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THE EFFECTS OF L-CARNITINE IN REDUCING HEPATOTOXICITY OF STATINS IN RATS

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ЕФЕКТИ Л-КАРНИТИНА НА СМАЊЕЊЕ ХЕПАТОТОКСИЧНОСТИ СТАТИНА КОД ПАЦОВА

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ABSTRACT

Objective. The first line of treatment for hyperlipidemia is statins. In this group, atorvastatin is the most popular and effective drug. Hepatic toxicity and myopathy are the two observed adverse effects of statins. The active form of carnitine is L-carnitine, a water-soluble compound found in food, the body, and the majority of dietary supplements. There are many uses for L-carnitine in the human body. It assists in the removal of free radicals from the body and lowers hydrogen peroxide production, both of which may guard against liver side effects brought on by statins.

Methods. Eighty rats were randomly divided into four main groups: control, L-carnitine, atorvastatin, and combination (L-carnitine + atorvastatin) groups. These groups were subdivided into three subgroups based on different doses of the drugs. The L-carnitine group was divided into L200, L300, and L400. The atorvastatin group was divided into A10, A15, and A20. The combination group was subdivided into AL10/200, AL15/300, and AL20/400. All groups received their treatments daily for one month.

Results. According to our findings, the effects of L-carnitine (200 mg/kg daily) on the increase in AST brought on by atorvastatin are not statistically significant, although they are significant on the increases in ALT, ALP and TSB. L-carnitine still has substantial impacts on ALT, ALP and TSB even at larger doses, while its impacts on AST levels had become significant.

Conclusion. Our research highlights the beneficial effects of supplementing with L-carnitine over a four-week period, which effectively mitigates the liver damage caused by atorvastatin.

Key words: *carnitine; atorvastatin; enzymes; chemical and drug induced liver injury.*

САЖЕТАК

Увод. Прва линија лечења хиперлипидемије јесу статини. Из ове групе, аторвастатин је најпопуларнији и најефикаснији лек. Хепатична токсичност и миопатија су два уочена нежељена дејства статина. Активни облик карнитина је Л-карнитин, једињење растворљиво у води које се налази у храни, телу и већини дијететских суплемената. Постоји много улога које Л-карнитин има у људском телу. Помаже у уклањању слободних радикала и смањује производњу водоник-пероксида, а оба могу да заштите јетру од нежељених последица изазваних статинима.

Методе. Осамдесет пацова је насумично подељено у четири главне групе: контролне, Л-карнитин, аторвастатин и комбиноване (Л-карнитин + аторвастатин) групе. Ове групе су подељене у три подгрупе на основу различитих доза лекова. Група Л-карнитина је подељена на Л200, Л300 и Л400. Група аторвастатина је подељена на А10, А15 и А20. Комбинована група је подељена на АЛ10/200, АЛ15/300 и АЛ20/400. Све групе су примале своје третмане дневно током месец дана.

Резултати. Према нашим налазима ефекти Л-карнитина (200 мг/кг дневно) на повећање АСТ изазваног аторвастатином нису статистички значајни, иако су значајни за повећање АЛТ, АЛП и ТСБ. Л-карнитин и даље има значајан утицај на АЛТ, АЛП и ТСБ чак и при већим дозама, док је његов утицај на нивое АСТ постао значајан.

Закључак. Наше истраживање наглашава корисне ефекте суплементације Л-карнитином током периода од четири недеље, што ефикасно ублажава оштећење јетре узроковано аторвастатином.

Кључне речи: *карнитин, аторвастатин, ензими, повреде јетре изазване хемикалијама и лековима*

INTRODUCTION

Statins are the first choice for the treatment of hyperlipidemia by inhibiting the biosynthesis of cholesterol, especially low-density lipoprotein cholesterol (1, 2). Atorvastatin is the most widely used and the most efficient one of this group (1, 3). Although this drug has a great ability to reduce cardiovascular diseases (4), statins are associated with two common adverse effects. One of them is myopathy, and the other is hepatotoxicity (5). The cause of statin-induced liver damage is not being not fully overlooked, but there are several expected mechanisms. One of them is that statins cause alterations to the lipids in the membrane of the hepatocyte, which enhance its permeability and cause liver enzymes to "leak" as a result (6). Another mechanism is increasing superoxide

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formation, which affects the function of mitochondria. Also, statins affect the respiratory chain of the mitochondria. Another possible mechanism of hepatotoxicity is cellular death stimulated by statins (7). According to Hy's rule, drug-induced liver injury (DILI) occurs when the serum alanine aminotransferase (ALT) concentration is three times or more than the normal level and the total serum bilirubin (TSB) level is two times the upper normal level (7-9). Hepatotoxicity induced by statins is either an asymptomatic elevation of the ALT level that occurred in about 3% of treated patients, an elevation of the ALT with symptoms of liver damage, or liver injury that occurred in 1% of patients treated with statins (5, 10, 11).

Atorvastatin is the common statin associated with hepatic adverse effects (4). According to studies, atorvastatin is associated with about three times the elevation of ALT and aspartate aminotransferase (AST) in six percent of study participants (12). Another study found that 45% of statin-induced hepatotoxicity is associated with atorvastatin use (13). Carnitine was demonstrated to stop the statin-induced damage of mitochondrial activities brought on by a rise in superoxide radical production (14).

Carnitine is a catch-all name for several compounds, including L-carnitine, acetyl L-carnitine, and propinyl L-carnitine. L-carnitine (beta-hydroxy-gamma-N-trimethyl aminobutyric acid), a water-soluble substance present in the diet, the organism, and most nutritional supplements, is the active form of carnitine (15-17) that can be produced by the biosynthesis of amino acids, particularly L-methionine and L-lysine (18). L-carnitine facilitates fatty acid transport through the mitochondria. Additionally, L-carnitine acts as a transporter for acetyl groups from the inner mitochondrial membrane to the exterior in the metabolism of glucose (19, 20).

L-carnitine serves a variety of purposes in the human body. It is involved in biological processes including transference of fatty acids to cellular mitochondria, oxidation of fats, lowering oxidative stress, raising pro-inflammatory cytokine expression, enhancing insulin resistance, and regulation of gluconeogenesis (15, 17, 21). Also, it helps in the scavenging of free radical species and reducing hydrogen peroxide formation (16, 22). It also has a significant impact on the development of several metabolic illnesses, including osteoarthritis, polycystic ovarian syndrome, diabetes, and hypertension. In addition, carnitine deficiency has reportedly been related to the occurrence of non-alcoholic fatty liver disorders (NAFLD) (16).

On the other hand, according to recent studies, there is a disease that may be facilitated by carnitine – atherosclerosis. This substance is converted to trimethylamine (TMA) by gut microorganisms, which use it as a fuel source. The portal circulation carries TMA to the liver, where it is quickly changed into Trimethylamine-N-oxide (TMAO) by host hepatic flavin monooxygenases. According to clinical investigations, there is a link between a higher plasma TMAO level and a higher chance of having serious adverse cardiovascular events (23-26). Some studies show a link between TAMO and steatosis promotion and NAFLD progression (28).

At the halfway point of the investigations, there was a ten-times rise in TMAO concentration that persisted until the end of the study due to L-carnitine intake (23). The TMAO metabolite is linked to the initiation of inflammatory and oxidative stress pathways, resulting in hepatotoxicity (29). Furthermore, TMAO affects cholesterol metabolism and raises the risk of atherosclerosis (30).

In the present work, we assess L-carnitine's properties in preventing hepatotoxicity brought on by atorvastatin.

MATERIALS AND METHODS

The ethical committee of the College of Veterinary Medicine at the University of Mosul provided oversight for this study's conduct. The study lasted two months, from August to October 2022, at the University of Mosul's College of Veterinary Medicine.

Materials: Atorvastatin tablet 20 mg (MICRO, India), L-carnitine capsule 500mg (Green Field Nutrition, USA)

Animals: Rats used in this study were male Wistar rats; their weights were between 200 and 250 grams. Their food was a commercial rodent diet, and rats were housed in cages at 22 ±3 °C, with a twelve-hour lighting cycle, and they had unrestricted access to food and drink. In all groups, the animals were fasted for twelve hours before treatment.

Study groups: The study aimed to investigate the effects of atorvastatin and L-carnitine combinations on the rats' liver enzymes. This was done by dividing the total of 80 rats randomly into four main groups: control, L-carnitine, atorvastatin, and combination (L-carnitine + atorvastatin) groups. Each of these groups was further subdivided into three subgroups based on different doses of the drugs.

The control group (C) received only a vehicle (distilled water). The L-carnitine group was divided into L200, L300, and L400, receiving doses of L-carnitine at 200mg/kg, 300mg/kg, and 400mg/kg, respectively(31,32). The atorvastatin group was divided into A10, A15, and A20, receiving doses of atorvastatin at 10mg/kg, 15mg/kg, and 20mg/kg, respectively(33,35). The combination group was subdivided into AL10/200, AL15/300, and AL20/400, receiving combinations of atorvastatin and L-carnitine at different doses. All subgroups and their doses are shown in Table 1.All groups received their respective treatments daily for one month.

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Dose Preparation: The medications were dissolved daily in 1 ml of sterile distilled water and administered by syringe to the animals based on their weight.

Blood Sampling: Serum levels of ALT, AST, alkaline phosphatase (ALP), and total serum bilirubin (TSB) have been measured after one month in all study groups. Blood was collected, allowed to coagulate in a gel tube, and then centrifuged at 4000 rpm for ten minutes to extract the serum, which was sent for laboratory testing.

Biological Tests: Assays of liver enzymes (ALT, AST, and ALP) and TSB were carried out using commercial kits and a spectrophotometer (Jintan, Jiangsu, China). The measurement of ALT was done by using the measurement kit (Linear Chemicals®, Spain). The principle of ALT measurement depends on lactate dehydrogenase, which serves as the indicator enzyme in a linked enzymatic reaction that reduces pyruvate to lactate and simultaneously oxidizes NADH, the standard assay method for ALT. Continuously recorded changes in absorbance at 340 nm are correlated with ALT activity (36). AST and TSB measurements were conducted using kits (Biolab, France). The principle of AST assay procedures follows the Karmen method's basic tenets, which contain an associated enzymatic activity using malate dehydrogenase as the indicator reaction, as well as ongoing observation of the variation in absorbance at 340 nm as NADH is converted to NAD+, which determines the activity of AST(36). The concentration of TSB measured depends on the Malloy-Evelyn method. Bilirubin pigments in serum react with a diazo reagent. Sulfanilic acid that has been diazotized reacts with the bilirubin molecule's core methylene carbon to split it into two azobilirubin molecules, where the azobilirubin generated has a reddish-purple colour with a maximum absorption wavelength of 560 nm (36).

ALP is measured using a Giesse Diagnostic® kit from Italy. ALP activity is measured depending on p-nitrophenol hydrolysis to form coloured p-nitrophosphate, the rise in absorbance at 405 nm is used to assess the amount of ALP activity (36).

Statistical analyses: The information was displayed as a mean and standard deviation. The statistical analysis was accomplished by the SPSS 25 statistical analysis software. The differences between the groups were evaluated using analysis of variance (ANOVA) by Duncan's multiple range test (DMRT). To find correlations, a two-tailed Bivariate Pearson Correlation is utilized. When the means of the analyzed groups differed significantly, a P-value of less than 0.05 was deemed statistically significant.

RESULTS

A total of eighty rats were separated into four groups (Control, L-carnitine, Atorvastatin, and Combination) that were comparable. Each group was subdivided into three groups depending on the received doses. After the treatment of animals with the medications, hepatic enzymes (AST, ALT, and ALP) and TSB were measured in the rats' serum.

The effects of L-carnitine (200) supplement on hepatotoxicity caused by Atorvastatin (10): Table 2 displays how L-carnitine affects the increase in ALT, ALP,

Table 1. Study groups with their treatment during the study

Name of group	Name of subgroup	Type of treatment
Control group	C	Without treatment
L-carnitine group	L200	200 mg/kg L-carnitine
	L300	300 mg/kg L-carnitine
	L400	400 mg/kg L-carnitine
Atorvastatin group	A10	10 mg/kg Atorvastatin
	A15	15 mg/kg Atorvastatin
	A20	20 mg/kg Atorvastatin
Combination group	AL10/200	10 mg/kg Atorvastatin + 200 mg/kg L-carnitine
	AL15/300	15 mg/kg Atorvastatin + 300 mg/kg L-carnitine
	AL20/400	20 mg/kg Atorvastatin + 400 mg/kg L-carnitine

Table 2. Serum level of hepatic enzymes after L-carnitine (200) and Atorvastatin (10) treatment in study rats

Variable	Control (n=8)	L200 (n=8)	A10 (n=8)	AL10/200 (n=8)
AST (IU/L)	84.44±3.9 a	106.24±2.0 ac	142.44±4.4 b	121.26±6.6 bc
ALT (IU/L)	33±1.3 a	37.12±2.1 a	52.58±2 b	43.78±1.2 c
ALP (IU/L)	141.4±17.4 a	155.2±10.1 a	454.4±19.5 b	187.6±16.5 a
TSB (µmole/L)	4.8±0.37 a	5.4±0.51 a	10.8±0.66 b	6±0.31 a

Data represented as Mean ± SD, Mean values followed by different lowercase letters (within rows) indicate that there is a significant difference between the study's groups at ($p < 0.05$), and vice versa, according to the Duncan test.

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Table 3. Serum level of hepatic enzymes after L-carnitine (300) and Atorvastatin (15) treatment in the study's rats

Variable	Control (n=8)	L200 (n=8)	A10 (n=8)	AL10/200 (n=8)
AST (IU/L)	90.46±5.2 a	107.6±2.9 ac	158.94±9 b	129.12±3.2 c
ALT (IU/L)	33±1.5 a	38.7±1.4 b	52.62±0.7 c	43.42±0.7 d
ALP (IU/L)	165.5±8.5 a	192.6±3.5 a	512±13.7 b	192.62±3.1a
TSB (µmole/L)	5.8±0.58 a	5.8±0.37 a	10.4±0.87 b	7.8±0.56 c

*see table 1 for legend

Table 4. Serum level of hepatic enzymes after L-carnitine (400) and Atorvastatin (20) treatment in the study's rats

Variable	Control (n=8)	L200 (n=8)	A10 (n=8)	AL10/200 (n=8)
AST (IU/L)	101.14±1.6 a	107.86±2.9 a	160.42±8.2 b	129.96±3.1 c
ALT (IU/L)	34.62±2.1 a	39.66±6.9 b	58.72±7.7 c	46.28±5.4 d
ALP (IU/L)	163.38±8.8 a	187.9±14.6 a	535.52±10.2 b	195.68±8.4 a
TSB (µmole/L)	6.6±0.4 a	6.6±0.81 a	12.6±1.8 b	8.2±0.58 a

*see table 1 for legend

Table 5. Correlation between L-carnitine and atorvastatin dosage with liver enzyme levels and TSB.

Correlation		AST	ALT	ALP	TSB
L-carnitine	Pearson Correlation	0.931	0.99	0.803	0.982
	P- value	0.238	0.089	0.407	0.121
Atorvastatin	Pearson Correlation	0.663	0.889	0.972	0.768
	P- value	0.538	0.303	0.151	0.443

and TSB caused by atorvastatin is statistically significant, while the implications of L-carnitine on the increase in AST level caused by atorvastatin are not.

The effects of L-carnitine (300) supplement on hepatotoxicity caused by Atorvastatin (15): L-carnitine protective effects on an atorvastatin-induced rise in AST level became statistically significant at higher doses. Also, L-carnitine protective effects on other parameters were still observed at higher doses, as shown in Table 3. Even though L-carnitine treatment alone increases liver enzymes level.

The effects of L-carnitine (400) supplement on hepatotoxicity caused by Atorvastatin (20): The elevation of doses did not affect L-carnitine's protective effects on hepatic enzymes, as shown in Table 4. There was a significant improvement in hepatic enzymes and TSB levels elevated by atorvastatin with adding L-carnitine to the rats' treatment. However, when L-carnitine was administered alone, it led to an increase in liver enzyme levels, particularly in ALT levels, which was statistically significant.

The statistical analysis revealed no correlation between the variation in liver enzymes and TSB and the dosage of atorvastatin and L-carnitine, as illustrated in Table 5.

DISCUSSION

One of the most prevalent negative consequences of atorvastatin is statin-associated hepatotoxicity, and aminotransferase increases were seen in up to 2% of individuals treated with statins (4). Recent research has indicated that L-carnitine has substantial protective effects in a variety of tissues, including the liver, testis, and stomach (37). Numerous studies have examined L-carnitine activity to decrease fat deposition in the liver in NAFLD patients, often with promising outcomes. These studies demonstrate that L-carnitine supplementation can help these patients' liver enzyme levels return to normal (27).

In the current investigation, rats were given three different dosages of atorvastatin and L-carnitine, followed by measurements of serum hepatic enzymes and total serum bilirubin. We noticed a shift in the way the liver enzymes of rats responded to various doses. Administering a dosage of 200 mg/kg of L-carnitine alone did not lead to any significant alterations in serum hepatic enzymes or TSB levels. This is comparable to the findings of the study conducted by Mohamed B. et al. (2022), who utilized the same dosage for the same period (21). Also, Demiroren K. et al. (2014) performed research and discovered that rats treated for six weeks with 200 mg/kg/day of L-carnitine resulted in an insignificant change in ALT and AST levels when compared with the control group (38). Oh H. et al. (2022) carried out a further meta-analysis to evaluate the impact of L-carnitine and its analogues on hepatic enzymes in patients with liver disorders by reviewing 10 clinical trials conducted between 2000 and 2016 that discovered significant effects of L-carnitine in lowering levels of ALT and AST in patients with liver disorders (39).

At higher dosages of L-carnitine (300 and 400 mg/kg), there was an elevation in liver enzymes particularly ALT

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level, which exhibited statistical significance. According to previous research, mice given large doses of L-carnitine had blood ALT and AST activity that were significantly greater than those of the control group, These effects were attributed to the hepatotoxic effects mediated by TMAO (40, 41). Based on a meta-analysis of 17 clinical trials, it was determined that the impact of L-carnitine on serum AST and ALT levels is contingent on factors such as the dosage administered, the duration of treatment, and the initial levels of AST and ALT at the beginning of the trial (42).

Treatment with atorvastatin alone resulted in a noteworthy and statistically significant rise in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total serum bilirubin (TSB) when administered at three different doses (10, 15, and 20 mg/kg/d) for one month. A meta-analysis of twenty-one clinical trials also reported significant elevations in liver enzyme concentrations in all of these trials ($p < 0.05$) (43). Another meta-analysis highlighted an increased risk of liver injury in individuals using statins, particularly among those using fluvastatin (44).

In contrast, a meta-analysis of 22 clinical trials carried out by Pastori D. et al. (2022) indicated that statins lower ALT and AST levels, although all of these trials were conducted on NAFLD patients who had elevated levels of hepatic enzymes (45). Other clinical trials conducted on thirty patients with cirrhosis who received simvastatin therapy for about one year found a reduction in ALT, AST, and ALP levels (46).

The current study's findings show a decrease in liver enzymes and TSB levels in the combination group (L-carnitine 200 mg/kg/d and atorvastatin 10 mg/kg/d) compared to atorvastatin monotherapy. However, this reduction is statistically insignificant at the AST level. On the other hand, there was a significant decrease in ALT, ALP, and TSB levels in the combination group, providing evidence of L-carnitine's protective effects against atorvastatin-induced hepatotoxicity.

Ahmed EA. et al. (2019) observed a significant elevation in ALT and AST levels in rats receiving atorvastatin (50 mg/kg once daily) for four weeks, while the addition of L-carnitine (300 mg/kg once daily) to atorvastatin for the same period resulted in a significant decrease in the level of ALT and AST (47). This is similar to the results of a study conducted by Ahmed SA. et al (2022) performed on twenty-four rats have osteoporosis found that 100 mg/kg daily of L-carnitine for one month decreased ALP level and the same dose of L-carnitine added to 10 mg/kg daily of simvastatin for the same period result in a substantial decline in ALT and AST values (48).

When the doses of L-carnitine and atorvastatin were increased to 300 mg/kg and 15 mg/kg daily, respectively, similar results were observed as with lower doses. These findings included a significant reduction in ALT, ALP, and TSB levels, while the effect on AST became significant at higher doses. The results remained consistent even with a further increase in L-carnitine dose to 400 mg/kg daily and atorvastatin to 20 mg/kg daily. This suggests that the protective effect of L-carnitine against atorvastatin-induced hepatotoxicity is independent of the specific doses of L-carnitine or atorvastatin, except for its influence on AST levels, which becomes more observable at higher doses of L-carnitine (300 and 400 mg/kg daily).

In conclusion, our research highlights the beneficial effects of supplementing with 200 mg/kg/d of L-carnitine over a four-week period, which effectively mitigates the liver damage caused by atorvastatin. Notably, we observed that the protective action of L-carnitine is further enhanced with an increase in its dosage. However, caution must be exercised as we also observed that L-carnitine monotherapy at high doses may potentially lead to hepatotoxicity. Therefore, careful consideration of the appropriate dosage is crucial when utilizing L-carnitine as a protective agent against atorvastatin-induced liver damage. Further studies are warranted to explore the optimal dosage and long-term effects of L-carnitine supplementation for liver health.

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