WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 86-100. Research Article ISSN 2277– 7105

IMPACT OF L-CARNİTİNE ON ATORVASTATİN İNDUCED LİVER, TESTES AND GASTRİC İNJURY İN RATS

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Article Received on
09 June 2020,

Revised on 30 June 2020,
Accepted on 20 July 2020,

DOI: 10.20959/wjpr20208-18243

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ABSTRACT

Statins are one of the most effective drugs for treating hyperlipidemia. High dose of statins has been reported to be more effective in cardiovascular diseases, but their side effects have been reported that essentially limited their prescription. L-carnitine is an antioxidant; its role in protection is still not clear. The current study is concerned to investigate atorvastatin on the liver, testes, stomach and the possible protective role of L-carnitine. Thirty adult male albino rats were used in this study and were divided into three groups. Group 1, control group received distilled water, group 2 received 80 mg/kg/day of atorvastatin, and group 3, received both L-carnitine at 100 mg/kg/day and atorvastatin at 80 mg/kg/day for four weeks. Hematoxylin and Eosin (H&E) stain, morphometric and statistical investigation were performed. Liver sections of atorvastatin group showed dilated congested blood sinusoids and focal cellular infiltrations. Testes sections of atorvastatin group showed disorganization of the majority of the seminiferous tubules with thick capsule contain congested dilated blood vessels with widening of interstitium. Sloughed spermatogenic and multinucleated giant germ cells in the lumen of some of affected tubules, necrosis, degeneration and few spermatozoa were seen in few of seminiferous tubules. Gastric sections of atorvastatin group showed disruption of fundic mucosal glands with widening of irregular gastric pits, focal cellular infiltrations and dilated congested blood vessels in the submucosa. Co-administration of L-carnitine with atorvastatin induced an apparent protection against these histological changes. L- carnitine prevent atorvastatin induced damage of the liver, testes and gastric.

KEYWORDS: Atorvastatin; L-carnitine; liver; testes; stomach.

1. INTRODUCTION

Statins are widely prescribed drugs used for prevention and treatment of hypercholesterolemia and atherosclerosis. Atorvastatin, one member of statins is widely used in the clinical practice because it is reported to have few side effects as compared with other statins.[1] Crucially, administration of high dose statins have been observed to be more effective for improving cardiovascular diseases than using lower dose statins, however, new concerns about the risks of acute kidney injury, diabetes mellitus, and memory loss have encouraged some researchers to discover the adverse effects of statins.[2] Most prospective and retrospective investigations have been implicated statin-suspected liver toxicity.[3] However, other study revealed that atorvastatin has antioxidant and anti-inflammatory properties against doxorubicin produced hepatic and renal injury.[4]

Also, statins are the subject of queries regarding their influence on male fertility. Researchers suggested that administration of statins by patients suffered from hypercholesterolemia could reduce sperm quality and circulating testosterone concentration.[5] Others recommended that atorvastatin alleviates testicular damages produced by radiation in mice.[6]

Regarding stain influence on gastric ulcer, some researchers suggested that atorvastatin act as a protectant against indomethacin-induced gastric ulcer.[7] In contrast, other researchers suggested that atorvastatin increased the ulcer index.[8] Divergence of atorvastatin results is probably due to different dose or combination used.

Antioxidants have been stated to play a crucial role in the protection by decreasing or inhibiting oxidative damage. L-carnitine is found at a high concentration in cardiac and skeletal muscles. It is biosynthesized from the amino acids methionine and lysine in the liver and kidney.[9] L-carnitine has been reported to have a wide-ranging of biological properties including anti-oxidant, anti-inflammatory and anti-apoptotic.[10] Recent investigations suggested that L-carnitine inhibited free radical generation and might play an important protective role in several tissues such as renal cortex[11], liver[12], testis[13], and stomach.[14] In the past few years, much concern had increased due to the possible adverse reactions of atorvastatin and the results discrepancy, with limited literature regarding the histological studies in different organs from animals treated with atorvastatin. So, the current work was conducted to evaluate the histological changes in the liver, testes and stomach after atorvastatin administration and the possible protective role of L-carnitine.

2. MATERIALS AND METHODS

2.1. Animals

Healthy thirty adult male albino rats of the Wistar strain weighing 200±5g, were supplied from the Animal House of the Assiut University, Assiut, Egypt. Animals were maintained at the animal care facility in the animal house, Faculty of Medicine, Assiut University, in stainless steel cages under controlled temperature (24 ± 2C), 12h light/dark cycle and appropriate humidity. Standard pellet rodent food and free access to water were available. Two weeks earlier to the start of experiments, rats were acclimatized to the new environment. Animals were kept and controlled according to the protocols from the Institutional Ethics Committee of Assiut University, procedures and guidlines from the National Institute of Health.

2.2. Experimental design

Thirty rats were equally divided into three groups (n=10) and the selected doses for this histological study was mentioned in our previously published work.[11]

Group 1 (G1): Control group in which rats received distilled water orally for 4 weeks.

Group 2 (G2): Atorvastatin group in which rats received 80 mg/kg/day of atorvastatin orally. Previous publication suggested that the human therapeutic dose of atorvastatin average is 10-80 mg/day.[15] So, the male rat's dose is calculated according to previous published method.[16] Atorvastatin tablets 40 mg (Lipitor) were produced from (EIPICO, Egypt).

Group 3 (G3): L-carnitine + atorvastatin group in which rats received atorvastatin a**t** 80 mg/kg/day and L-carnitine at 100 mg/kg/day (Mepaco Co, Egypt) orally by gastric tube for four weeks.

2.3. Histological Study

Liver, testes and stomach specimens were excised from each group and were fixed in 10% formalin. Then, specimens were dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin. Sections of 5 µm thickness using rotary microtome were cut and mounted on slides and stained with H&E stain.[17] The investigation and the photography of all stained sections were evaluated using light microscope at the Mycology and Biotechnology Unit, Al-Azhar University, Cairo, Egypt.

2.4. Morphometric Study

Measurements of the height of the germinal epithelium in H&E stained testes from non-overlapped sections in the different studied groups were conducted in fifty randomly

seminiferous tubules from three rats /group. All the measurements used were calibrated against micrometers and taken from the equidistant points from the basement membrane to the latest phase of germinal epithelium, spermatids, in which four different epithelium heights for each seminiferous tubule sections viewed at 400 x magnifications. Also, measurements of thickness of the submucosal layer of stomach were conducted from stained H&E gastric sections. Ten assessments were considered in five non-overlapped fields for each group at magnification of x100 using image J software.

2.5. Statistical Study

Morphometric data was analyzed using one way analysis of variance, ANOVA, followed with post hoc Tukey's test for different comparisons. The values are represented as mean ± standard error of the mean. All statistical analysis was done using SPSS software, version 16 (SPSS, Chicago, Illinois, USA). The differences between studied groups were considered statistically significant when P value is less than 0.05 ($P < 0.05$).

3. RESULTS

3.1. Histological results of liver

H&E liver stained sections of the control group showed regular histological architecture of hepatic lobules (Figure 1a). Polyhedral shape hepatocytes were arranged in the form of branching cords radiating from regular small central vein. Hepatocyte cells appeared acidophilic cytoplasm with central rounded vesicular nuclei. Blood sinusoids were detected separating the cords and lined by flattened endothelial cells (Figure 1a). Liver sections of atorvastatin treated group showed some hepatocytes with cytoplasmic vacuolations and some nuclei appeared deeply stained. Obviously, dilated central vein and hepatic sinusoids and focal areas of cellular infiltration were also detected (Figure 1b, c). Liver sections of atorvastatin-+L-carnitine treated group showed a noticeable improvement in the hepatocytes compared with those treated with atorvastatin. Most of the hepatocytes were nearly similar to those of the control group, however, few of cells had slightly dark nuclei (Figure 1d).

3.2. Histological results of testes

H&E testes sections of the control group showed that numerous regular packed seminiferous tubules within the testicular parenchyma separated from each other by narrow interstitial space. Seminiferous tubules contained numerous spermatozoa and tubules lining consist of stratified germinal epithelium with different stages of spermatogenesis (Figure 2a). Sequential stages of transformation of spermatogonia into spermatozoa in the seminiferous

were detected **(**Figure 2a**).** Sections of the testes of atorvastatin treated rats showed that the majority of the seminiferous tubules were lost their normal architecture and disorganized **(**Figure 2b, c). The seminiferous tubules widely separated from each other with the interstitial spaces and gap spaces among the germinal epithelium layers are observed. Thickened testicular capsules appeared surrounding seminiferous tubules which contain congested and dilated blood vessels (Figure 2b). Lumina of seminiferous tubules appeared wide and characterized by the accumulation of sloughed, exfoliated and multinucleated giant germ cells inside the affected tubules (Figure 2c). Degeneration, necrosis of few of seminiferous tubules and few spermatozoa were seen in the lumen of tubules (Figure 2c). Sections of the testes of the atorvastatin +L-carnitine group showed that the seminiferous tubules regained nearly normal histological architecture. Most of seminiferous tubules were packed together with regular shape and surrounding by thin capsule, narrow interstitium, and germinal epithelial layers revealed different stages of spermatogenesis. Notably, sperms were detected inside their lumina, however, few irregular seminiferous tubules can be seen (Figure 2d).

3.3. Histological results of stomach

H&E stained gastric sections obtained from the control group showed normal histological architecture with regular intact mucosa and submucosa (Figure 3a). Gastric glands in the mucosa appeared narrow, straight and vertical to the surface epithelium and opened into surface by regular narrow gastric pits (Figure 3a). In contrast, H&E stained gastric sections obtained from the atorvastatin treated group revealed disruption and dilatation of the gastric glands in the mucosa with widening of gastric pits and area of congestion in submucosa (Figure 3b). Importantly, edema, dilatation of congested blood vessels and focal cellular infiltrations in the submucosa can be clearly seen (Figure 3c). Examination of H&E gastric sections obtained from the atorvastatin +L-carnitine group showed restoration of normal architecture of gastric mucosa and submucosa (Figure 3d). However, slight thickening of muscularis mucosa can be noticed (Figure 3d).

3.4. Morphometric results

Morphometric results obtained from the germinal epithelium height of testes sections revealed that significant decrease in atorvastatin group (53±5.06) as compared to the control (107±9.33) *(P* < 0.001). However, significant increase in atorvastatin + L-carnitine group (102±8.57) in comparison to atorvastatin group (*P* < 0.001) (Figure 4). Also, morphometric results obtained from thickness of submucosa layer of stomach sections showed that

significant increase in atorvastatin group (224±15.24) as compared to the control (121±10.26) ($P < 0.001$). However, significant decrease in atorvastatin+L-carnitine group (128± 12.45) ($P < 0.001$) as compared to the atorvastatin group (Figure 5).

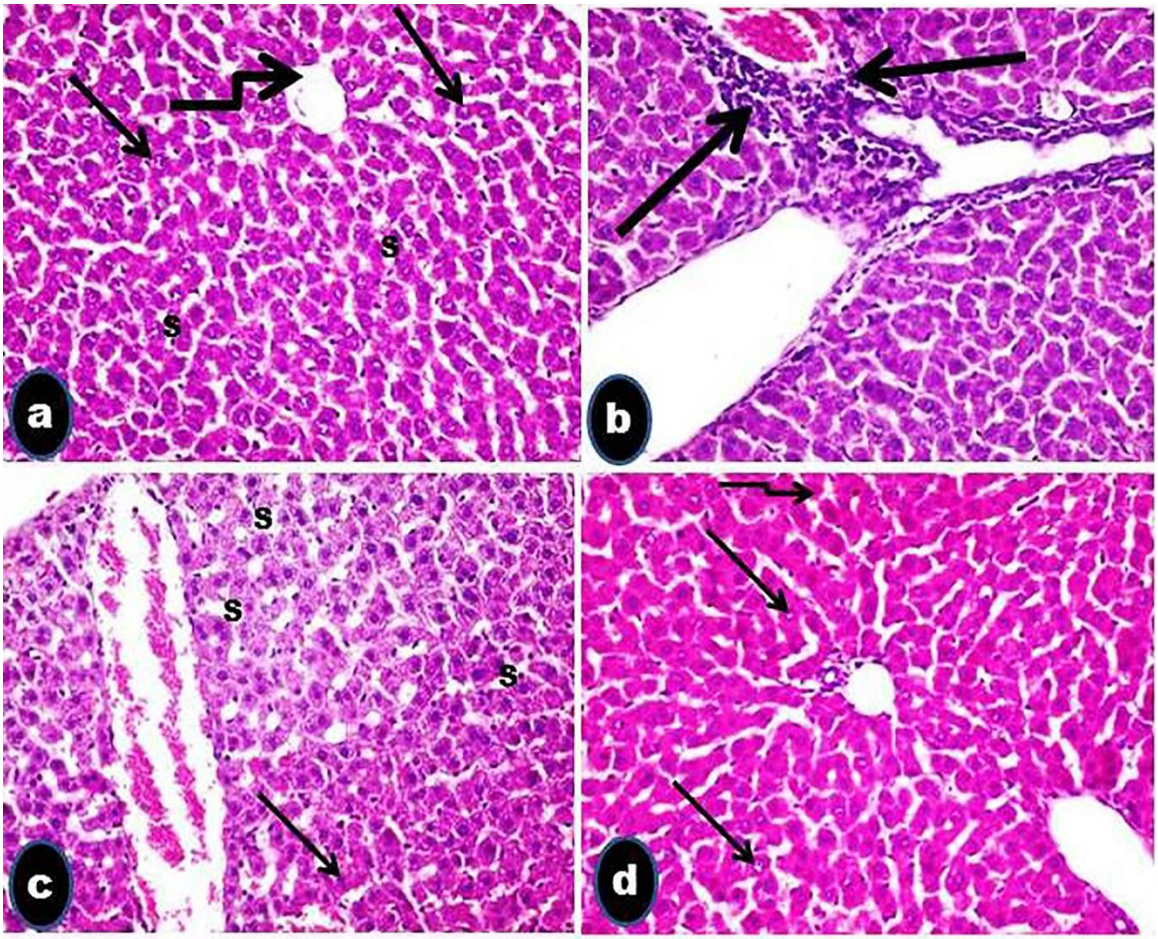

Figure 1: Photomicrographs of the liver sections from different studied groups. (a) Control group section showing cords of polyhedral hepatocytes with acidophilic cytoplasm and rounded central vesicular nuclei (black arrows) radiating from a central vein (curved arrow) and separated by blood sinusoids (S). (b) Atorvastatin group section showing extensive inflammatory cellular infiltrations (arrows). (c) Atorvastatin group section showing dilated congested blood sinusoids (S). Apparently, few cells with deep acidophilic cytoplasm and small dark nuclei can be noticed (arrow). (d) Atorvastatin +L-carnitine group section showing that most of the hepatocytes regain their normal appearance (arrows), whereas few cells have dark nuclei (curved arrow). H&E, x400.

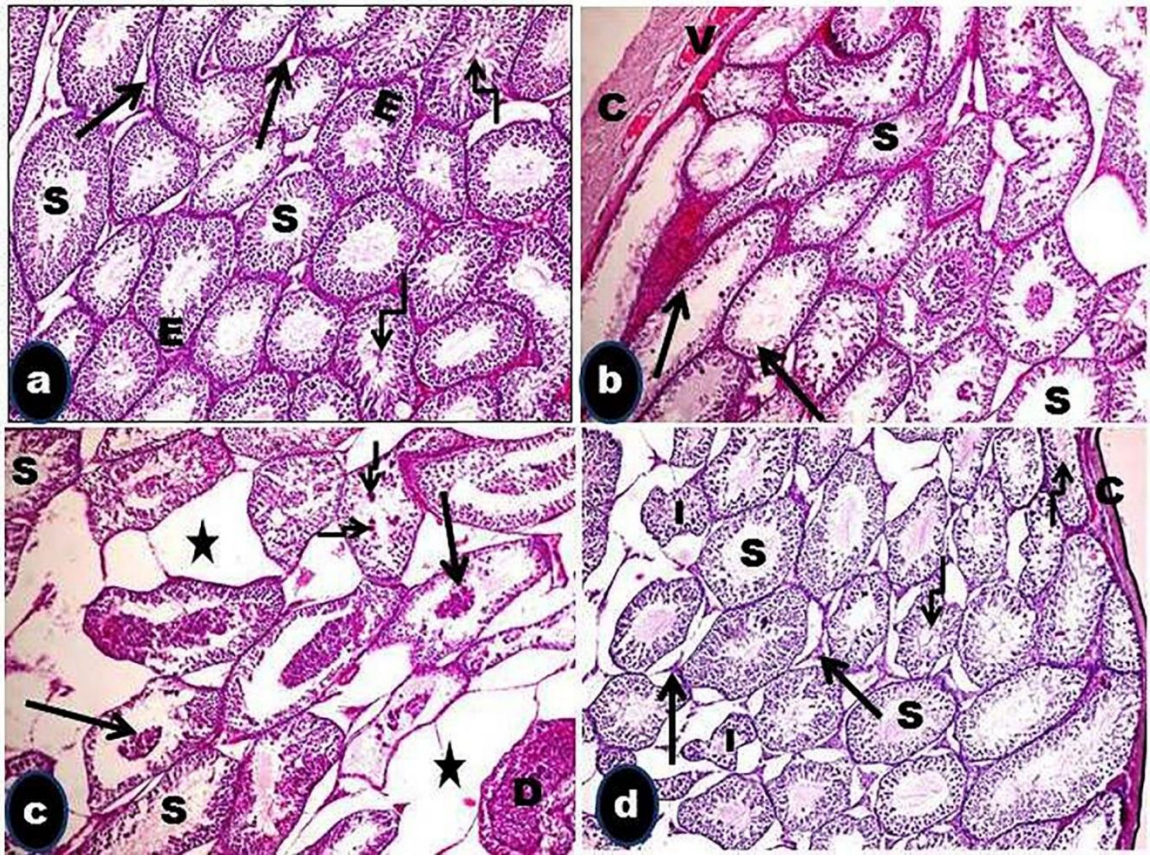

Figure 2: Photomicrographs of testes sections from different studied groups. (a) Control group section showing normal architecture of closely packed seminiferous tubules (S) lined with stratified germinal epithelium (E) and surrounded by narrow interstitium (arrows). Numerous spermatozoa in the tubular lumen can be seen (curved arrows). (b) Atorvastatin group section showing marked degeneration of most of seminiferous tubules with few germ cells (arrows) and tubules surrounded by thick capsule (C) containing congested blood vessels (V). (c) Atorvastatin group section showing disorganized seminiferous tubules and widening of spaces in between tubules (stars), sloughing germ cells (arrows), multinucleated giant germ cells (curved arrows), necrosis and degeneration (D). (d) Atorvastatin +L carnitine group section showing most of seminiferous tubules (S) regain their normal histological appearance in between narrow interstitial space (arrows), abundant spermatozoa (curved arrows) and thin capsule (C), however, few irregular (I) seminiferous tubules can be observed. H&E, x100.

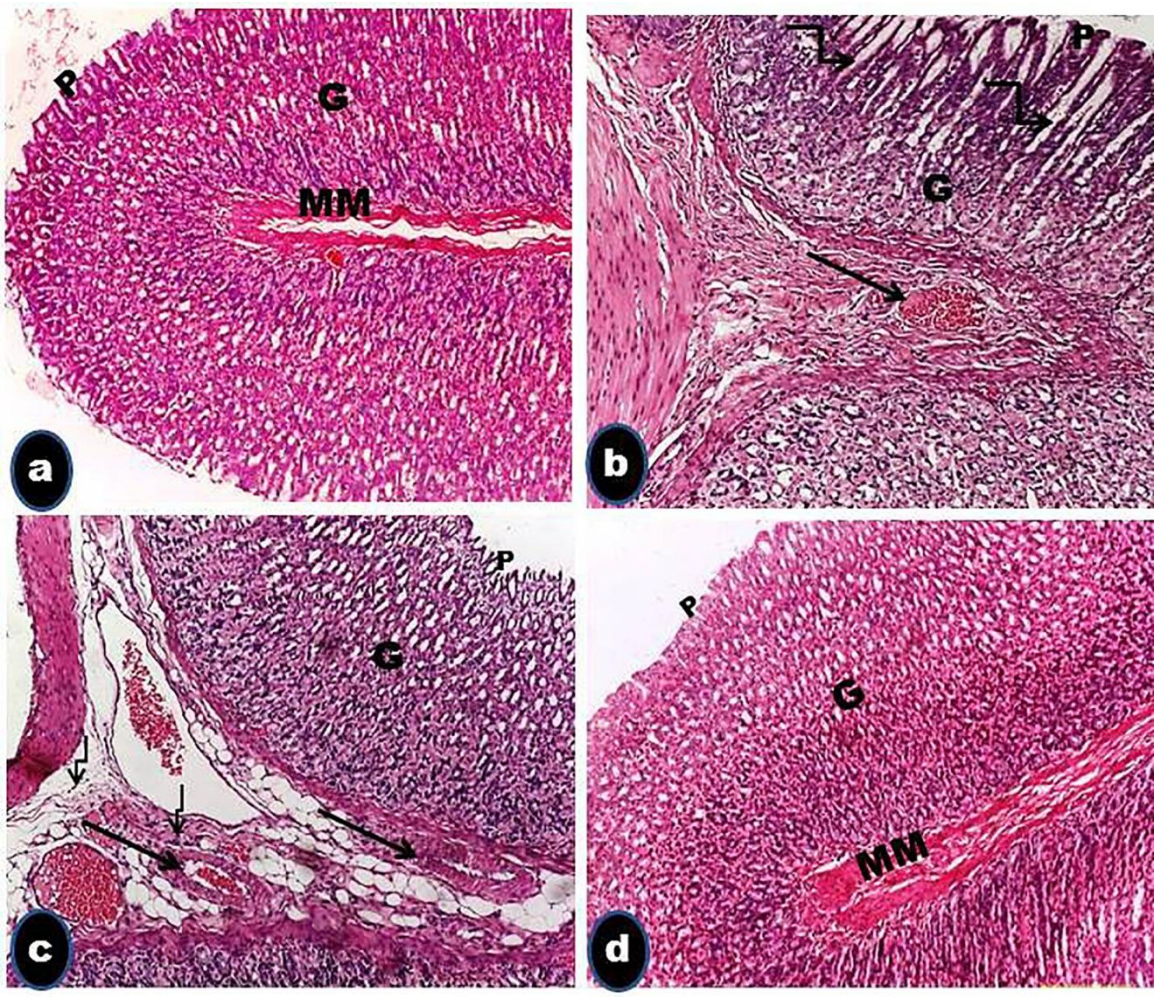

Figure 3: Photomicrographs of gastric sections from different studied groups. (a) Control group section showing normal architecture of glandular mucosa with plentiful tightly packed glands. Each gland has narrow luminal gastric pits and normal muscularis mucosa. (b) Atorvastatin group section showing separated distorted mucosal glands (curved arrows) and irregular widening of gastric pits and area of congestion (arrow) in the submucosa. (c) Atorvastatin group section showing dilated congested blood vessels in the submucosa (arrows) and focal cellular infiltrations (curved arrows). (d) Atorvastatin + L-carnitine group section showing regularly arranged fundic glands which open into luminal surface by narrow pits and slightly thickening of muscularis mucosa can be seen, glands (G), pits (P), and muscularis mucosa (MM). H&E, x100.

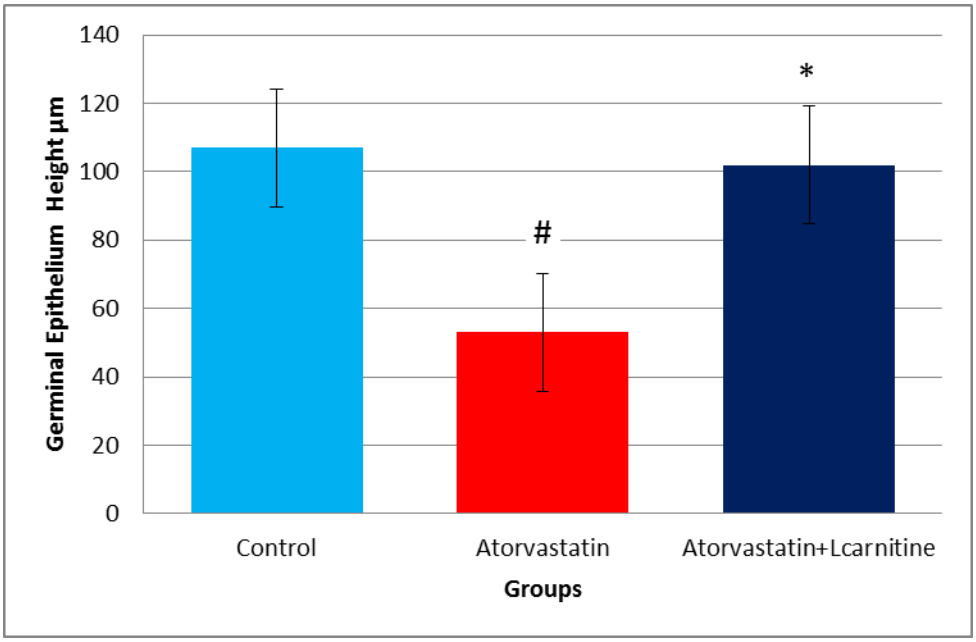

Figure 4: Changes in the germinal epithelium height in testes in different experimental groups. Morphometric data are expressed as mean± SEM. # significant differences of atorvastatin group from the control. * significant differences of atorvastatin+L-carnitine group from atorvastatin group (P < 0.001).

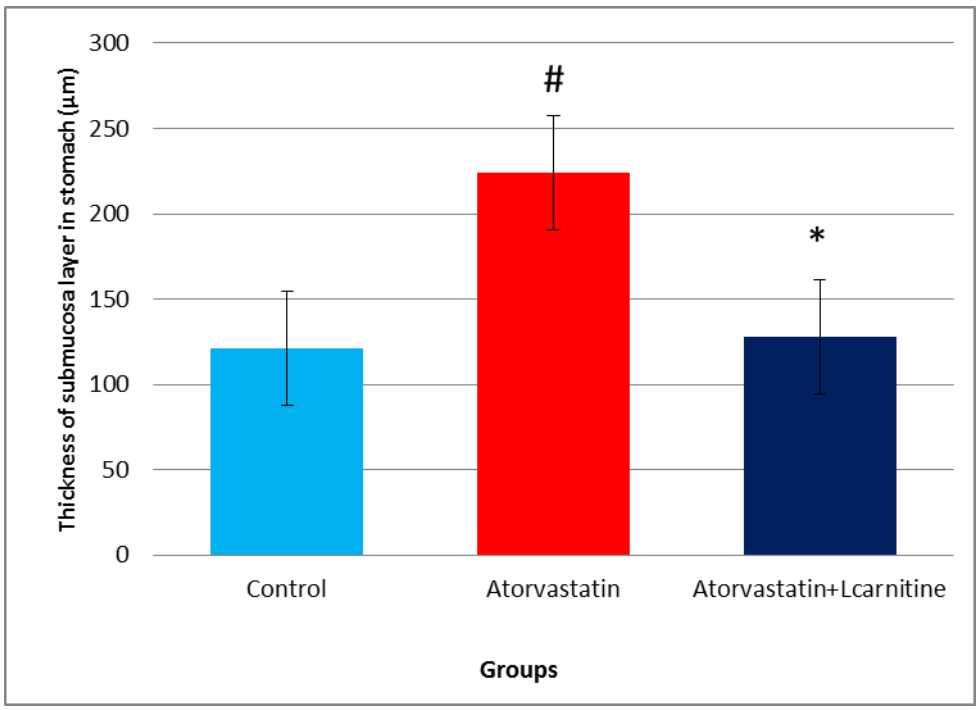

Figure 5: Changes in the thickness of submucosal layer in gastric area in different experimental groups. Bars are represented as mean± SEM. # Significant difference of atorvastatin group from the control. * Significant difference of atorvastatin +L-carnitine group from atorvastatin (P < 0.001).

4. DISCUSSION

Some drugs when taken with high dose or even when presented within therapeutic ranges, may hurt the diverse organs. Atorvastatin, a lipid lowering drug, recommended for prevention and treatment of several diseases such as hypercholesterolemia, and atherosclerosis. In the present study, histological investigations of liver sections of atorvastatin group revealed dilatation of blood sinusoids with hepatocytes cytoplasmic vacuolations, dark nuclei and focal cellular infiltrations. The present results are in agreement with the results of some researcher who report a case of a 58-year-old woman that illustrates a mixed structure of statin-induced liver damage. Her liver biopsy revealed a mixed inflammatory cellular infiltration expanding the portal triad and neutrophilic destruction of bile duct.[18] Consistently, atorvastatin has been linked with elevation of liver function test.[19] Significantly, earlier investigations reported six cases of autoimmune hepatitis induced by statins and five of them were related to atorvastatin.[20] Similar changes to the present work have been recorded in other experimental models of liver injury, for instance, the harmful effect of orlistat in liver rat.[21]

In the present study, administration of atorvastatin leads to various histological changes in the rat testes in the form of congestion and dilatation of blood vessels, widening of interstitial spaces and sloughing of germ cells. These findings are in line with other investigators who reported that congestion of blood vessels was linked to high oral atorvastatin use.[22] In the present work, some seminiferous tubules showed loss of cellularity, others were disorganized and distorted. Crucially, other studies suggested that intake of atorvastatin for five months by normo-cholesterolaemic healthy subjects significantly affected sperm morphology, number, motility, vitality, acrosome reaction and affected their composition of seminal fluid.[23]

In the current work, histological results of gastric region in the atorvastatin group showed that disrupted and widening of gastric pits in mucosa, edema and dilatation of congested blood vessels, cellular infilterations in the submucosa and confirmed by significant increased thickening of submucosa by morphometric and statistical analysis. These findings were in agreement with researchers used acute and subchronic rat models. They found that the high dose of atorvastatin at 50 mg/kg, significantly worse ulcer injuries induced by indomethacin.[24] Similarly, atorvastatin at higher dose has been shown to cause gastrointestinal bleeding and might induce colon carcinogenesis.[25]

L-carnitine is a potent anti-oxidant prevent free radical generation act as anti-reactive oxygen species medications. Presently, the hepatoprotective effect of L- carnitine was observed from the animals treated with L- carnitine + atorvastatin as the liver renovated its normal histological architecture and the hepatocytes appeared with normal arrangement. Studies have recommended the possible use of L-carnitine for the treatment of lipotoxicity under pathological diseases including steatohepatitis.[26] Importantly, decrease or prevention of β-oxidation caused insult and accumulation of lipids within liver hepatocytes. The antioxidant of L-carnitine specifically related to transport of fatty acids into mitochondria for the β-oxidation and consequently decrease lipid and lead to defense liver from reactive oxygen species and free radicals through the increasing of hepatic mitochondria β-oxidation.[27]

In the current work, the protective effect of L-carnitine on testes of adult male albino rats in the atorvastatin+L-carnitine group was observed. Sections of the testes revealed nearly normal histological appearance of packed seminiferous tubules and most of them restored their normal epithelial stratification and abundant sperms can be seen inside their lumina. L-carnitine has been proved to play a fundamental role in the maturation of spermatozoa.[28] It acts via an anti-oxidant properties and increased the glucose uptake by sperm and finally improved motility of sperm.[29] Significantly, L- carnitine played a vital role in the diabetes induced infertility. Indeed, L-carnitine reduces the level of serum glucose, inhibits apoptosis of germ cells and improves the thickness and the diameter of the epithelium of spermatogenic cells.[30] Importantly, researchers confirmed the link between carnitine diminishing the DNA injury and its protective role on stem spermatogonia. The stem spermatognia had broad DNA renovating mechanisms. Hence, the capacities of the testes to improve spermatogenesis influenced by the persistence of some stem spermatogonia and their capability to repopulate the testes with differentiate cells.[31]

In the present work, the potential protective role of L- carnitine in gastric mucosa and submucosa in atorvastatin +L-carnitine group was detected. Nearly normal histological architecture of gastric mucosa and submucosa can be seen. In agreement with the current results, it was reported that administration of both L-carnitine and vitamin C could prevent the adverse effects of cisplatin on gastric tissue.[32] L-Carnitine reported to inhibit gastric injury induced by chronic restraint stress by firming the gastric mucosal barrier and by decreasing lipid peroxidation.[33] Further investigation to improve atorvastatin toxicity using

co- administration with L- carnitine at different doses, duration and procedures should be carried out to know the exact protective mechanisms of L-carnitine.

5. CONCLUSION

From the current results, it is concluded that atorvastatin at high dose led to deleterious effect on the liver, testes and stomach of the adult male albino rats. L-carnitine has a potential protective role against toxicity induced by atorvastatin.

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