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Article

Study of Some Physiological, Biochemical and Histological Changes of Different Doses of L-Carnitine in Male Albino Rats

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Abstract: This study was designed to determine the physiological, biochemical and histological effects of double and excessive doses of L-Carnitine on male albino rats by estimating the concentration of urea and creatinine, the activity of liver enzymes by measuring (ALT) Alanine-amino-transferase and (AST) Aspartate-amino-transferase, and histological sections of the liver and kidney.This experiment was conducted in the animal house in the College of Education, Department of Life Sciences, where (15) animals were used in the experiment, with ages ranging from (3-5) months, and they were orally dosed with liquid L-carnitine for a full month, where the animals were randomly divided into three groups, with 5 animals in each group.The first group included the control group: This group was given water and food for a month. The second group: The double dose of L-Carnitine group: The animals in this group were given a double dose of L-Carnitine (56 mg/kg). Group 3: L-Carnitine overdose group: Animals in this group were given an excessive dose of L-Carnitine (112 mg/kg) via tube feeding at a rate of two doses per day. The animals were then starved and killed to obtain blood serum and tissue sections used in the experiment (liver and kidney).

The results showed that dosing rats with a double dose of L-Carnitine (56 mg/kg) caused significant differences ($P \leq 0.05$) in the levels of urea and creatinine compared to the control group. Treating male rats with an overdose of L-Carnitine (112 mg/kg) led to a significant increase ($P \leq 0.05$) in the levels of urea and creatinine compared to the control group. The results showed a significant difference in the liver enzymes AST and ALT when rats were treated with the double (56 mg/kg) and overdose (112 mg/kg) of L-Carnitine, compared to the control group. Histological sections of the livers of the double L-Carnitine (56 mg/kg) and overdose (112 mg/kg) groups showed hepatocellular degeneration, renal glomerular fragmentation in the double L-Carnitine group, and indistinguishable urinary tubules (UT) and marked hemorrhage within the kidney tissue in the overdose (112 mg/kg) of L-Carnitine group.

Keywords: L-Carnitin , Kidney , Liver , Creatinine, ALT, AST, Urea.

Introduction

L-Carnitine (LC), chemically identified as β-hydroxy-γ-N-trimethylaminobutyric acid, is a naturally occurring dietary supplement synthesized from the essential amino acids lysine and methionine [1; 2]. The biosynthesis of LC within the human body requires several cofactors, including vitamins B6, B12, C, folate, niacin, and iron, which act as catalytic agents enhancing its endogenous production [3].

L- Carnitine was first isolated in 1905 from an extract of beef muscle, a discovery that inspired its nomenclature—the term "Carni", derived from the Latin word for "meat," itself originating from "Carnivore," meaning "meat-eater" [4]. Small amounts of LC are biologically generated in the kidneys and liver [5;6].

L-Carnitine mainly plays the role of transporting long-chain fatty acids (FAs) to the mitochondria, where they are subjected to 2-oxidation to produce metabolic energy [7].

The biological form L-carnitine, D-carnitine, which prevents LC from being absorbed, and acetyl-L-carnitine (ALCAR), the most beneficial form for improving brain function, are among the several structural forms of carnitine [8]. Recent studies suggest that ALCAR may be used to treat brain degenerative diseases [4]. Another derivative that is essential for cardiovascular health is propionyl-L-carnitine, which improves blood flow, relieves vascular diseases, and may reduce blood pressure. Meanwhile, it has been demonstrated that L-carnitine L-tartrate, which is frequently present in athletic dietary supplements and has a high absorption rate, considerably lessens muscle soreness during exercise [5]. For general use, L-carnitine and acetyl-l-carnitine are believed to be the most effective; nevertheless, the right form must be chosen according to the physiological requirements of the body [6].

Additionally involved in a variety of liver and renal functions, L-carnitine is occasionally used to treat liver and kidney disorders. It is claimed to help treat hepatic fibrosis and increase red blood cell counts in hemodialysis patients [7].
Even while carnitine has many health benefits, in situations where fatty acid 2-oxidation is high, any amount above the prescribed limits may be harmful to bodily tissues, particularly the liver and kidney. Cell plasma membranes may oxidize as a result, ultimately impairing the ability of cells and organs to operate [8].

Material

Fifteen experimental animals in all were used, and they were divided into three groups at random as follows:

1. The control group received 30 days of treatment with distilled water.
2. LM group: For 30 days, the group received daily doses of L-carnitine (56 mg/kg body weights).
3. LC high dose group: L-carnitine was administered daily for 30 days at a dose of 112 mg/kg body weight.

At the conclusion of the experiment, all animals were sacrificed after being starved for 24 hours and then put to sleep using chloroform. After obtaining serum samples using heart puncture, the samples were centrifuged for 15 minutes at 3000 rpm. The serum was stored at -45C in new, clean plastic tubes until it could be used in the required biochemical investigations.

Techniques in Histology

Following a thorough dissection, all remaining blood traces were eliminated by cleaning the kidney and liver with physiological saline solution. The organs were then preserved in 10% neutral buffered formalin (NBF) for the duration of the night. To remove any remaining fixative, the tissue samples were washed under running tap water after fixing for 30 minutes. After that, the specimens were subjected to a routine histological examination using the method proposed by Bancroft and Stevens. To evaluate the histological changes in the renal and hepatic tissues of each experimental

group in comparison to the control group, thin tissue slices were produced and seen under a compound light microscope (Olympus) at different magnifications.

To perceive the microscopic changes in the renal and hepatic architecture of each treated experimental group in contrast to the control group, the histological sections were seen at different magnifications using an Olympus compound light microscope. Following analysis and the selection of the most representative portions, photomicrographs were taken with an HP P4 computer system and a Mitotic photomicroscope fitted with a Mercury digital camera. After that, color prints of the acquired photos were made for record-keeping and comparison.

Results

4.1 Physiological Parameters

It was observed from the data that treatment of male rats with double and excessive doses of *L-Carnitine* resulted in a significant ($P \leq 0.05$) increase in serum urea and creatinine levels compared with the control group. Moreover, a significant elevation ($P \leq 0.05$) in the activities of hepatic enzymes *Aspartate Aminotransferase (AST)* and *Alanine Aminotransferase (ALT)* was recorded in rats treated with both the double and excessive doses of *L-Carnitine* relative to the control group.

Table 1: Concentrations of Liver Enzymes, Urea, and Creatinine in Blood Serum

Parameters / Group	Urea (mg/dl)	Creatinine (mg/dl)	AST (m IU/ml)	ALT (m IU/ml)
Control group	45 ± 1 b	0.38±0.1 c	140±2 c	46±2 c
Double dose of L-Carnitine (56 mg/kg)	50±3 a	2.30±0.2 b	154**±3** b	55**±3** b
Excessive dose of L-Carnitine(112 mg/kg)	53±3 a	4.3**±0.3** a	165**±4** a	60±4 a

- **Values are expressed as Mean ± Standard Error (SE).**
- **Different superscript letters within the same column indicate significant differences at $P \leq 0.05$.**
- **Each group consisted of 5 animals.**

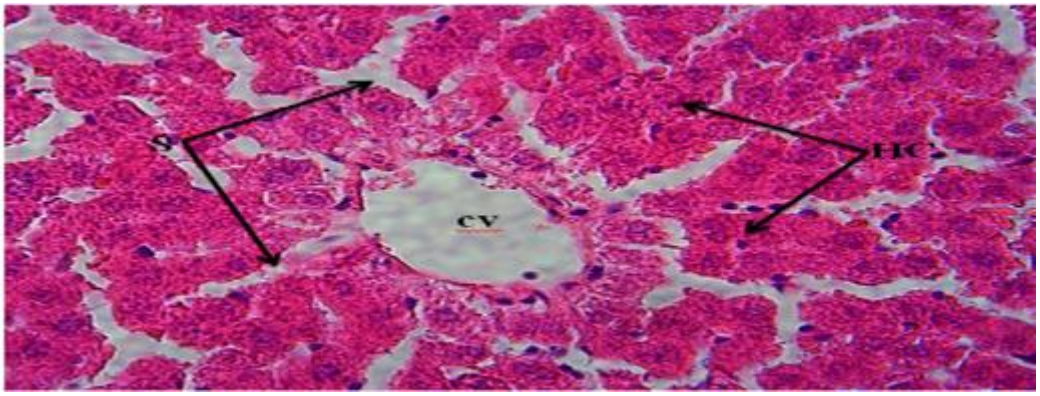

Figure 1:Histological section of the liver from the control group showing the central vein (CV) surrounded by hepatocytes (HC) arranged in hepatic cords, with visible blood sinusoids (S). Stained with H&E, 400× magnification.

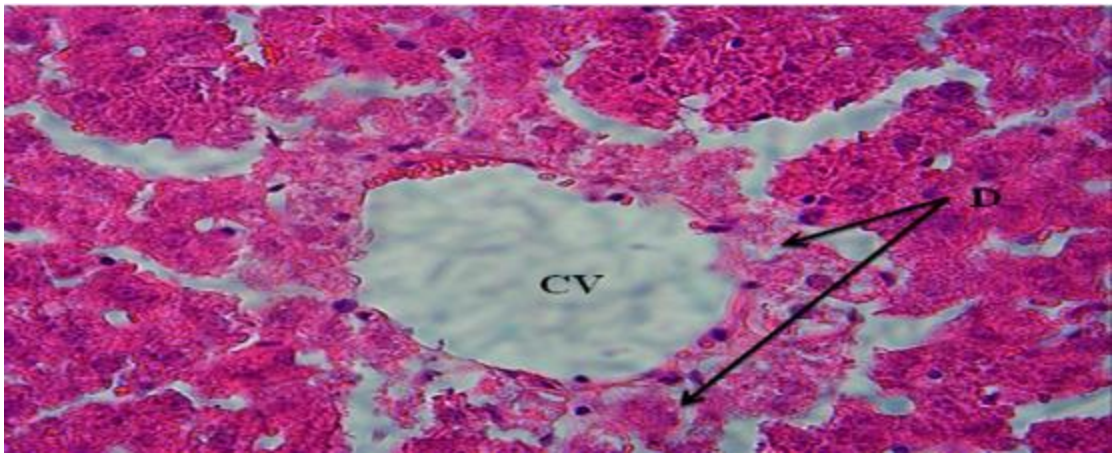

Figure 2:Histological section of the liver from the double-dose L-Carnitine group showing the central vein (CV) with hepatocellular degeneration (D) surrounding it. Stained with H&E, 400× magnification.

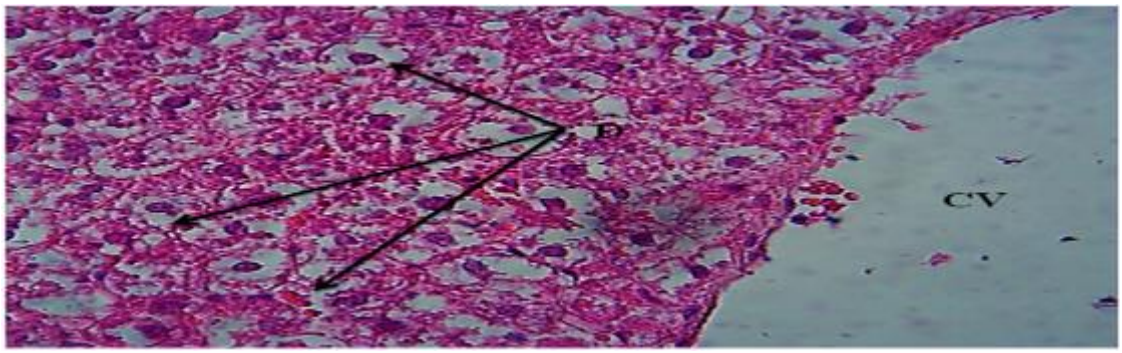

Figure 3: Histological section of the liver from the excessive-dose L-Carnitine group showing the central vein (CV) with hepatocellular degeneration (D) within the hepatic parenchyma. Stained with H&E, 400× magnification.

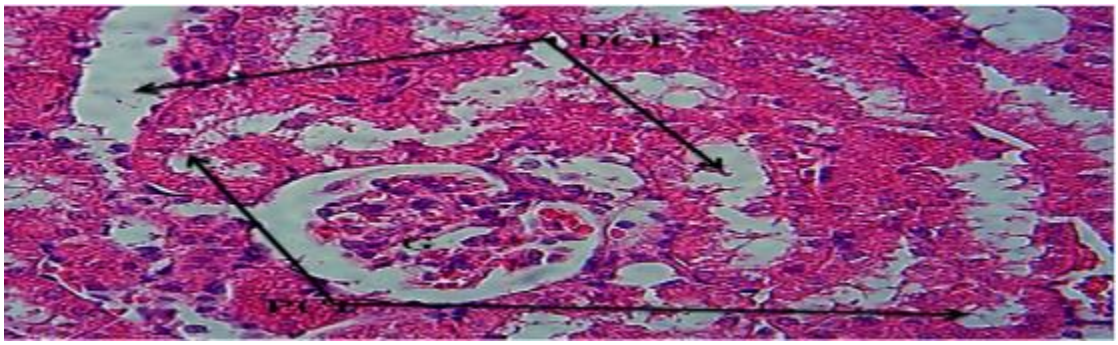

Figure 4: Histological section of the kidney from the control group showing the glomerulus (G), proximal convoluted tubules (PCT), and distal convoluted tubules (DCT). Stained with H&E, 400× magnification.

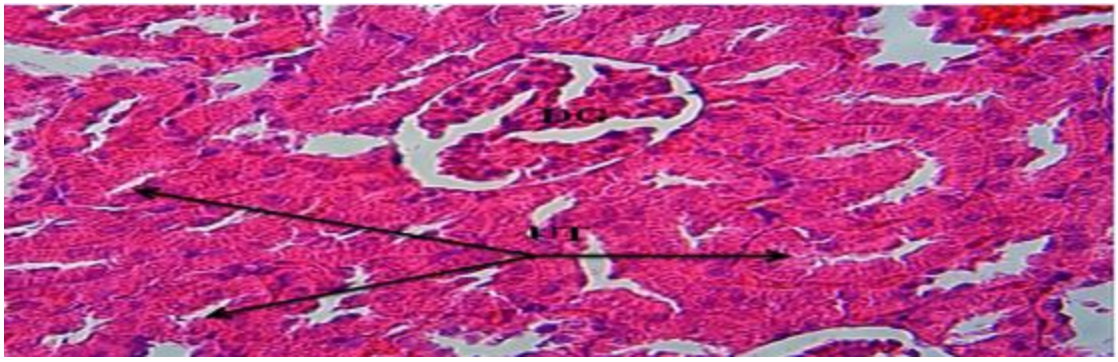

Figure 5: Histological section of the kidney from the double-dose L-Carnitine group showing the urinary tubules (UT) and glomerular fragmentation (DG). Stained with H&E, 400× magnification.

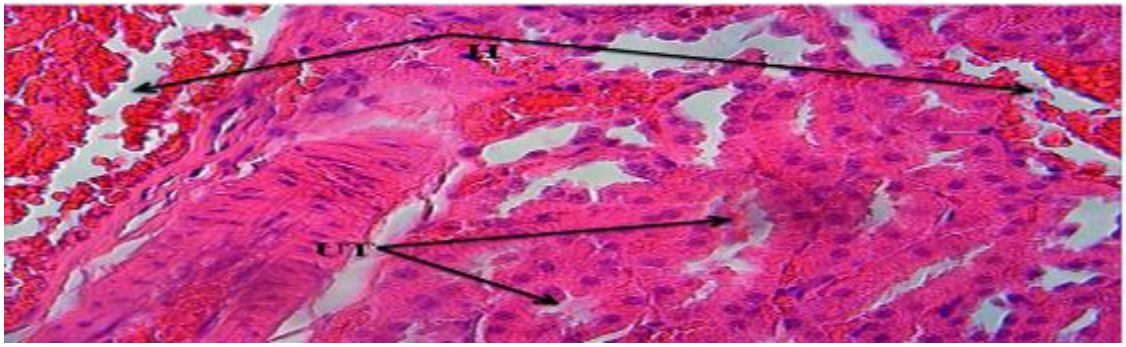

Figure 6: Histological section of the kidney from the excessive-dose L-Carnitine group showing indistincturinary tubules (UT) and prominent hemorrhage within the renal tissue (H). Stained with H&E, 400× magnification.

Discussion

Serum levels of urea and creatinine are important indicators of kidney function. The observed elevation in urea and creatinine levels in the groups treated with double (56 mg/kg) and excessive (112 mg/kg) doses of L-Carnitine indicates that these doses adversely affected renal function. The primary physiological role of L-Carnitine is to transport fatty acids from the cytoplasm into the mitochondria for β-oxidation and energy production [9]. Previous studies have shown that L-Carnitine is generally safe, with minimal side effects at normal physiological levels, and does not cause significant harm to the body, including the liver and kidneys [10; 11]. Nevertheless, there were rat's studies on the same that L-Carnitine high or excessive dosing can cause nephrotoxicity [12]. This is not a direct result of L-Carnitine toxicity, but because of the generation of trimethylamine (TMA), a product formed by gut microbiota of L-Carnitine, and by oxidative stress and inflammation due to high levels of the substance in circulation and renal excretion [13].

To a significant degree, a significant part of orally delivered L-Carnitine is transformed in the gut by the microbiotes into TMA [14]. TMA is excreted into the blood and taken to the liver and oxidized by the liver enzymes to produce trimethylamine N-oxide (TMAO) [15]. The kidneys filter TMAO out of the blood and release it in urine, which exposes renal tissue to elevated local levels and can result in nephrotoxicity and worsen renal performance [16]. TMAO facilitates the production of reactive oxygen species (ROS), i.e., free radicals in the cells of the kidneys, especially the tubular cells, and results in oxidative damage of lipids, proteins, and DNA, consequently, causing dysfunction of the cells and cell death [17; 18]. Besides, TMAO triggers inflammatory processes, prompts the production of cytokines, including TNF-a and IL-6, that attract immune cells and trigger inflammation of renal tissues, glomerular damage, and glomerulosclerosis [19; 14]. Thickening of the glomerular basement membrane and fibrosis also have been linked to high levels of TMAO, which decreases the filtering capacity of the kidney [20]. These processes indicate why there was a large rise in serum urea and creatinine in the double- and excessive-dose groups of this research

High liver enzyme levels are a signifier of dysfunction of the liver. In this research, the two (56 mg/kg) and excessive (112 mg/kg) doses of L-Carnitine depicted significant increases in the AST and ALT levels of the two treatment groups and not the control group, which reflects hepatic toxicity. Too much L-Carnitine will result in liver damage due to the conversion to TMA by gut microbiota followed by the transportation to the liver and oxidation of TMAO by flavin-containing monooxygenase 3 (FMO3) (2; 14). The symptoms of hepatic toxicity are the disrupted lipid and cholesterol metabolism, resulting in the fat buildup and hepatic steatosis [11]. Also, TMAO activates inflammatory signatures in hepatocytes, which leads to liver inflammation [21] and elevates oxidative stress by producing ROS damaging hepatic proteins, lipids, and nucleic acids [22]. Very high doses may cause the disruption of the usual activity of the endoplasmic reticulum, the site of protein synthesis and lipid metabolism, causing ER stress and the activation of apoptosis pathways in hepatocytes [8; 19]. This metabolism imbalance will affect the liver and its metabolic and detoxification efficiency [11]. In this research the high level of hepatic enzymes is a confirmation that the liver functions were impaired by the double and excessive doses of L-Carnitine on the treated rats.

Histological Observations

In the case of the kidneys, histological analysis of both the kidneys with the double dose L-Carnitine (56 mg/kg) showed the presence of urinary tubules and glomerular fragmentation as opposed to the control group. In the excessive dose group (112 mg/kg), the kidney samples had vagueness with distinct hemorrhage in the urinary tubules of the renal tissue compared to controls. High levels of TMAO are linked with the failure of kidney functioning and a higher risk of developing chronic kidney diseases. As the main organ involved in the excretion of TMAO, the kidney is the most susceptible to the toxicity of high TMAO levels, which undermines the renal performance [17]. TMAO build-up in the blood leads to the development of a vicious cycle of kidney cell injury [16].

One of the adverse effects of converting L-carnitine into TMAO, which causes oxidative stress, inflammation, and renal fibrosis, is renal toxicity in rats due to large dosages [12]. Raised renal functioning indices and elevated blood urea and creatinine concentrations are good indicators of low GFR and impaired kidney functioning [22]. Previous studies showed that renal tubular epithelial cells were damaged and degenerated by too high dosages of L-carnitine [6]. In severe cases, high TMAO levels may result in tubular necrosis [18].

Doubled and overdosed L-carnitine causes oxidative stress, the generation of malondialdehyde (MDA), and the down-regulation of antioxidant activity of enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) in renal tissue [13]. Renal tissue fibrosis, renal tissue death, and the formation of fibrous scars between tubules are most likely caused by the inflammatory process of cell infiltration, which involves macrophages and lymphocytes [19]. Additionally, elevated renal tissue inflammatory pathways (TNF-alpha and IL-6) have been reported [22].

Hepatocellular deterioration surrounding the central vein was observed in the double dosage (56 mg/kg) and high dose (112 mg/kg) L-Carnitine groups compared to the controls, according to histological study of the liver. Rats that receive excessive doses of L-carnitine have been shown to develop hepatocyte necrosis and die [11]. Hepatic steatosis, the localization of lipids in hepatocytes brought on by defects in cholesterol and lipid metabolism, is associated with elevated levels of TMAO in the plasma [23]. It is believed that the gut bacteria converts L-carnitine to trimethylamine (TMA), which is subsequently carried to the liver and oxidized to TMAO, resulting in hepatocellular degeneration [15].

Elevated levels of the liver enzymes AST and ALT are accurate indicators of inflammation or damage to the liver hepatocytes, according to Oh et al. [24]. Other studies have also demonstrated a

direct correlation between higher levels of plasma TMAO and the degree of hepatic injury, which in turn shows the degree of hepatocellular injury.

Conclusions

Administration of L-carnitine produced dose-dependent physiological, biochemical, and histopathological changes in male albino rats.

Different doses of L-carnitine exerted variable effects on biochemical parameters, indicating that its biological activity depends on the administered dose. Histopathological examination supported the biochemical findings by revealing tissue alterations that varied according to the level of L-carnitine exposure.

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