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# Effect of Simvastatin drug on liver function parameters in men patients with hyperlipidemia in Al-Najaf province

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**Abstract :** The current study was carried out in Al-Hakeem Hospital in Al-Najaf province. The study was undertaken to evaluate the effect of simvastatin drug that's used to treatment of hyperlipidemia on liver function criteria (ALT,AST,ALP, and bilirubin) in a number of hyperlipidemic males patients. Forty-eight male patients who are taking this drug to reduced cholesterol concentration in the plasma participated in the study, their ages ranged from (36-65) years divided into two groups (24/group) according to simvastatin doses 10 and 20 mg once daily. Also, eighteen healthy males contribute as control subjects, their ages ranged from (33-66) years.

Results of this study revealed, that simvastatin administration at different doses to hyperlipidaemic patients with different ages causes a significant elevation of ALT, AST, ALP and bilirubin levels which increased relatively with the doses of simvastatin and patients ages. On the other hand, the results obtained there was an effect of interaction between different doses of simvastatin and ages of hyperlipidaemic patients that treated with it on liver function tests particularly at the higher doses and ages , and this effect was represented by increased of these parameters. The study was suggested that the therapy with simvastatin may be causes lesions in liver tissues indicated by elevation of serum liver function criteria levels and this effect was dependent on simvastatin doses and patients' ages.

## Introduction

Drug-induced hepatic injury becomes to be a prevalent health challenge participating about fifty percent of severe liver failure disease[1]. Yearly, many patients who suffered from hepatotoxicity prompted by medication were illustrated, part of whom requires fast transplantation due to irreversible liver injury [2].Various types of investigations are used in the diagnosis of drug-induced hepatotoxicity, liver function tests are measured; these include serum bilirubin, transaminases, alkaline phosphatase, gamma-glutamyl transferase and albumin[3]. The attention of studying drug hepatotoxicity had increased when a number of fatal hepatic toxicity cases were demonstrated with 2 drugs of the thiazolidinedione antidiabetic agents (troglitazone and rosiglitazone) which caused acute hepatic failure and severe hepatocellular injury [4]. Among the drugs which are investigated to have hepatic toxicity potential are antihypertensive agents e.g. methyldopa and antidiabetic agents e.g. acarbose[5].

Also, one of the cases in which drug cause hepatotoxicity is Hyperlipidemias, increasing of lipid concentration in blood plasma regarded as the indicator of a dysfunction in the composition and regression of lipoproteins (LPs) in plasma and may result from a genetic defect or by several diseases e.g. diabetes mellitus, chronic renal failure, beta blockers, thiazide diuretics and corticosteroids, thus, a major problem in hyperlipidemia patients is increased the atherosclerosis risk and consequently ischaemic heart disease[6]. The best drugs for hyperlipidaemia treatment is statins or 3-hydroxy -3-methylglutaryl coenzyme A reductase inhibitors

used to lower cholesterol levels by inhibiting (HMG-CoA reductase) which plays a central role in the production of cholesterol in the liver due to of statin drugs are like to the molecular structure of HMG-CoA (C25H38O5),so it replaced of HMG-CoA in the enzyme and diminish the rate by which it can create mevalonate which considered as the following molecule in the pathway that forms cholesterol[7, 8]. Therefore, the most common type of statins is simvastatin which is valuable, but their conflicting action, hepatotoxicity, is constantly troubling for both patients and physicians[9]. The first clinical studies on HMG-CoA reductase inhibitor reported a low incidence of liver toxicity, but this is followed by observations of a large number of cases on simvastatin therapy with hepatic toxicity by incidence of elevated serum liver enzymes and bilirubin [5, 10, 11]. Due to lack of information about the hepatotoxicity of statin drug in Al-Najaf population, the current study was worked to assess the hepatic disorders by investigation the activities of the alanine transaminases (ALT), aspartate transaminases (AST), alkaline phosphatase (ALP) and total bilirubin concentration in serum of men patients with hyperlipidemia who are treated with simvastatin.

## Material and Methods:

### Patients:

This study was conducted during the period from 2015/7/12 till 2016/3/22 in Al-Hakeem Hospital in Al-Najaf province. Forty-eight male hyperlipidaemic patients who took simvastatin therapy (SIMVORRANBAXY- laboratories limited India) to lower their high blood lipid concentration participated in the study , Their ages ranged from (36-65) years divided into three groups according to the ages (36-45, 46-55, 56-65). The forty-eight patients divided into two groups ( 24/group) according to simvastatin doses 10 and 20 mg once a day at bedtime. This study excluded the patients who have other illnesses that may lead to change the concentration of liver function parameters; these diseases included hepatitis, cirrhosis, obstructive jaundice, pancreatitis, heart attack, heart failure and gallstones disease. Also, patients who used other drugs to treat any other diseases were not included in the current study; these may be supported by clinical and physical checking of the patients and also by taking a history of patients.

### Controls:

Also, contribute eighteen healthy males as control subjects, their age ranged from (33-66) years, subjects with any disease or continuous administration of any drug were excluded from the study.

### Collection of samples:

About 5 ml of venous blood were taken from patients and controls. Serum was separated by centrifugation and used for estimation of AST, ALT, ALP and bilirubin.

### Methods:

### Determination of enzymes Activity and total bilirubin in Serum:

Serum activities of aspartate aminotransferase (AST), alanine aminotransferase (AST) and alkaline phosphatase (ALP) measured using ready to use (AST, ALT, ALP ELISA bioMerieux kits), while serum total Bilirubin measured by using (Bilirubin ELISA Biocon kit). For all these parameters, ELISA technique is used[12].

### Statistical analysis

Mean ±SD used in all these results. Statistical analysis was achieved with SPSS, version 20. One-way analysis of variance (ANOVA) was used to detect simvastatin effects according to ages of men hyperlipidaemic patients and simvastatin doses and on liver functions criteria, also this test used to detect the interaction between the ages and simvastatin doses .Pearson's correlation test detects the correlation between all the used parameters. The p-value $< 0.05$ was regarded significant[13].

## Results:

**Effect of different doses of simvastatin on liver functions parameters in men hyperlipidaemic patients:**

To determine the effect of various simvastatin doses on the selected liver functions parameters ( ALT, AST, ALP, and Bilirubin), a one-way ANOVA was used to analyze the data. Table (1) shows that ALT levels were increased significantly ($p < 0.005$ , $p < 0.0001$) in patients treated with first dose (D1) and second dose (D2) when compared with the control group (C) . This table also indicates that AST levels increased significantly ($p < 0.0001$) in D1 when compared with control, In contrast, this enzyme levels increased significantly ($p < 0.0001$, $p < 0.04$) in D2 when compared with C and D1 respectively.

**Table (1) Liver functions parameters in men hyperlipidaemic patients who treated with different doses of simvastatin:**

| Parameters | Group | Simvastatin doses (mg/day) | SD ± Mean |
|---|---|---|---|
| **ALT (**U/L) | C | 0 | 0.52 ±13.14 |
| | D1 | 10 | 1.03**a** ±14.17 |
| | D2 | 20 | 1.57**a**±14.68 |
| **AST** (U/L) | C | 0 | 0.95 ±19.62 |
| | D1 | 10 | 1.59**a**±22.58 |
| | D2 | 20 | 2.21**ab**±23.60 |
| **ALP** (U/L) | C | 0 | 1.15 ±31.89 |
| | D1 | 10 | 1.41 ±32.92 |
| | D2 | 20 | 2.41**ab**± 35.69 |
| **Bilirubin** (μmol/L) | C | 0 | 0.39 ±8.84 |
| | D1 | 10 | 0.94 ±9.11 |
| | D2 | 20 | 0.85**ab**± 10.15 |

**C:control, D1, D2: patients groups treated with simvastatin**
**a: a significant difference between (D1, D2) and control group. b: significant differences between D2 and D1.**
**C : 18 healthy males. D1, D2: 24 male hyperlipidaemic patients/groups.**

On the other hand, ALP and bilirubin levels elicited a significant increase ($p < 0.0001$ ) in D2 when compared with the control group and D1 respectively, whereas don't obvious any significant changes in D1 when compared with C in each ALP and bilirubin .

**Effect of different ages of men hyperlipidaemic patients who are treated with simvastatin on liver functions parameters:**

To determine the effect of different ages of men hyperlipidaemic patients on liver functions tests, a one-way ANOVA was used to analyze the data, in this approach of analysis, the effect of dosing level is neglected and the data was collected taking in our consideration the result of patients´ ages of (A1), (A2) and (A3) that mean 36-45, 46-55 and 56-65 years respectively. Table (2) shows that ALT levels were increased significantly ($p < 0.005$, $p < 0.0001$) in A2 and A3 respectively when compared with A1 .While AST levels increased significantly ($p < 0.01$) in A2 when compared with A1, also this enzyme increased significantly ($p < 0.0001$, $p < 0.01$ ) in A3 when compared with A1 and A2 respectively.

In respect to ALP, the results demonstrated that enzyme increased significantly ($p < 0.05$, $p < 0.01$ ) in A2 and A3 respectively when compared with A1.In contrast, bilirubin levels increased significantly ($p < 0.0001$ , $p < 0.01$) in A3 when compared with A1 and A2 respectively.

**Table (2) Effect of different ages of men hyperlipidaemic patients who are treated with simvastatin on liver functions parameters:**

| Parameters | Group | Ages (years) | SD± Mean |
|---|---|---|---|
| **ALT (**U/L) | A1 | 36-45 | 0.46±13.16 |
| | A2 | 46-55 | 0.86**a**±14.20 |
| | A3 | 56-65 | 1.65**a**±14.87 |
| **AST** (U/L) | A1 | 36-45 | 1.12±20.58 |
| | A2 | 46-55 | 1.75**a**±22.15 |
| | A3 | 56-65 | 2.74**ab**±23.71 |
| **ALP** (U/L) | A1 | 36-45 | 1.64±32.60 |
| | A2 | 46-55 | 2.11**a**±33.98 |
| | A3 | 56-65 | 2.95**a**±34.36 |
| **Bilirubin** (μmol/L) | A1 | 36-45 | 0.50 ±9.03 |
| | A2 | 46-55 | 0.60 ±9.30 |
| | A3 | 56-65 | 1.07**ab**± 9.91 |

**A1 A3: different ages.**
**a: significant differences between (A2 ,A3) and A1.**
**b: significant differences between A3 and A2 number of participated males :22/group**

**Effect of interaction between different doses of simvastatin and ages of men hyperlipidaemic patients who are treated with it on liver function parameters:**

Table (3) show the effect of this interaction on ALT enzyme that indicates this enzyme there increased significantly ($p < 0.001$, $p < 0.01$) in patients treated with 10mg when compared with control at 46-55 and 56-65 years ages groups respectively, also it found that ALT increased significantly ($p<0.0001$, $p<0.002$ ) in patients treated with 20mg when compared with control at 46-55 and 56-65 years old ages groups respectively.

**Table (3) Effect of interaction between different doses of simvastatin and ages of men hyperlipidaemic patients who are treated with it on ALT enzyme:**

| Ages (years) / Doses (mg/day) | Mean ± SD | | |
|---|---|---|---|
| | **36-45** | **46-55** | **56-65** |
| Control | 0.51±12.99 | 0.59 ±13.18 | 0.52 ±13.23 |
| 10 | 0.47±13.10 | 0.58**a**±14.31 | 0.75**a** ±15.12 |
| 20 | 0.42±13.33 | 0.49 **a**± 14.87 | 2.00**a** ±15.84 |

**a: a significant difference between (10 and 20mg) and control group.**

**Table (4) Effect of interaction between different doses of simvastatin and ages of men hyperlipidaemic patients who are treated with it on AST enzyme:**

| Ages (years) / Doses (mg/day) | Mean ± SD | | |
|---|---|---|---|
| | **36-45** | **46-55** | **56-65** |
| Control | 0.59±19.38 | 0.95 ±19.60 | 1.05 ±19.87 |
| 10 | 0.73**a**±20.70 | 0.46**a**±22.86 | 0.74**a** ±24.18 |
| 20 | 0.83**a**±21.36 | 0.76 **a**± 23.34 | 1.32**ab** ±26.11 |

**a: means there is a significant difference between (10 and 20mg) and control group.**
**b: means there are significant differences between 20 mg and 10mg** .

On the other hand, table (4) explain the effect of this interaction on AST enzyme that elicited there are a significant increased ($p<0.008$, $p<0.0001$ and $p<0.0001$) in AST of patients treated with 10 mg when compared with control at all different ages groups respectively , also the significant **(**$p<0.0001$) in the patients treated with 20 mg when compared with control at the same different ages groups respectively, While the ($p<0.001$) in the patients treated with 20 mg when compared with 10 mg at 56-65 years old.

Whereas table (5) illustrate the effect of this interaction on ALP enzyme that demonstrated this enzyme increased significantly ($p<0.0001$, $p<0.004$) in patients treated with 20mg when compared with control and 10mg groups respectively at 46-55 years old ages, also the significant increased ($p<0.0001$) in ALP of patients treated with the same dose when compared with control and 10mg groups respectively at 56-65 years old ages.

**Table(5)Effect of interaction between different doses of simvastatin and ages of men hyperlipidaemic patients who are treated with it on ALP enzyme:**

| Ages (years) / Doses (mg/day) | Mean ± SD | | |
|---|---|---|---|
| | **36-45** | **46-55** | **56-65** |
| Control | 1.28±31.83 | 1.28 ±32.04 | 1.09 ±31.79 |
| 10 | 1.52±32.34 | 1.41±33.52 | 1.19 ±32.91 |
| 20 | 1.78±33.45 | 1.61**ab**± 35.90 | 1.68**ab** ±37.73 |

**a: a significant difference between (10 and 20mg) and control group.**
**b: significant differences between 20 mg and 10mg group**.

**Table(6)Effect of interaction between different doses of simvastatin and ages of men hyperlipidaemic patients who are treated with it on bilirubin enzyme:**

| Ages (years) / Doses (mg/day) | Mean ± SD | | |
|---|---|---|---|
| | **36-45** | **46-55** | **56-65** |
| Control | 0.38 ±8.80 | 0.43 ±8.77 | 0.43 ±8.94 |
| 10 | 0.50 ±8.82 | 0.42±9.15 | 0.42 ±9.38 |
| 20 | 0.37**ab**±9.43 | 0.40**ab**±9.86 | 0.48**ab** ±11.17 |

**a: a significant difference between (10 and 20mg) and control group.**
**b: significant differences between 20 mg and 10mg group**.

While table (6) point up the effect of the interaction on bilirubin that confirmed there are a significant increased ($p<0.01$) in bilirubin of patients treated with 20mg when compared with control and 10mg groups respectively at 36-45 years old ages, in addition the significant ($p<0.0001$, $p<0.003$) in patients treated with 20mg when compared with control and 10mg groups respectively at 46-55 years old ages , besides the significant ($p<0.0001$) at 56-65 years old ages in the same compared groups above.

## Discussion:

The measurement of liver enzyme activities is considered as a useful tool to assess the integrity and function of the liver, thus it is a constructive quantitative marker of the degree and type of liver diseases [14]. Worldwide, cardiovascular disease (CVD) regarded is one of the main reasons of death [15] and statins becomes one of the essential treatments for CVD due to this drug lowered of lipid effects, stabilizing atherosclerotic plaque and improving the function of endothelial layer. Nevertheless, it has several adverse effects especially toxicity of liver indicated by increased of serum liver enzymes and bilirubin [16,17].

Concerning the effect of the simvastatin doses on liver functions criteria, the present study revealed a significantly increased in ALT, AST, ALP and bilirubin in patients groups who are treated with two doses of simvastatin when compared with control group and in some cases between dosing levels, these increased take

place when the level of dosing increased, the difference becomes significant in patients who treated with higher dose of simvastatin. The data from the present study can confirm with results obtained from a studies which cleared that the effect of simvastatin on hepatic parameters are dose related, that's mean they are higher at high doses[18-23]. Similar findings were reported also by several studies as Spreckelsen et al. who uses 48 years-old men treated with simvastatin at a dosage of 10,20 mg daily, they had increased serum liver enzymes and bilirubin levels after 2 months of the administration[24] . Koornstra et al. reported that symptomatic hepatic damage by elevation of ALT,AST,ALP, and Bilirubin was diagnosed in 6 patients at different ages during treatment with simvastatin, these results obtained after administration different doses of this drug for 45 days [25]. Tolman observed that the elevations in liver enzymes and bilirubin show in male primary hypercholesterolemia patients who are administrated 10,20mg simvastatin/day[26]. Chalasani et al. emphasized that liver enzymes levels are increased significantly in 68% of 342 hyperlipidemic patients who are treated with simvastatin for the 6-months period [27]. In contrast, the present findings were inconsistency by Scott et al. and Vuppalanchi that showed no significant effect on liver functions parameters in hyperlipidemic patients that treated with simvastatin[28,29].

Ages distribution of the measured hepatic parameters in the age groups in the present study revealed an elevation of these parameters according to age-elevation, these results may demonstrate a positive correlation between age and the hepatic parameters, i.e. higher values are associated with high ages, suggesting that the effect of simvastatin on the liver is age-dependent. These data were supported by previous studies [25, 30-32]. Similar results are also in agreement with this study such as Brocard et al. who performed a study with simvastatin which is administered to 46 patients their ages ranged 40-70 years old with primary hypercholesterolaemia during one year, at the end of this study, he declared that the effect of simvastatin on AST,ALT,ALP and Bilirubin is intensified by high ages of patients [33]. Kiortsis et al. who used one hundred and three hyperlipidemic patients of both sexes aged 31–74 years were administrated simvastatin for 24 weeks, abnormal levels liver enzymes were observed at different ages but the highest levels of it showed at high ages [34]. Zhang et al. that participated four hundred and eighty-two ischemic stroke patients aged (≥65 years) treated with simvastatin, they showed that the rising of liver enzymes and bilirubin in patients who aged more than 65 years old was higher significantly than those younger than 65[35].

Elevations of all liver criteria in this study were showed. These elevations reflect that the liver toxicity caused by simvastatin which causes hepatocellular damage (elevation of AST and ALT) and cholestasis (elevation of ALP and bilirubin) [26,36]. Injury of the liver can take the form of hepatocellular necrosis, cholestatic disease or disease of mixed pattern such as granulomatous hepatitis, in most instances toxic drug metabolites or the immune responses to these metabolites mediate the damage, selective impairment of certain vital cellular functions may result in lethal injury to hepatocytes, whereas selective impairment of the bile secretary apparatus may result in cholestasis [37]. Thus, several studies reported that simvastatin may be causes acute hepatocellular necrosis and reflect the release of serum transaminase (ALT and AST) levels from the cytoplasm of dying cells [38-40]. The rupture of the hepatocyte membrane may be attributed to the covalent binding of simvastatin to proteins in the intracellular region which lead to reduce ATP and causes disruption of actin in the surface of the liver cells which causes necrosis of liver cell membrane and blebs formation [41]. On the other hand, simvastatin is one of the drugs that damage liver cells which reduce the organ's capacity to conjugate bilirubin leading to a raised serum level bilirubin, in cholestasis there is obstruction to bile flow, conjugated bilirubin then appears in the blood in very high concentration also ALP levels elevated in serum[42].

Simvastatin hepatotoxicity may belong to this drug causes apoptotic lesions by induced TNF and Fas (immune mediated) may lead to the cascade of caspases in intracellular region, which causes apoptosis and elevation of serum liver enzymes and bilirubin[43]. This observation supported by Kubota et al. that stated the simvastatin causes an apoptotic injury in cultured human hepatocytes. Also, simvastatin hepatotoxicity may result from stimuli cytochrome P450 enzymes that critical in hepatotoxicity to produces two principle types of reactive, toxic metabolites: electrophiles and free radicals [44]. This drug increases electrophiles production this lead to electrophiles bind to glutathione in the cells which restrain the capacity of this protein to protective liver against the toxic effect of simvastatin and lead to hepatotoxicity, also simvastatin stimuli-free radicals construction through cytochrome P450 ,these radicals bind to proteins or unsaturated lipids causing lipid peroxidation the overall result of lipid peroxidation is to alter the chemical and physical properties of membranes (damage membranes) and liberate of serum liver transaminase, ALP, and bilirubin[37, 45].

These results also pointed out there is an interaction between the dosing level and ages on the serum liver enzymes levels and bilirubin , that indicates these parameters levels increased when the doses and ages raised, these observings were conformity with preceding conclusions[18, 46].

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