# Effect of atorvastatin, with or without ezetimibe, on serum lipid profile and ALT in hyperlipidemic patients

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## Abstract

**Background and objectives:** Hyperlipidaemia is raised serum levels of one or more of total cholesterol, low-density lipoprotein and triglycerides. Many drugs have been used for the treatment of this disorder. This work compares the effects of atorvastatin with or without ezetimibe on lipid profile, atherogenic index and serum alanine aminotransferase.

**Methods:** This study covers 90 subjects, 60 untreated hyperlipidemic patients, and 30 healthy subjects. Patients were divided into 2 groups, the first group included 30 patients treated with atorvastatin 20 mg/day alone, the second group included 30 patients treated with a combination of 2 drugs (atorvastatin 10 mg plus ezetimibe 10 mg) taken daily at night. Serum lipid profile, atherogenic index and serum alanine amniotransferase were measured after 12 hours fasting for the patients in 3 intervals: before, and after 8 weeks and 16 weeks of treatment.

**Results:** After therapy for both groups of patients, as compared to the levels before treatment, has shown that serum total cholesterol, triglycerides, low density lipoprotein cholesterol and very low density lipoprotein cholesterol were significantly reduced while high density lipoprotein cholesterol was significantly increased. Serum alanine aminotransferase increased by both groups of treatment with no significant difference between the two modes of treatment which has the same findings in comparison to the control group.

**Conclusion:** Combination of atorvastatin 10 mg and ezetimibe 10 mg daily, is more effective than atorvastatin 20 mg taken alone.


**Key words**: hyperlipidaemia ,atherogenic index , atorvastatin ,ezetimibe, alanine aminotransferase

## Introduction

Primary hyperlipidemia occurs due to abnormalities in gene encoding of LDL-C receptors which causes a decrease in the functioning of LDL-C receptors. This leads, in turn, to an increase in the LDL-C concentration since the major pathway of the removal of LDL-C is via LDL-C receptors in the liver cells. Increased production of VLDL, which is the precursor to LDL-C, could also result in elevated LDL-C concentration.[1] Secondary hyperlipidemia occurs as a complication of conditions such as diabetes where poor control of glucose levels could lead to elevated triglyceride levels. Other medical conditions associated with hyperlipidemia include hypothyroidism, liver disease, and Cushing's syndrome[2]. In addition, use of alcohol and drugs such as corticosteroids, thiazide diuretics, estrogen and beta-blockers have also been associated with hyperlipidemia [3]. HMG-CoA reductase inhibitors presently provide the most potent drug treatment for hypercholesterolemia[4].These compounds are structural analogs of HMG-CoA. Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin which belong to this class. They are most effective in

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reducing LDL-C[5] . Ezetimibe monotherapy is recommended as an option for treatment for adults who are intolerant to statin therapy, co-administered with initial statin therapy, is recommended as an option for treatment of adults who have been initiated on statin therapy when serum TC or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy [6].

## Methods

This study was carried out in the outpatient department of Rizgary Teaching Hospital in Erbil city, for a period of 6 months. It covered 60 untreated hyperlipidemic patients whose ages ranged between 32-53 years (39.9±4.71) (41 males and 19 females).It consisted of two groups: Group 1 comprised of 30 patients receiving atorvastatin, 20mg daily at bed time and Group 2 comprised of 30 patients receiving combined drug of (atorvastatin 10 mg and ezetimibe 10 mg) daily at bed time. Any Patient with other diseases or on other medications that might affect the study was excluded. Thirty normal subjects (normolipidemic) were included as a control group. Their ages ranged between 25-43 years (35.16±4.77) (18 males and 12 females). Fasting blood samples of control group, and patients groups (before treatment and after) was collected. Serum was separated and total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT) were estimated by enzymatic colorimetric method.

**Statistical analysis:**

The variables' differences were compared to each other with student t-test. Values less than 0.05 ($p<0.05$) were regarded significant [7].

## Results

The results presented are based on the analysis of a patient-control comprising 60 hyperlipidaemic patients (30 patient on atorvastatin and other 30 patient on combine treatment atorvastatin and ezetimibe) with 30 healthy subject as control group. Table( 1 ) shows the effect of atorvastatin on serum, total cholesterol (TC) , triglycerides(TG), high density lipoprotein cholesterol (HDL-C) , low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) , alanine aminotransferase (ALT),and atherogenic index (TC/HDL-C) in hyperlipidemic patients after 8 and 16 weeks of treatment with atorvastatin as compared to before starting the treatment .It is to be noted that atherogenic index, serum lipid profile, (except HDL-C ) were significantly reduced while serum HDL-C was significantly increased after 8 and 16weeks of treatment- in comparison to before treatment ; and at the same time a significant difference also was observed in comparison to control group. Alanine aminotransferase has significantly changed after 8 weeks and 16 weeks of treatment when compared to before starting the treatment, while no significant difference if compared to control group. As shown in (Table 2 ) group 2, the effect of atorvastatin plus ezetimibe on serum lipid profile, atherogenic index and alanine aminotransferase in hyperlipidemic patients after 8 and 16 weeks of treatment, when compared to before starting the treatment, serum total cholesterol, triglycerides, low density lipoproteins, and very low density lipoproteins were significantly reduced while serum high density lipoprotein was significantly increased After 8 and 16 weeks of treatment a significant difference between serum lipid profiles of this group was detected when compared with control group (normal subjects). Alanine aminotransferase was significantly changed after the 2 intervals of treatment when compared to before starting the treatment, but nonsignificant if compared to control group. A significant reduction in atherogenic index (TC/HDL) noticed after both intervals of treatment in comparison to before starting the treatment.Comparison effect of atorvastatin (group 1) with drug combination of

(atorvastatin plus ezetimibe) (group 2) are displayed in Table( 3 ) in respect to serum lipid profile atherogenic index (TC/HDL), and ALT after 8 weeks of taking treatment.
No significant difference was detected between 2 groups in respect to serum lipid profile but significant difference noticed in atherogenic index (TC/ HDL), while in comparison of these two groups with respect to the control one there was a significant difference between them in all study markers at level ($p<0.05$). There was no significant difference between the two groups as for Serum ALT after 8 weeks of treatment at level ($p<0.05$). Comparison, effect of atorvastatin (group 1) with drug combination of (atorvastatin plus ezetimibe) (group 2) was explained in Table( 4 ) in respect to serum lipid profile atherogenic index (TC/ HDL), and ALT after 16 weeks of treatment. A significant difference was detected between 2 groups in respect with serum total cholesterol, triglycerides low density lipoproteins, very low density lipoproteins and atherogenic index (TC/HDL) but non significant difference in serum high density lipoproteins was detected in respect with mean values at level ($p<0.05$).Concerning serum ALT no significant results obtained for the same period of treatment.

**Table 1:** Effects of Atorvastatin on serum total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins, alanine aminotransferase, and atherogenic index (TC/HDL) before, after 8 and 16 weeks of treatment.

| **Parameters** | **Control (n=30)** | **Group (1) patients treated with Atorvastatin (n=30)** | | |
|---|---|---|---|---|
| | | Before treatment | After 8 weeks of Treatment | After 16 weeks of Treatment |
| TC mmol/L | 3.71±0.20a | 6.41±0.91b | 5.18±0.53c | 4.47±0.39d |
| TG mmol/L | 1.54±0.17a | 2.90±0.44b | 2.30±0.34c | 1.99±0.33d |
| HDL-C mmol/L | 1.21±0.09a | 0.97±0.12b | 1.07±0.12c | 1.14±0.12d |
| LDL-C mmol/L | 1.74±0.25a | 4.10±0.98b | 3.05±0.57c | 2.41±0.40d |
| VLDL-C mmol/L | 0.30±0.03a | 0.57±0.08b | 0.46±0.06c | 0.39±0.06d |
| Atherogenic index | 2.97±0.29a | 6.66±1.15b | 4.88±0.72c | 3.91±0.58d |
| ALT IU/L | 15.1±3.12a | 12.86±3.29b | 14±3.02a | 15.4±3.15a |

*Data represented by mean ± SD.
*Values with non-identical superscript (a, b, c, d) are representing significant difference at level P< 0.05.

**Table 2:** Effect of (Atorvastatin plus Ezetimibe) on serum total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins, alanine aminotransferase, and atherogenic index (TC/HDL) after 8 and 16 weeks of treatment.

| **Parameters** | **Control (n=30)** | **Group (2) patients treated with Atorvastatin plus ezetimibe (n=30)** | | |
|---|---|---|---|---|
| | | Before treatment | After 8 weeks of Treatment | After 16 weeks of Treatment |
| TC mmol/L | 3.71±0.20a | 6.28±0.54b | 4.97±0.34c | 4.14±0.30d |
| TG mmol/L | 1.54±0.17a | 2.90±0.26b | 2.22±0.22c | 1.83±0.17d |
| HDL-C mmol/L | 1.25±0.09a | 0.98±0.08b | 1.09±0.09c | 1.19±0.08d |
| LDL-C mmol/L | 1.74±0.25a | 3.95±0.54b | 2.85±0.37c | 2.09±0.30d |
| VLDL-C mmol/L | 0.30±0.03a | 0.58±0.05b | 0.44±0.045c | 0.36±0.34d |
| Atherogenic index | 2.97±0.29a | 6.45±0.70b | 4.55±0.50c | 3.46±0.34d |
| ALT IU/L | 15.1±3.12a | 12.20±3.57b | 13.76±3.23a | 16.63±2.91a |

*Data represented by mean ± SD
*Values with non-identical superscript (a, b, c, d) are representing significant difference at level P< 0.05.

**Table 3:** Comparison of effect of Atorvastatin with (Atorvastatin plus Ezetimibe) on serum total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins, alanine aminotransferase, and atherogenic index (TC/HDL) after 8 weeks of treatment.

| Parameters | Control (n=30) | Group 1 Atorvastatin (n=30) | Group 2 Atorvastatin plus zetimibe (n=30) |
|---|---|---|---|
| TC mmol/L | 3.71±0.20a | 5.18±0.53b | 4.97±0.34b |
| TG mmol/L | 1.54±0.17a | 2.30±0.34b | 2.22±0.22b |
| HDL-C mmol/L | 1.21±0.09a | 1.07±0.12b | 1.09±0.09b |
| LDL-C mmol/L | 1.74±0.25a | 3.05±0.57b | 2.85±0.37b |
| VLDL-C mmol/L | 0.30±0.03a | 0.46±0.06b | 0.44±0.045b |
| Atherogenic index | 2.97±0.29a | 4.88±0.72b | 4.55±0.50c |
| ALT IU/L | 15.1±3.12a | 14±3.02a | 13.76±3.23a |

*** Mean values with non-identical superscript (a, b, c, d) are representing significant difference at level P< 0.05.**

**Table 4:** Comparison effect of Atorvastatin with (Atorvastatin plus Ezetimibe) on serum total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins, alanine aminotransferase, and atherogenic index (TC/HDL) after 16 weeks of treatment.

| Parameters | Control (n=30) | Group 1 Atorvastatin (n=30) | Group 2 Atorvastatin plus Ezetimibe (n=30) |
|---|---|---|---|
| TC mmol/L | 3.71±0.20a | 4.47±0.39b | 4.14±0.30c |
| TG mmol/L | 1.54±0.17a | 1.99±0.33b | 1.83±0.17c |
| HDL-C mmol/L | 1.21±0.09a | 1.14±0.12b | 1.19±0.10b |
| LDL-C mmol/L | 1.74±0.25a | 2.41±0.40b | 2.09±0.30c |
| VLDL-C mmol/L | 0.30±0.03a | 0.39±0.06b | 0.35±0.34c |
| Atherogenic index | 2.97±0.29a | 3.91±0.58b | 3.46±0.34c |
| ALT IU/L | 15.1±3.12a | 15.4±3.15a | 16.63±2.91a |

***Data represented by mean ± SD.**
***Values with non-identical superscript (a, b, c, d) are representing significant difference at level P< 0.05.**

## Discussion

Concomitant elevation of circulating levels of triglyceride-rich VLDL and cholesterol-rich LDL is recognized as being associated with an increased risk of premature coronary artery disease[8],.and is characteristic of subjects who exhibit a lipid phenotype typical of combined hyperlipidemia [9]. Table ( 1 ) shows that total cholesterol and LDL-C were significantly reduced in hyperlipidemic patients treated with atorvastatin after 8 and 16 weeks of treatment. These results are in agreement with results of studies conducted by[10,11] they found that atorvastatin has reduced plasma cholesterol up to 45% in patient with primary hypercholesterolemia. The mechanism underlying the decrease in total cholesterol and LDL-C levels observed during atorvastatin therapy: Atorvastatin is a synthetic reversible competitive inhibitor of HMG-CoA

reductase which is the rate limiting enzyme of cholesterol biosynthesis[12,13] . It is interesting to note that atorvastatin may also lower plasma cholesterol levels by inhibiting hepatic synthesis of cholesterol in VLDL-C which is the source of LDL-C, resulting in the reduced levels of LDL-C[14]. Since atorvastatin diminishes the synthesis of cholesterol in hepatic cells, and cholesterol is essentially required in the normal production of VLDL particles, the inhibition of cholesterol synthesis may impair VLDL particle assembly and secretion, decrease the VLDL-C levels in plasma, and further decrease the LDL-C level in plasma[15]. Table( 1 ) shows that TG and VLDL-C were significantly reduced in hyperlipidemic patients treated with atorvastatin after the 2 intervals of treatment. These results are in agreement with a study conducted earlier [16], who found that atorvastatin daily dose significantly reduced TG by 31%, while other result[17] did not find a significant decrease in TG after 6 months of treatment by atorvastatin 20 mg daily dose, serum TG baseline was (135 ± 12) mg/dl, after 6 months of treatment was (132 ± 10) mg/dl.

It is clearly shown in (Table 1 ) that HDL-C was significantly increased in hyperlipidemic patients, this result was quite similar to that reported by other study[18], who found that atorvastatin daily doses significantly increased HDL-C for 12 weeks. Available evidence suggests that increases in HDL-C with statin therapy results from a combination of increased expression of apoA-I and reduced HDL-C remodeling as a consequence of lowering triglyceride levels[19,20]. As showed in the (Table 1), atherogenic index (TC/HDL-C) was significantly reduced in hyperlipidemic patients, this result was quite similar to that reported [21] , who found that atorvastatin 20 mg daily dose for 6 weeks of therapy significantly reduced atherogenic index (TC/HDL-C) by 32.3%, and serum alanine aminotransferase (ALT) levels were significantly increased in hyperlipidemic patients treated with atorvastatin after 8 and 16 weeks of treatment in comparison with the ones before treatment, yet within normal ranges when compared to normal subjects (controls). These results coincide with that reported by [22], who found that atorvastatin 20 mg for several weeks increase ALT from (12 ± 3) as the baseline to (16 ± 6) but they showed that all regimens was well tolerated and none of patients had a significant elevation of liver enzymes ( ≥ 2 times the baseline). Regarding the comparison effects of drug combination and atorvastatin alone shows the synergetic effect of ezetimibe when combined with statins[23]. In this study both groups were significantly reduced serum lipid profile compare to control but the differences between both groups were non significant as shown in (Table 3 ). In accordance with a study reported by [24] , they found that serum LDL-C and TG significantly reduced by drug combination of (ezetimibe 10 mg plus atorvastatin 10 mg) than atorvastatin 40mg alone after 4 weeks of treatment but the change between both groups was non significant, the HDL-C level did not change in either groups. Results revealed that the effect of drug combination on serum total cholesterol, LDL-C and triglyceride reduction is significantly greater than atorvastatin 20 mg alone after 16 weeks of treatment as shown in (Table 4). These results are in consistence with the results of study conducted by [25] who found that atorvastatin 10 mg plus ezetimibe 10 mg was significantly reduced serum total cholesterol, LDL-C and triglyceride than 20 mg atorvastatin after 12 weeks of treatment. Effect of drug combination on serum HDL-C is found to be insignificant between both groups after 16 weeks of treatment as shown in (Table 4), and the effect on atherogenic index TC/ HDL reduction is significantly greater than atorvastatin 20 mg alone . These results agree with those of [26,28] where they found that combination therapy with ezetimibe 10 mg and atorvastatin 10 mg provided significantly greater reduction in ratio of total cholesterol to serum HDL than atorvastatin 20 mg alone after 4 weeks of therapy. The serum ALT has increased significantly by

both modes of treatment after 8 weeks compared to ones before treatment (Table 1) but no significant difference was noticed between both groups after 16 weeks of treatment and are still within normal ranges when compared to normal subjects (control groups) as shown in (Table 4 ). These results supported by [24,27] they found that serum ALT has increased from (28.9±1.8) as a baseline to (33.0±4.2) for drug combination of (ezetimibe 10 mg atorvastatin 10 mg) while atorvastatin alone has increased serum ALT from (26.9±1.8) as a base line to (30.0±3.0) after 4 weeks of therapy. Other study [28] found that the combination of ezetimibe plus atorvastatin was well tolerated, with an overall safety profile similar to that of atorvastatin alone. All elevations in hepatic enzymes were asymptomatic, and no hepatitis, jaundice, or other clinical signs of liver disfunction were reported.

## Conclusion

Combination of atorvastatin 10 mg and ezetimibe 10 mg daily is more effective than atorvastatin 20 mg alone.

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