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# The effect of atorvastatin therapy on skeletal muscle function in hyperlipidemia patients in khartoum

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## Abstract

**Background:** Atorvastatin is a lipid-lowering medication that causes skeletal muscle side effects by altering serum levels of skeletal muscle biomarkers. The aim of this study is to assess the effect of atorvastatin on muscle function and biomarker serum levels of CK, LDH, AST, Myoglobin, and Troponin I in Sudanese patients.

**Method**: The total study group of hindered participants, including 60 case group (under Atorvastatin treatment) and 40 healthy as a control group, was matched with age and sex for the case group. The serum CK, LDH, myoglobin, and lipid profiles in the study groups were estimated by automated chemistry analyzers in this study.

**Result:** Muscle pain was reported in case studies (55 = 91%). There was a significant increase in CK, LDH, and myoglobin among case studies when compared to the control group. The dose of drug showed no significant difference among the studied parameters. No correlation was found between CK and LDH with the duration of drug administration.

**Conclusion**: Atorvastatin medication causes skeletal muscle pain among case study and increase muscle biomarkers such as CK, LDH, and myoglobin levels.

**Keywords:** Atorvastatin; Muscle pain; Ck; LDH; ALT; Myoglobin; Troponin I

## 1. Introduction

Atorvastatin, often known as Lipitor, is a calcium salt that belongs to the statin medication class. It lowers blood cholesterol and is a synthetic lipid-lowering drug. Additionally, it prevents plaque and protects against strokes through anti-inflammatory and other mechanisms. (1). HMG-CoA reeducation is competitively inhibited by atorvastatin. But unlike most others, it is an entirely synthetic substance. The rate-limiting step in the synthesis of hepatic cholesterol is the reduction of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) to mevalonate, which is catalyzed by HMGCoA. The expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes increases as a result of the enzyme's inhibition because denovo cholesterol production is reduced. By increasing LDL uptake by hepatocytes, this lowers blood LDL cholesterol levels (2).

As a result, the majority of statin users do not have issues with their skeletal muscles. We observed FKBP12 dissociation from RyR1 in the skeletal muscle of statin-treated humans and rats, which led to a ROS/RNS-dependent Ca2+ spark-

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mediated SR Ca2+ leak. Heart failure, aging, and muscular dystrophy are just a few pathologies that have been associated to this instability of RyR1 and muscle dysfunction (3,4,5). In light of this, we noticed indicators of pro-apoptotic signaling in statin-treated individuals. In the rodent model, however, statin-induced FKBP12 dissociation from RyR1 and Ca2+ sparks was not accompanied by any obvious problems in the overall management of [Ca2+]i at rest or during tetanic stimulation, and force production was not reduced. The clinical image that shows that most patients do not experience statin-related severe muscle symptoms, despite the fact that statin medication raises the risk of myopathy, aligns with unaltered muscle function despite potentially harmful alterations in cellular Ca2+ processing. In fact, despite the absence of muscle symptoms, investigation of the mitochondrial DNA and muscle gene expression profiles in a small group of patients using simvastatin for 8 weeks found indications of mitochondrial damage, pro-apoptotic signaling, and altered Ca2+ flux (6). Muscle cramps, soreness, weariness, weakness, and, in a minority of cases, a fast breakdown of muscles that can result in death, are the side effects of statin use that are most frequently reported. These negative effects can frequently be felt during or after strenuous exercise. Recent study has found some common causing elements, despite the fact that the processes by which statins alter muscular performance are not well understood. (7). although statins are thought to be quite efficient at lowering cholesterol, they do have negative effects. Myopathy is the most well-known side effect and it is a prevalent problem worldwide. Elevated levels of creatinine kinase (CK), lactate dehydrogenase (LDH), and myoglobin provide as biochemical indicators for the assessment of statin-induced myopathy (8). Rhabdomyolysis, a potentially fatal kind of muscle breakdown, has been associated with higher statin doses. This may result in death, unconsciousness, and irreversible kidney damage. Fatigue, muscle aches, tenderness, weakness, nocturnal cramps, and tendon pain are among the symptoms. The mechanism of statin-induced myopathy could be altered cholesterol synthesis, altering the behavior of the membranes in myocytes and the molecules involved in the cholesterol pathway (coenzyme Q10), and decreased levels of isoprenoids, which stop myofibrils from apoptosis (9, 10,11 ). When a doctor has decide whether or not to prescribe a statin to a patient who is qualified but already has a known muscle problem, it might provide a significant clinical conundrum. Statins may be contraindicated in some metabolic myopathies, including myophosphorylase deficiency, mitochondrial encephalopathy, and others, although it is considered that they do not provide an additional risk to people with muscular dystrophies (12).

Genetic elements or the presence or absence of particular genotypes may have an impact on the muscle toxicity associated with statin therapy. It is interesting that certain genetic risk factors for statin-induced myopathies either affect drug metabolism or muscle metabolism (13). According to Vladutiu, (13)

The SLCO1B1 gene's C allele was discovered to be altered in more than 60% of the 85 patients with myopathic symptoms, according to the SEARCH collaborative group. The SLCO1B1 gene's encoded polypeptides play a role in controlling the hepatic absorption of statins (14). Another potential route for statin-induced myopathy involves genetic changes or decreases in particular coenzymes, like CoQ10. Oh et al. (15) discovered that a genetic polymorphism in CoQ10 was linked to an increased likelihood of statin intolerance, as determined by muscular symptomatology. They compared 133 participants who were statin intolerant with 158 matched controls who were statin tolerant. The second enzyme in the biosynthesis process for CoQ10 is coenzyme Q2 (16).

Therefore, the present study was conducted to compare the lipid profile, myoglobin, creatine kinase, and lactate dehydrogenase among hyperlipidemia patients on statin therapy in Khartoum State, Sudan.

## 2. Material and methods

From August to January 2022, a cross-sectional hospital-based study was conducted in Khartoum, Sudan's military hospital. The study included 100 Sudanese patients; sixty of them were in the case group using the Atorvastatin drug, in addition to forty healthy volunteers as the control group.

### 2.1. Inclusion & Exclusion Criteria's

Sudanese Patients using the atorvastatin drug, in addition to healthy people, were included.

Patients using other lipid-lowering drugs than atorvastatin and patients with renal and liver problems or chronic disease were excluded.

### 2.2. Ethical Consideration

The study was revised and ethically approved by the ethical and scientific committee of the Medical Laboratory Sciences Colleague, University of Alzaiem Alazhari. Samples were taken with verbal consent from patients or their relatives. All volunteers will be excused before taking the sample and encouraged by informing them of the reasons and benefits of this study.

### 2.3. Data Collection

Data was collected by using an interview-administered questionnaire with case and control groups to obtain clinical data. All the procedures were known to the participants in their native language and informed consent was taken from them before participating in the study.

### 2.4. Sample collection

Venous blood was collected under aseptic conditions and minimal stasis from each subject using a sterile syringe and needle from the antecubital vein. a 2ml sample of hyperlipidemic blood in a vacutainer with heparin, mix the blood sample well by inversion, centrifuge for 3 minutes at 6000, transfer the plasma into a plain container to avoid re-mixture plasma with blood, and store it at -40°C.

### 2.5. Examination of Biochemical and Clinical Profile

Blood samples were obtained from the patients along with the initial laboratory tests on the first admission to the clinic hospital. Demographic features, clinical characteristics, and laboratory parameters were analyzed. age, BMI (kg/m2), blood examination, serum lipid profile (cholesterol, triglyceride, HDL, LDL tests performed by enzymatic methods using chemical analyzer Mindary BS800), serum enzyme activity (Creatine Kinase, Aspartate aminotransferase a, and Lactate Dehydrogenase enzymes performed by automated kinetic method using chemical analyzer Mindary BS800). Serum levels of myoglobin and troponin I were performed according to the manufacturer's specifications using mindary CL 1200.

### 2.6. Statistical analysis

Data was analyzed using the IBM Statistical Package for the Social Sciences.

T test, crosstabs, and correlation were performed using the (SPSS) program version 25. with differences in categorical data. P-values less than 0.05 are considered significant

## 3. Results

The study will be conducted in Khartoum state with a total study group of 100, and 60 hyperlipidemic patients using Atorvastatin as a case group and 40 healthy individuals as a control group . The age of the study group is between 44 and 68 years.

Muscle pain was reported in this study among case studies. 55 = 91%

- Figure 1 shows the percentage of gender distribution among the study group (cases and controls).
- Table 1: Demographic Characteristics of the Study Population
- Table 2: compares the mean of biochemical markers measured among the study population. They showed a significant increase in the case group.
- Figure 2: A comparison of the mean biochemical measured across different atorvastatin drug doses revealed an insignificant difference in the case group.
- Figures 3-5: Correlation of CK, LDH, and Myoglobin with Duration of Medication

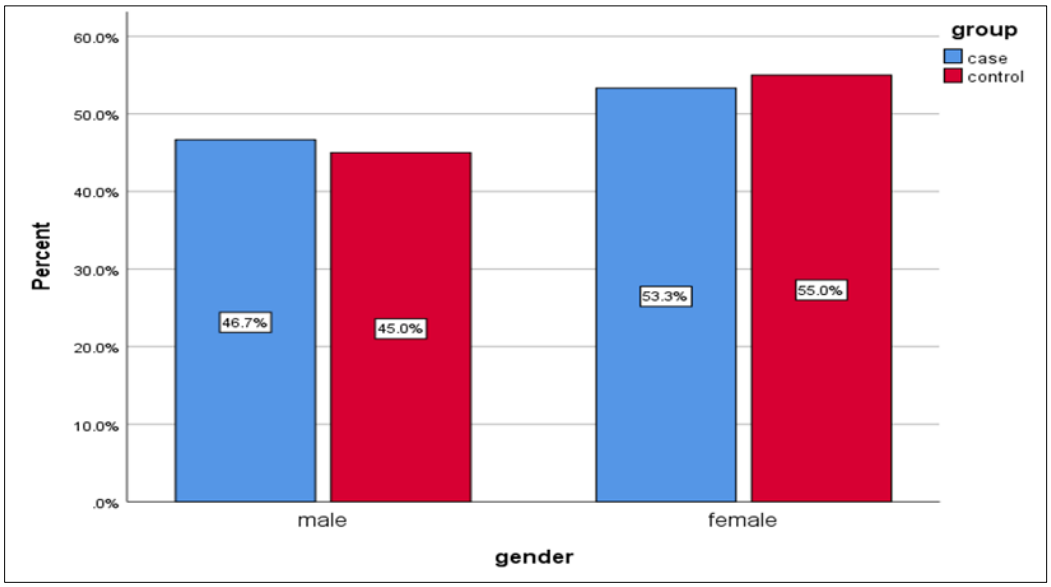


**Figure 1** Gender distribution in the study group as a percentage

**Table 1** The study group's demographic and clinical characteristics

| | **Case group (60)** | **Control group (40)** | **P value** |
|---|---|---|---|
| Age/years | 57.7 ± 7.3 | 57.4 ± 8 | 0.87 |
| Duration/month | 4 ± 2 | - | - |
| BMI (kg/m$^2$) | 33.7 ± 5.1 | 23.9 ± 2.3 | 0.000 |
| SBP | 134.2 ± 9.2 | 108.2 ± 8.1 | 0.000 |
| DBP | 87.1 ± 8.8 | 74.7 ± 4.3 | 0.000 |
| Muscle pain (%) | 55=91% | - | - |

**Table 2** Comparison of Laboratory Parameters between Study Groups

| **Tests** | **Case group (60)** | **Control group (40)** | **P value** |
|---|---|---|---|
| CK (U/L) | 40 ± 15 | 12 ± 3 | 0.000 |
| LDH ( U/L) | 200 ± 41 | 155 ± 26 | 0.000 |
| Triglyceride ( mg/dl) | 264 ± 33 | 183 ± 20 | 0.000 |
| Cholesterol (mg/dl) | 225 ± 37 | 95 ± 16 | 0.000 |
| LDL (m/dl ) | 226 ± 45 | 66 ± 6 | 0.000 |
| HDL ( mg/dl ) | 98 ± 14 | 56 ± 8 | 0.000 |
| Myoglobin (ng/L) | 89 ± 27 | 47 ± 14 | 0.000 |
| Troponin I (ng/L) | 0.041±.03 | 0.040 ±.013 | 0.20 |
| AST (U/L) | 22.6±8.2 | 21.3±7.6 | 0.445 |

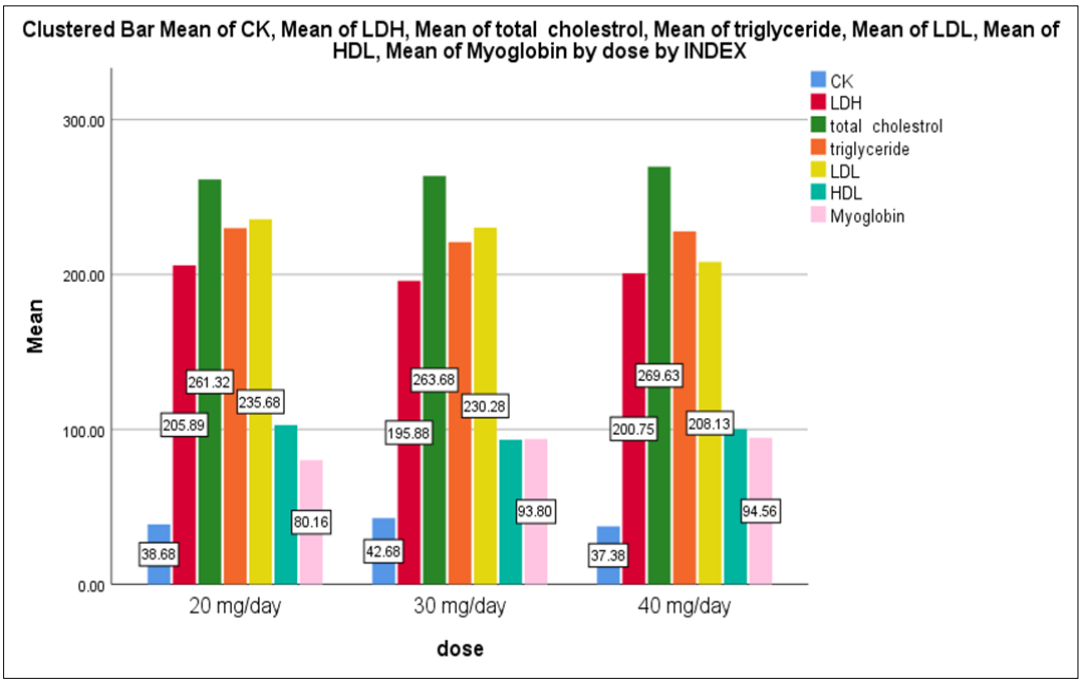


**Figure 2** Comparison of Biochemical measured among different dose of atorvastatin drug

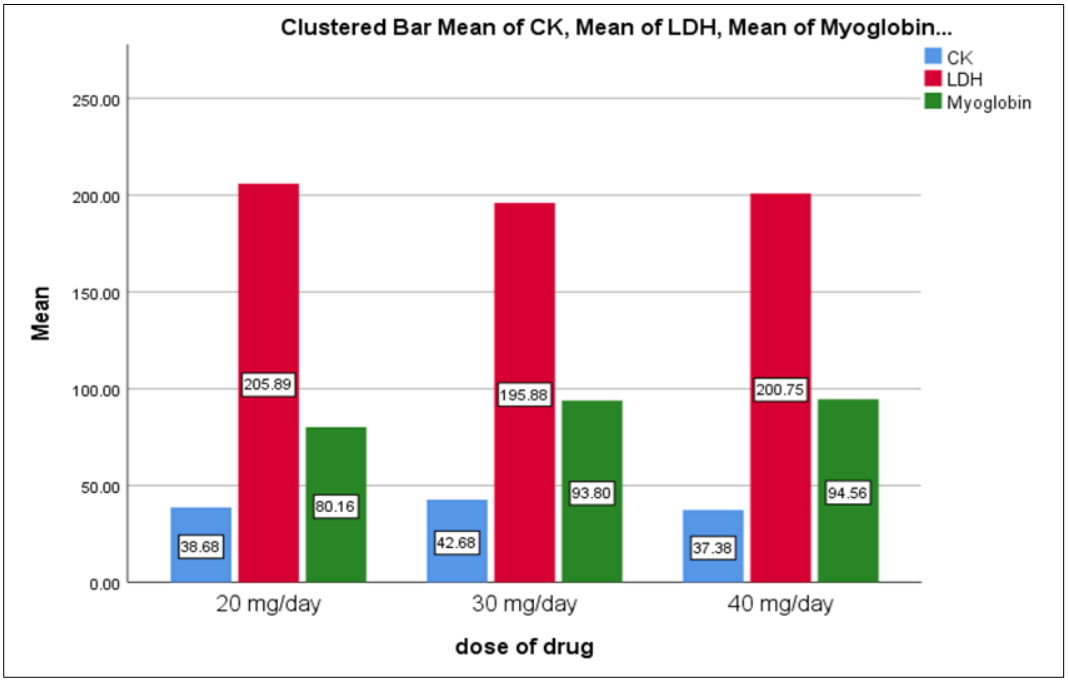


**Figure 3** Mean levels of CK, LDH, and myoglobin according to drug dosage

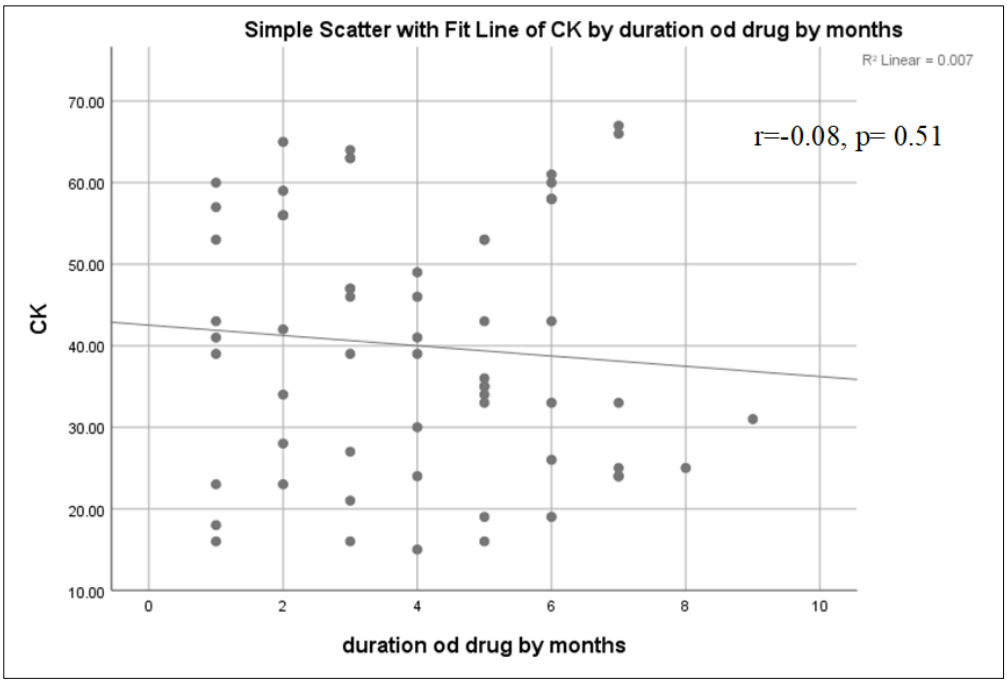


**Figure 4** Correlation between serum CK and Drug duration per year in Study group

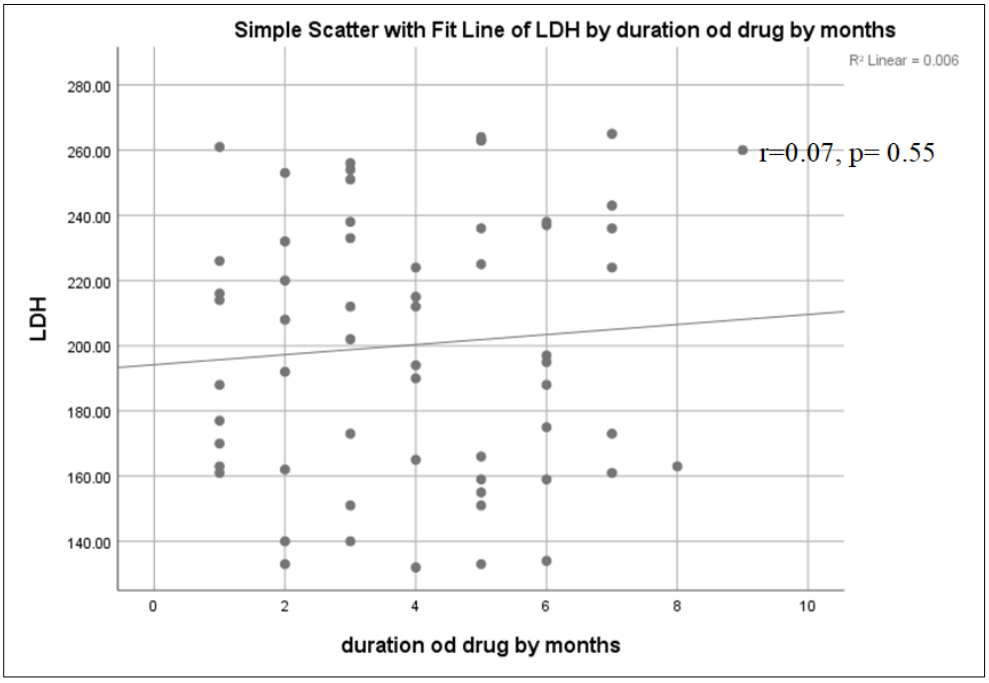


**Figure 5** Correlation between the serum level of LDH enzyme and duration of drugs in Study group

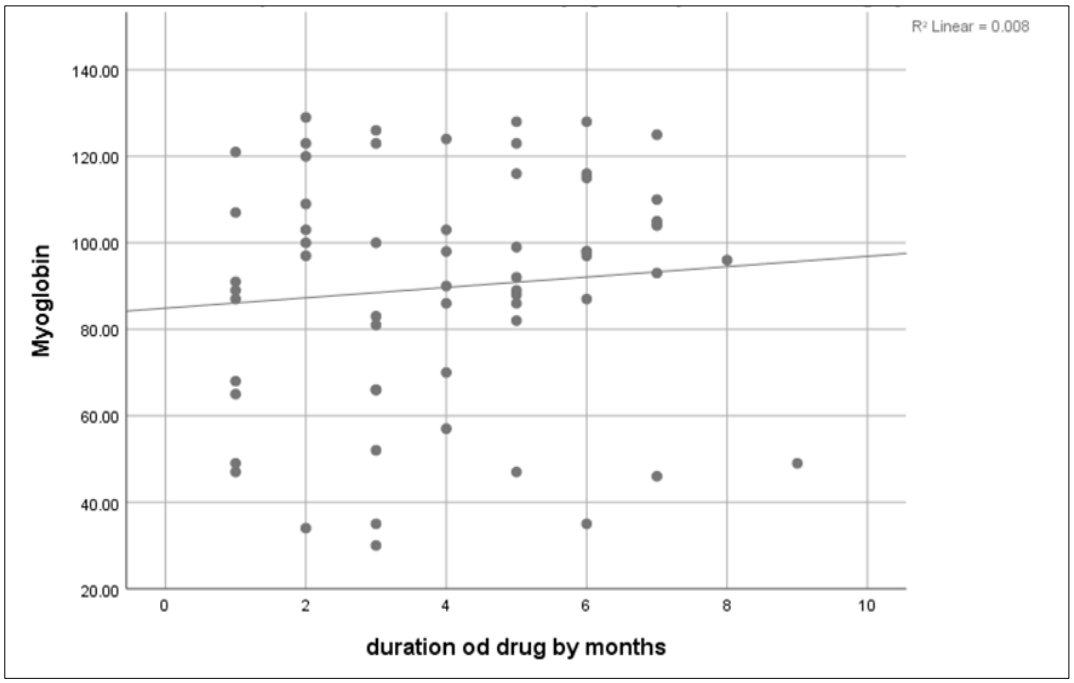


**Figure 6** Correlation between myoglobin and drug duration by months (r= 0.09, p value 0.48)

## 4. Discussion

One of the metabolic disorders with the most distinct symptoms is dyslipidemia. The most common drug for lowering LDL cholesterol and a key player in preventing atherosclerotic cardiovascular problems is Atrova, an HMG-CoA reductase inhibitor. (9) It improves LDL-C clearance from the blood and upregulates LDL-C receptors on the surface of liver cells by inhibiting HMG-CoA reductase. HMG-CoA reductase is the enzyme that restricts the rate of cholesterol production. Due to its decreased serum triglyceride levels, it also focuses and changes endothelial function, inflammatory responses, plaque stability, and thrombus development. The risk of coronary heart disease (CHD) and all-cause mortality so appears to be greatly decreased as a result of this treatment. (17,18)

The only RCT specifically designed to investigate the impact of statins on skeletal muscle symptoms and performance is the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study .(39)

Fluvastatin or atorvastatin, at doses lower than simvastatin, significantly decreased the resting chloride conductance (gCl), increased sarcolemmal excitability, and shifted the mechanical threshold for contraction towards more negative potentials, according to biochemical, histological, and electrophysiological studies. (20) At the level of the muscular membrane, statins are effective antagonists of the chloride (Cl-) channel(21). The International Lipid Expert Panel (ILEP) group suggested an ideal strategy for treating professional athletes, who typically reported significant difficulty taking statins, in order to allow intensive training without the need for prolonged statin discontinuation and to lower the risk of potential muscle AEs.(22)

These latter people saw an improvement in quality of life without any aggravation of muscle problems (23). These findings support the value of lifestyle changes as a supplement to statin medication and may improve adherence (24).

According to the current study, all study groups' mean serum values for serum lipid profile panels were higher than those of the control group, which may be related to obesity. A study conducted by Borle et al. lends credence to this (25) The study was carried out to assess the lipid profile in obese patients, which revealed that 86% had dyslipidemia; the increase in HDL in this study is a good indicator due to the atorvastatin drug, and pad indicators increase in cholesterol, triglycerides, and LDL. Atorvatatins remain among the most frequently prescribed drugs and constitute a cornerstone in the prevention of cardiovascular disease. However, muscle symptoms are often reported in patients on statins. In this study, muscle symptoms are frequently reported as adverse events associated with statin therapy in this study, muscle pain was reported in 91% of the cases studied.

Statins are associated with adverse effects, the most frequently reported of which are muscular pain syndromes. The true rate of statin-associated muscle symptoms (SAMS) is difficult to quantify, as it may be transient, often resolves spontaneously, and may be caused by several factors Statin-associated muscle pain should be evaluated seriously, and statins can be discontinued or changed to a less frequent dosing schedule to see if muscle pain resolves. It is important to understand which patients have symptoms due to statins only and to study this group for identification of biomarkers and alternative therapies to distinguish these from patients having symptoms due to other causes and manage them separately(26)

There is some hypothesis that a lower dose may be more effective and well-tolerated, but there isn't sufficient data to support this (27). A recent meta-analysis was unable to show a dose-dependent association between statins and muscle adverse effects. While it is occasionally suggested that patients take a lower dose of a statin to treat SAMS(28,29)

Similar findings included myalgia and complaints of the muscles. Participants who took statins developed myalgia in patients. Interventional studies (30) 22 occurrences of CK increases were observed among simvastatin-treated patients in the 5.4-year follow-up of the 4S trial, as opposed to 15 cases among placebo-treated individuals. (31) In the Phillips et al. report(32), a group of 30 patients using statins who had substantial muscle pains and normal CK showed improvement after stopping the medication.

In registries and observational studies, the prevalence of statin-induced muscular complaints ranges between 7% and 29%. (33) As a result, the majority of statin use do not have issues with their skeletal muscles. In a previous study, 10.5% of the patients reported experiencing muscle soreness, with the average beginning occurring one month after the start of medication. Drug-induced autoimmune hepatitis is the cause of the liver damage. (34) Atorvastatin was mostly used in other studies. (35) as well as with additional statins. (36).

No significant changes in myalgia were seen between patients using high-dose and low-to-moderate dose statin therapy in an Australian study of patients. High-dose therapy in this trial was specified as atorvastatin 20 mg, simvastatin 80 mg, and rosuvastatin 10 mg. All doses of atorvastatin and fluvastatin were regarded as low to moderate, whereas other doses were considered to be low to moderate. (37). The present research found muscle pain in all participants, not just those receiving the maximum dose of atorvastatin.

According to many study findings, statins have a possibility of causing side effects. One of the most significant of these are the so-called statin-associated muscle symptoms (SAMS), which include myalgia (generalized muscle pain) and myopathy (diseases that cause muscle weakness). (38)

An assessment of the changes in liver enzymes with increasing statin doses in another trial showed that, for any 10% reduction in LDL-C, the rates of elevated liver enzymes increased considerably with higher statin doses .(39)

CK levels have historically been utilized to assist in the identification of myopathy brought on by statin usage. (40). Utilizing CK levels as the only indicator to determine whether myopathy is present could be misleading. (40,41,42,43) Increased CK levels are frequently found as a result of exercise and can occur without myopathic effects. (44,45). Clarkson and others (44) measured myoglobin and CK levels as well as other markers of muscle damage. In the absence of muscle complaints and elevated bilirubin, elevated transaminases, which are frequently detected with statin treatment, do not indicate a major risk to the patient. (46,47) Another biomarker used to diagnose myocyte injury is elevated myoglobin, which frequently coexists with elevated circulatory CK levels. (42,44) Myoglobin release from damaged cells can cause renal failure by building up in the renal tubules. (44)

In the current study, the case group's mean values of CK, LDH, and myoglobin were noticeably higher than those of the control group. This might be because Atrova medications can harm muscle cells by impairing the production of coenzyme Q10 (ubiquinone), which is essential for mitochondrial activity, depleting isoprenoids, and disturbing the integrity of cell membranes. (48)

This result is supported by a study done by Parker et al.(49) and Dragos et al.(25) who showed that atrovastatin-induced elevation of CK and increased muscle-related side effects. In this study, however, there was no difference in the mean level of CK, LDH, myoglobin, and lipid profile when compared according to drug dose, which could be due to the fact that the majority of the study patients were on a treatment binge. This result agrees with a study done by Pedro-Botet et al.(10) that indicated a high dose and long duration is necessary to achieve the desired plasma goal.

Finally, this study showed that there was no correlation between CK, LDH, and the duration of drug. This result disagrees with A study done by Calza et al. (50) showed that atrova drug-induced elevation of CK and LDH is positively related to the duration of drug use.

A non-significant relationship in this study may be due to the absence of a high drug dose, and most study participants are at the beginning of treatment. When compared to unrelated painful muscular symptoms, CK levels are sometimes used to better biomarker define SAMS or to confirm its diagnosis. (51). However, the validity of a raised CK level as a reliable indicator of SAMS has been challenged. Even though some patients did not feel any muscular soreness, the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study found that atorvastatin 80 mg raised CK levels in patients. (53) Serum levels of Ck, LDH, and Myoglobin are best for atorvastatin drug diagnosis and follow-up, as well as evaluating side effects such as muscle symptoms in patients. The tests for Troponin I and Aspartate aminotransferase have less sensitivity and specificity than Ck , LDH, and Myoglobin. The present study results found no significant change in the levels of Troponin I and Aspartate aminotransferase among the case studies when compared with the control group.

## 5. Conclusion

This study concludes that: Atorvastatin is a drug associated with side effects like muscle pain and inflammation. The serum muscle enzymes CK and LDH increase in patients with muscle pain or statin-associated muscle symptoms.

The serum enzyme tests CK and LDH are more accurate and sensitive biomarkers for the diagnosis of muscle pain or statin-associated muscle symptoms than other biomarkers like transaminases enzymes and myoglobin. All different atorvastatin drug doses cause increase the level of serum CK, LDH, and myoglobin. Muscle pain or statin-associated muscle symptoms are found in all different doses of atorvastatin.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

No conflict of interest.

### *Statement of ethical approval*

The study was revised and ethically approved by the ethical and scientific committee of the Medical Laboratory Sciences Colleague, University of Alzaiem Alazhari. Samples were taken with verbal consent from patients or their relatives. All volunteers will be excused before taking the sample and encouraged by informing them of the reasons and benefits of this study.

### *Statement of informed consent*

All volunteers will be excused before taking the sample and encouraged by informing them of the reasons and benefits of this study.

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