



## Changes in Blood Lipids and Enzymatic Reactions in Response to Atorvastatin Administration Following a High-Fat Diet in a NAFLD Rat Model

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### ABSTRACT

**Background and objectives:** Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease caused by the accumulation of large amounts of fat in the hepatocytes. Given that atorvastatin is effective for treatment of NAFLD, the present study investigated effects of high-fat/fructose diet (HFFD) with atorvastatin on liver enzymes and lipid profile in a NAFLD rat model.

**Methods:** Thirty-two male Wistar rats were divided into four groups: 1) normal control, 2) HFFD control, 3) HFFD + atorvastatin, and 4) normal + atorvastatin. The groups received HFFD for 15 weeks to induce hepatosteatosis. Atorvastatin was administered at the dose of 10 mg/kg/day. Lipid profile and liver enzymes were measured after eight weeks of intervention.

**Results:** Triglyceride, cholesterol, gamma-glutamyl transferase, and aspartate transaminase were significantly reduced in the HFFD + atorvastatin group compared with the HFFD control group. In addition, cholesterol, high-density lipoprotein, alkaline phosphatase, and gamma-glutamyl transferase were significantly increased in the normal + atorvastatin group compared with the normal control group. Low-density lipoprotein increased significantly in the HFFD + atorvastatin group and the normal + atorvastatin group compared with other groups. There was a significant difference in the alanine transaminase levels between the groups taking atorvastatin. In fact, alanine transaminase level was lowest in the normal + atorvastatin group.

**Conclusion:** Atorvastatin improves the lipid profile and fatty liver and controls liver enzymes. Therefore, it can be used with caution to improve the lipid profile and reduce the complications of NAFLD.

**Keywords:** [Atorvastatin](#), [Diet High-Fat](#), [Non-alcoholic Fatty Liver Disease](#).

## INTRODUCTION

The liver is one of the most important organs, which is involved in many functions; however, its role in fat absorbance and defense against microbes and toxins absorbed through food should not be overlooked (1). Non-alcoholic fatty liver disease (NAFLD) is histologically similar to alcoholic hepatitis but not related to alcohol consumption (2). It shows a spectrum of gradual fat accumulation in the liver, which could be life-threatening (3). The disease refers to the deposition of fat, especially triglycerides (TG) in the liver (4), which occurs when the metabolism of fatty acids shifts towards lipogenesis rather than lipolysis. This clinical condition includes diverse liver damages ranging from simple hepatitis to hepatitis steatosis, advanced fibrosis, cirrhosis, and liver cancer (5). Also, the most important hypothesis in the etiology of NAFLD is called the two-stage theory, which includes insulin resistance and oxidative damage (6). In obese patients, NAFLD is mainly associated with other components of metabolic syndrome, such as hypertension, hyperglycemia, and hyperlipidemia (7).

Aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and especially alanine aminotransferase (ALT) are the most important indicators of liver health (8). Serum levels of liver enzymes including ALP, AST, GGT, and ALT are commonly elevated in patients with NAFLD (9). These enzymes are also increased in conditions such as diabetes and alcoholism (10). Factors such as obesity, hyperglycemia, and inactivity increase the risk of developing NAFLD. Of course, some medications can also cause fat build up in the liver. Rapid weight loss in people who are already obese can also lead to this complication. According to reports, NAFLD is one of the leading causes of liver disease-associated mortality, and due to the potential progression of this disease to cirrhosis and liver failure, a lot attention has been given to detect this disease and its associated factors (11).

Carbon tetrachloride (CCl<sub>4</sub>) has been used for many years to induce liver damage and fibrosis in animal models. When combined with a Western diet rich in fat and fructose, it can induce oxidative stress, inflammation, and apoptosis. As fibrosis progresses in hepatocytes, fatty liver leads to steatosis; CCl<sub>4</sub>

induces NAFLD through this mechanism (12-14). Due to variable doses and durations of CCl<sub>4</sub> injection for the induction of NAFLD, besides the possibility of hepatotoxicity rather than NAFLD induction, a diet-based method is needed to develop an optimal model.

Several medications, including atorvastatin, are prescribed for treatment of NAFLD. Atorvastatin is a subset of statin drugs that if administered for long-term and in high-dose, can cause hepatic complications and increased cell apoptosis. It can also reduce blood cholesterol, TG, and low-density lipoprotein-cholesterol (LDL-C) and increase high-density lipoprotein-cholesterol (HDL-C) levels. Atorvastatin is prescribed in different doses to cardiovascular patients and patients with high cholesterol. Atorvastatin have antioxidant, anti-apoptotic, and anti-inflammatory properties (15,16). The anti-inflammatory properties of this drug are mediated via alteration of expression of pro-inflammatory and anti-inflammatory factors (17). Given that atorvastatin is effective for treatment of NAFLD, the present study investigated effects of a high-fat/fructose diet (HFFD) with atorvastatin on liver enzymes and lipid profile of a NAFLD rat model.

## MATERIALS AND METHODS

### *Animals and diet*

In this study, 32 male Wistar rats weighting 200-250 g were obtained from the Shahid Mirghani Research Institute, Iran. The animals were divided into four groups of eight: 1) normal diet 2) HFFD 3) HFFD + atorvastatin, and 4) Normal + atorvastatin. Atorvastatin was prescribed at the dose of 10 mg/kg (diluted in 6% dimethyl sulfoxide) for eight weeks. The animals were fed ad libitum and housed in pairs in plastic cages, under a controlled temperature (22 ± 2°C) with 12-h light/dark cycles. The normal diet contained 4.30 kcal per gram including 3.87% fat (soy oil), 17.46% casein protein, 68.7% carbohydrates, 8.97% minerals, and 1% vitamins. Hepatosteatorosis was induced according to a protocol described previously (18).

### *Measurement of biochemical indices*

The rats were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (5 mg/kg, Merck, Germany). Blood samples were collected and centrifuged at 3,000 rpm for 10 minutes. Levels of AST, ALT, ALP,

and GGT were determined by standard enzymatic techniques, and serum cholesterol, TG, LDL, and HDL levels were evaluated using an auto-analyzer (BT-3500, Biotechnica Instruments, Italy).

#### Statistical analysis

Results are presented as mean  $\pm$  standard deviation. Data were initially analyzed by one-way analysis of variance (ANOVA). Post hoc Tukey HSD test was applied for group comparisons. A *p*-value of less than 0.05 was considered to be statistically significant. Statistical analysis of data was carried out in SPSS Statistics (version 22).

#### Ethical statement

The study was performed in accordance with

the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH publication No. 85–23, revised 1996). The study protocol was approved by the local ethics committee (IR.GOUMS.REC.1397.274).

All efforts were made to minimize animal suffering and reduce the number of animals used.

## RESULTS

There was no significant difference in the mean weight of rats before the study, but after 15 weeks of HFFD, a significant difference was observed in the mean weight of animals in all study groups (Table 1).

Table 1-Mean weight of rats before consuming normal diet and HFFD and after 15 weeks of consuming HFFD

Group	Before consuming normal diet/HFFD	After 15 weeks of consuming HFFD
	Mean $\pm$ SD	Mean $\pm$ SD
Normal control	238.29 $\pm$ 11.52	390.43 $\pm$ 14.32
HFFD control	243.35 $\pm$ 7.05	380.44 $\pm$ 16.74
HFFD +ATO	229.66 $\pm$ 19.44	343.16 $\pm$ 12.21
Normal + ATO	231.14 $\pm$ 18.21	256.16 $\pm$ 12.21
<i>p</i> -value	0.124	0.005 *

ATO: Atorvastatin, SD: standard deviation

After 15 weeks of consuming a normal and a high-fat diet, the two groups received atorvastatin for eight weeks, and then, the weight of the rats was measured. The mean weight of rats in the normal control, HFFD

control, and normal + atorvastatin groups increased significantly after eight weeks. However, the mean weight of rats in the HFFD + atorvastatin group did not change significantly (Table 2).

Table 2-Mean weight of rats after atorvastatin administration

Group	First week Mean $\pm$ SD	Second week Mean $\pm$ SD	3 <sup>rd</sup> week Mean $\pm$ SD	4 <sup>th</sup> week Mean $\pm$ SD	5 <sup>th</sup> week Mean $\pm$ SD	6 <sup>th</sup> week Mean $\pm$ SD	7 <sup>th</sup> week Mean $\pm$ SD	8 <sup>th</sup> week Mean $\pm$ SD
Normal control	390.77 $\pm$ 23.16	420.84 $\pm$ 26.98	443.53 $\pm$ 26.26	418.18 $\pm$ 26.27	427.63 $\pm$ 16.23	450.41 $\pm$ 22.38	452.01 $\pm$ 19.86	454.99 $\pm$ 19.27
HFFD control	384.96 $\pm$ 25.83	378.19 $\pm$ 10.01	392.36 $\pm$ 32.24	439.59 $\pm$ 12.23	427.79 $\pm$ 24.85	441.47 $\pm$ 15.75	449.91 $\pm$ 17.08	461.36 $\pm$ 17.81
HFFD + ATO	343.86 $\pm$ 27.84	334.30 $\pm$ 41.08	337.13 $\pm$ 37.13	330.57 $\pm$ 46.53	332.99 $\pm$ 40.99	328.47 $\pm$ 46.95	343.51 $\pm$ 40.36	338.84 $\pm$ 45.27
Normal + ATO	256.23 $\pm$ 21.51	267.86 $\pm$ 18.52	302.63 $\pm$ 15.39	319.35 $\pm$ 17.62	333.48 $\pm$ 21.46	342.56 $\pm$ 27.77	339.65 $\pm$ 23.02	353.52 $\pm$ 23.84
<i>p</i> -value	0.000 *	0.000 *	0.000 *	0.000 *	0.000 *	0.000 *	0.000 *	0.000 *

ATO: Atorvastatin, SD: standard deviation.

There was a significant difference between TG, cholesterol, LDL, HDL, and LDL/HDL ratio between all groups; but, there was no significant difference in the cholesterol/HDL ratio between the groups. The results indicate a significant difference between the liver enzymes of rats in the study groups. Moreover, TG and cholesterol in the HFFD + atorvastatin group were significantly decreased compared with the HFFD control group. In addition, cholesterol and HDL were significantly increased in the normal + atorvastatin group

compared with the normal control group. Serum LDL was significantly increased in the HFFD + atorvastatin and the normal + atorvastatin groups compared with other groups.

In liver enzymes, AST was significantly reduced in the HFFD + atorvastatin group compared with the HFFD control. There was a significant difference in the ALT level between the groups taking atorvastatin. In fact, ALT level was lowest in the normal + atorvastatin group. There was a significant

Increase in the level of ALP and GGT in the normal + atorvastatin group compared with the normal control group. There was also a

significant decrease in GGT in the HFFD + atorvastatin group compared with the HFFD control group ([Table 3](#)).

Table 3- Comparison of lipid profile and liver enzymes between all study groups

Variable	Normal control Mean±SD	HFFD control Mean±SD	HFFD + ATO Mean±SD	Normal + ATO Mean±SD	F	p
TG (mg/dl)	55.00±13.11	114.42±11.81	86.50±6.71	85.84±28.27	38.186	0.000*
CHO (mg/dl)	52.33±4.93	69.57±6.05	44.33±3.72	81.50±3.50	50.605	0.000*
LDL (mg/dl)	13.33±2.05	2.45±1.02	5.10±1.11	20.13±2.05	135.247	0.000*
HDL (mg/dl)	30.56±5.97	38.74±10.99	32.20±6.11	62.13±7.77	9.492	0.001*
LDL/HDL	0.44±0.06	0.06±0.02	0.16±0.05	0.32±0.01	62.061	0.000*
CHO /HDL	1.75±0.33	1.92±0.61	1.41±0.27	1.32±0.19	2.044	0.151
AST (IU/L)	118.40±41.90	249.30±26.48	172.48±18.02	116.30±4.30	30.539	0.000*
ALT (IU/L)	65.50±25.30	141.65±56.12	107.21±28.24	52.00±9.27	6.237	0.006*
ALP (IU/L)	215.00±22.00	409.42±77.68	369.00±38.97	377.00±12.00	11.022	0.000*
GGT (IU/L)	1.66±0.60	3.14±0.17	1.10±0.36	3.50±0.40	50.769	0.000*

ATO: Atorvastatin, SD: standard deviation, CHO: cholesterol

\* Statistically significant. Data were analyzed by one-way analysis of variance.

## DISCUSSION

The results of histological and biochemical evaluations showed a significant increase in the effects of atorvastatin in the HFFD group. In addition, a significant reduction in the activity of serum liver enzymes was noted, which indicates the improvement of tissue lesions. This effect was also confirmed by histological findings. Due to the significant increase in the prevalence of NAFLD in the world, exploiting prevention and treatment methods has become essential. The disease is directly related to lifestyle and diet. Dietary changes in developing countries and the consumption of HFFD as well as physical inactivity have led to an increase in the prevalence of NAFLD. Animal models of NAFLD are widely used due to the limitations of obtaining human liver tissue samples.

Cholesterol synthesis in mammalian cells, including the hepatocytes, is governed by negative feedback loop involving the rate-limiting enzyme for cholesterol synthesis 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR). Inhibitors of HMGCR, commonly called statins, are widely used for the treatment of hypercholesterolemia ([19](#)). Both HMGCR and LDL receptor are of critical importance in cholesterol homeostasis, and their expression is greatly influenced by intracellular cholesterol levels. Early in vitro and animal studies demonstrated that the decreased production of cholesterol induced by statins was accompanied by a marked compensatory increase in HMGCR and LDL

receptor expression ([20](#)). More recent studies have found a considerable increase in HMGCR mRNA in response to statins in HepG2 cells ([21](#)), rats ([22](#)), and miniature pig livers ([23](#)). It has been also emphasized that the post-transcriptional modifications affect HMGCR levels, at least in rats ([19](#), [22](#)). Despite the importance of oral statin administration in patients with hyperlipidemia, there have been remarkably few studies on the effects of statins on HMGCR or LDL receptor expression in humans ([24](#), [25](#)). These studies have used mononuclear cells, with the regulation of cholesterol metabolism in such cells having been shown to be similar to that of other tissues ([26-29](#)).

Statins can influence the kidney in two main pathways. Rhabdomyolysis is the most serious adverse effect of statin use, though it occurs quite rarely (incidence rate of less than 0.1%). Rhabdomyolysis can induce tubular obstruction, causing tubular injury and ischemia. Statin therapy can be associated with a benign proteinuria due to inhibition of the tubular reabsorption of small molecular weight proteins. The clinical significance of this mild proteinuria is unknown, as the protein differs from that of other glomerular diseases. There has been no evidence of long-term renal dysfunction from statin therapy ([30](#), [31](#)). In the present study, the induction of NAFLD caused an increase in liver enzymes. After administering atorvastatin in the HFFD group, the level of liver enzymes reduced



significantly compared with the HFFD control group. It has been reported that NAFLD is associated with cell damage as well as increased serum levels of AST and ALT. The increase in these factors is greater than the increase observed in metabolic syndrome. Atorvastatin acts as a reducer of bad cholesterol by inhibiting the enzyme  $\beta$ -Hydroxy  $\beta$ -methylglutaryl-CoA (HMG-CoA) in the liver, and HMG-CoA plays a key role in cholesterol biosynthesis. It is rapidly absorbed through the gastrointestinal tract. Active drug metabolites are responsible for about 70% of the inhibitory effect of HMG-CoA reductase (32). Most drugs used to treat various diseases are metabolized in the liver. Inability of the enzymatic systems in refining these metabolites cause acute and chronic damage to the liver tissue and is directly associated with liver toxicity (33). According to Ji et al., atorvastatin can lower serum fat and liver enzyme profiles, reduce inflammation, and improve liver function (34). In the present study, in addition to liver enzymes, other biochemical markers that are usually increased in NAFLD were also examined. Almost all indicators confirmed the development of NAFLD. The groups receiving atorvastatin in the present study had improved lipid profiles, and TG and cholesterol levels were significantly reduced compared with the control group.

## CONCLUSION

According to the results of the present study, atorvastatin can be used as a potentially suitable medication for the treatment of NAFLD. However, additional studies are needed to determine the exact mechanism of action and its effect on NAFLD complications.

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## DECLARATIONS

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## Ethics approvals and consent to participate

The study was performed in accordance with the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH publication No. 85–23, revised 1996). The study protocol was approved by the local ethics committee (IR.GOUMS.REC.1397.274). All efforts were made to minimize animal suffering and reduce the number of animals used.

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