P value 0.05), while there was insignificant decrease in the level of ALP (P value > 0.05), and insignificant increase in the level of CK NAC (P value > 0.05). Both of total protein and total bilirubin were decreased insignificantly (P value > 0.05) (table 4).

**Table 4:** The effects of Atorvastatin on chemical parameters after the experiment

Variable	before Study		After study		P value
	Mean	+/- SD	Mean	+/- SD	
Cholesterol	220.757	55.4	201.909	53.63	0.019
Triglyceride	265.018	210.41	223	178.67	0.025
HDLC2	44.75	9.48	47.41	11.71	0.352
LDLC	121.63	42.011	112.51	37.82	0.349
Glucose	229.79	76.87	221.78	82.36	0.571
ALP	88.12	24.69	93.00	33.38	0.638
TP	8.22	0.44	7.98	0.32	0.319
AST	20.69	12.10	14.97	7.86	0.05
CKNAC	105.33	59.75	92.79	54.93	0.663
Total bilirubin	0.38	0.192	0.3048	0.18	0.290

### Discussion

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

decrease significantly (p value 0.349). The findings for cholesterol and triglycerides indicate that 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 (Doustar Yousef, 2011, Kwang Kon Koh, 2010). Our findings are consistent results reported by Eliasson B (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 VG (2011).

Treatment by atorvastatin reduced glucose level insignificantly (p value 0.571). In our study, glucose level decreased but not significantly while , a study reported by Anagnostis P (2011) showed increased level after statin therapy.

Our results showed decreased level of AST significantly (p value 0.05). This finding showed improvement of liver enzymes and consistent with reported findings of Athyros VG (2011). It was also found no significant decrease in liver ALP, total proteins, CKNAC and total bilirubin (p value > 0.05 for all). These findings can be attributed to the fact that most participants were not hepatic patients , according to Athyros VG (2011), 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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