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# Effect of L-Carnitine in amelioration of hormonal profile and sperm parameter disorder in cimetidine-treated rats

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## Abstract

This study aimed to evaluate the ameliorative effects of L-Carnitine on sperm quality and hormonal profile in rats treated with cimetidine. Mature thirty adult male laboratory (8-10 weeks) rats were randomly divided into three groups: control group C1 was given tap water; group C2 animals were given cimetidine (150mg/kg i.p.) daily for 65 days, and group C3 animals were given L- Carnitine (200mg/kg i.p.) and cimetidine (150mg/kg i.p.) daily for 65 days. At the ending of the treatment period, blood was taken to determine the levels of testosterone, follicle-stimulating hormone, and luteinizing hormone in the serum. Body weight was recorded, then the animals were anesthetized. Histological sections of the right testis were prepared for histopathological examination, including the thickness and diameter of seminiferous tubules, as well as the number of Leydig's cells. While samples taken from the epididymis of the left testes were used for the estimation of sperm evaluation parameters. Cimetidine caused a significant decrease in serum testosterone, FSH, and LH concentrations, as well as a significant decrease in the ratio of testis' weight to body weight and sperm parameters (count, viability, and morphology) compared to other treated groups. Furthermore, a histological inspection of the testes indicated a significant increase in the thickness of epithelial cells and the diameter of seminiferous tubules of the testes and a reduction in the number of Leydig's cells. Whereas, the results showed that LC has a positive effect on improving previous parameters against cimetidine (C3) via a significant increment in hormone concentration, sperm parameters (count, viability, and morphology), and thus the number of Leydig's cells. Besides, LC reduced the deleterious effects of cimetidine on testicular tissues represented by a normal arrangement of seminiferous tubules with more and/or less complete spermatogenesis, the thickness of interstitial tissue in most seminiferous tubules, as well as the normal structure of the epididymis filled with normal sperm.

**Keywords: Cimetidine, Carnitine, Testosterone, Leydigs cells, Rats.**

## Introduction

Cimetidine is an important, competitive blocker of H2 receptors and is widely recommended for oral and injectable peptic ulcers (Scheinfeld,2003 ). Cimetidine is a prophylactic medication for malignant colorectal development, in addition to treating Zollinger syndrome – Ellison syndrome, heartburn, esophagitis, upper gastrointestinal bleeding, paracetamol overdosage, and Tinea capitis (Matsumoto *et al*., 2002 and Hansbrough *et al*., 1986).

According to studies (Pereira, 1987), cimetidine causes impotence and loss of libido in males. In addition, Franca et al., (2000) and Winters et al. (1979) reported cimetidine's antiandrogenic effects. Cimetidine is being taken without prescription for the time being and is currently being marketed as the counter drug category (Anand and Van Theil 1982). In Iraq, as in different nations, cimetidine was imported from different nations and commonly used in centers and medical clinics that prescribed its deleterious effects for long-term care in a chronic disease program. (Al-Janabi, 2007)

(L-carnitine) is a water-soluble antioxidant found in the mitochondrial membrane of all animals (Dunning and Robker, 2012; Surai, 2015, El-Sherbini et al., 2017). L-carnitine is relatively safe and has antioxidant properties (Liu et al., 2015).As such, it is used to prevent and treat OS and other health disorders (Xiang et al., 2013; Ahmed et al., 2014). That facilitates the transportation of long-chain fatty acids by the mitochondrial membrane, which is used for the production of energy. By conserving and protecting antioxidant enzyme levels (SOD, CAT, and

glutathione peroxidase), it plays a essential role as an antioxidant against the generation of reactive oxygen species (ROS) and scavenging free radicals (Go´ Mez-Amores *et al*., 2007 ).

LC is listed as having benefits in infertility management (Abdelrazik and Agarwal, 2009; Dunning and Robker, 2012 ; Al-Shammari and Alsaidi , 2020). The effect of LC on male infertility is now well understood. It is stated to be associated with spermatozoa epididymal maturation (Aliabadi *et al*., 2012). LC plays the role of an intramitochondrial carrier for the acyl group, which serves as a substratum for the oxidation process in the form of acyl-CoA. This process generates energy that is used for sperm respiration and motility ( Cheng and Chen, 2008, Aliabadi et al.,2012). It was also observed to improve sperm abnormalities such as depletion of ATP contributing to defective axonemal phosphorylation, lipid peroxidation, viability and loss of motility, as well as decrease the effect of ROS and free radical-triggered oxidative stress (Dokmeci,2005). In accordance with this, the current investigation evaluated the ameliorative effect of LC in male rats against several aspects of cimetidine-induced testicular damage**.**

## Materials and Methods

Thirty adult male laboratory rats (8-10 weeks) weighing (200-250) gm were randomly divided into 3 groups: control group C1 was given tap water; group C2 was given daily doses of cimetidine (150mg/kg i.p.) for 65 days; and group C3 was given cimetidine (150mg/kg i.p.) in addition to L-Carnitine (200mg/kg i.p.) daily for 65 days.

At the 65th day of the experiments, blood samples were taken from each animal under anesthesia by performing a cardiac puncture. The samples were then centrifuged at 3000 rpm for 15 minutes, after which the sera were separated and refrigerated at-18 °C until analysis. Testosterone, hormone-stimulating follicle (FSH), and hormone-luteinizing (LH) concentrations were determined by making use of immunoenzymometric assay kits (Monobind Inc, USA).In addition, testis in 10 percent formalin buffer solution was excised and fixed. According to Luna (1968), the tissues were first fixed in paraffin blocks, and several tissue sections with a thickness of 6 were prepared, and then they were stained with hematoxylin and eosin. Using a Java-based image processing program, the average number of Leydig cells per millimeter square was determined by counting the cells between every three seminiferous tubules. Using a light microscope (less than 40X) and a Java-based image processing program, ten cross-sections per rat were taken and the average number of Leydig cells per millimeter square was calculated. (Ballesterose et al., 2012). The statistical data was analyzed with one-way analysis of variance (ANOVA), and the significance level was set at ($P< 0.05$). The Least Significant Differences (LSD) test was utilized in order to investigate particular group differences. (Snedecor and Cochran, 1973**).**

## Results and Discussion

Figure 1 shows the results of serum reproductive hormones (T, FSH, and LH) concentrations in mature male rats. The concentration of reproductive hormones (T, FSH, and LH) in C2 in the cimetidine-treated group decreased significantly ($P < 0.05$) after 65 days of the experiment. In contrast, when rats were given cimetidine together with LC (C3), these parameters increased significantly ($P < 0.05$) when compared to the mean values of the reproductive hormone-treated group (C2).

Data pertaining, in fig **2-A** clarifies the changes in sperm quality ( sperm count, sperm viability, abnormal morphology) in the cauda epididymis of male rats at 65 days. Depending on the statistical analysis of the mean values of sperm parameters showed a significant ($P< 0.05$) decrement in male rats who received the cimetidine C2 group compared with other groups. Fig. 2-B illustrates a statistically significant ($P < 0.05$) decrease in sperm motility in the Cimetidine C2 group compared to the C1 and C3 groups. In contrast, LC in combination with cimetidine C3 caused a significant ($P < 0.05$) increase in these measures (fig 2-A and fig 2-B), with the exception of the sperm count parameter, which showed nonsignificant ($P > 0.05$) differences between the C3 and C1 groups after 65 days of experiments.

The statistical analysis of the diameter and thickness of seminiferous tubules showed a significant reduction in the C2 group relative to the C1 and C3 group. While results of C3 exhibited significant elevation in thickness epithelial & diameter of seminiferous tubules as compared with the C2 group ( fig 3-A). Moreover, the highest values in the thickness of epithelial tissue were that of group C3 with mean values were (43.09±0.2 ) as compared with a control group of 41.92±0.1.

In addition, the ratio of testicular weight to body weight decreased significantly in the cimetidine-treated group (C2). Meanwhile, the combination of cimetidine and LC (group C3) resulted in a statistically significant increment in this parameter compared to group C2 (fig 3-B).

Furthermore, the histological section of rats' testes revealed a significant decrement in the number of Leydig's cells in group C2 (fig 3-C, fig 5,6) compared to the control group (fig 4), wherein mean values were 4.8±0.2 and 8.6±0.2 respectively. In contrast, the number of Leydig's cells in group C3 treated with LC showed a significant increase in this parameter (9.80.2) when compared to the number of Leydig's cells in the other groups. Besides, proliferation of Leydig's cells in group C3 treated with LC as shown in fig 7 .

Besides, Figure 8 appear a normal arrangement of seminiferous tubules with complete spermatogenesis. The histological section of epididymis treated with cimetidine showed deformity in shape and structure figure 9, while rats treated with cimetidine concurrently with LC showed normal structure and were filled with normal sperm Figure 10.

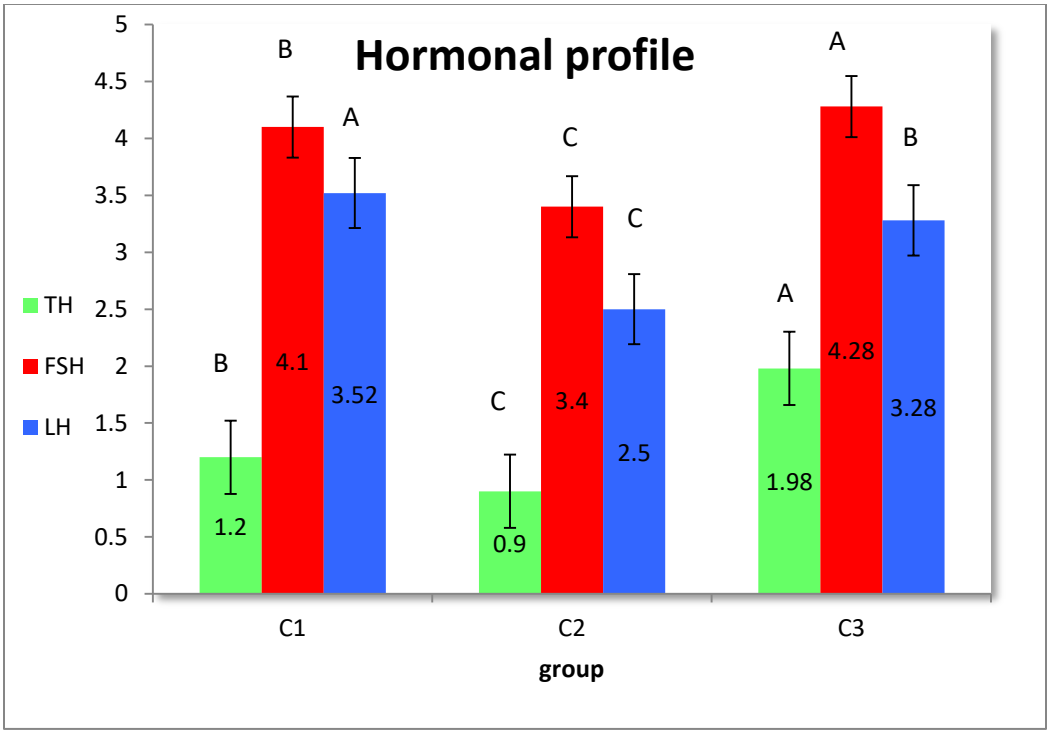


**Figure. (1): Effect of LC on testosterone, FSH, and LH concentrations in Cimetidine-treated adult male rats The values are display as the mean ± standard error, with n = 10 for each group. Capital letter represent a significant difference between groups (p <0.05) ; C1: control group, C2 : received daily dose of cimetidine (150mg/kg i.p.) , C3 : received L-carnitine (200mg/kg, i.p.) and cimetidine (150mg/kg i.p.).**

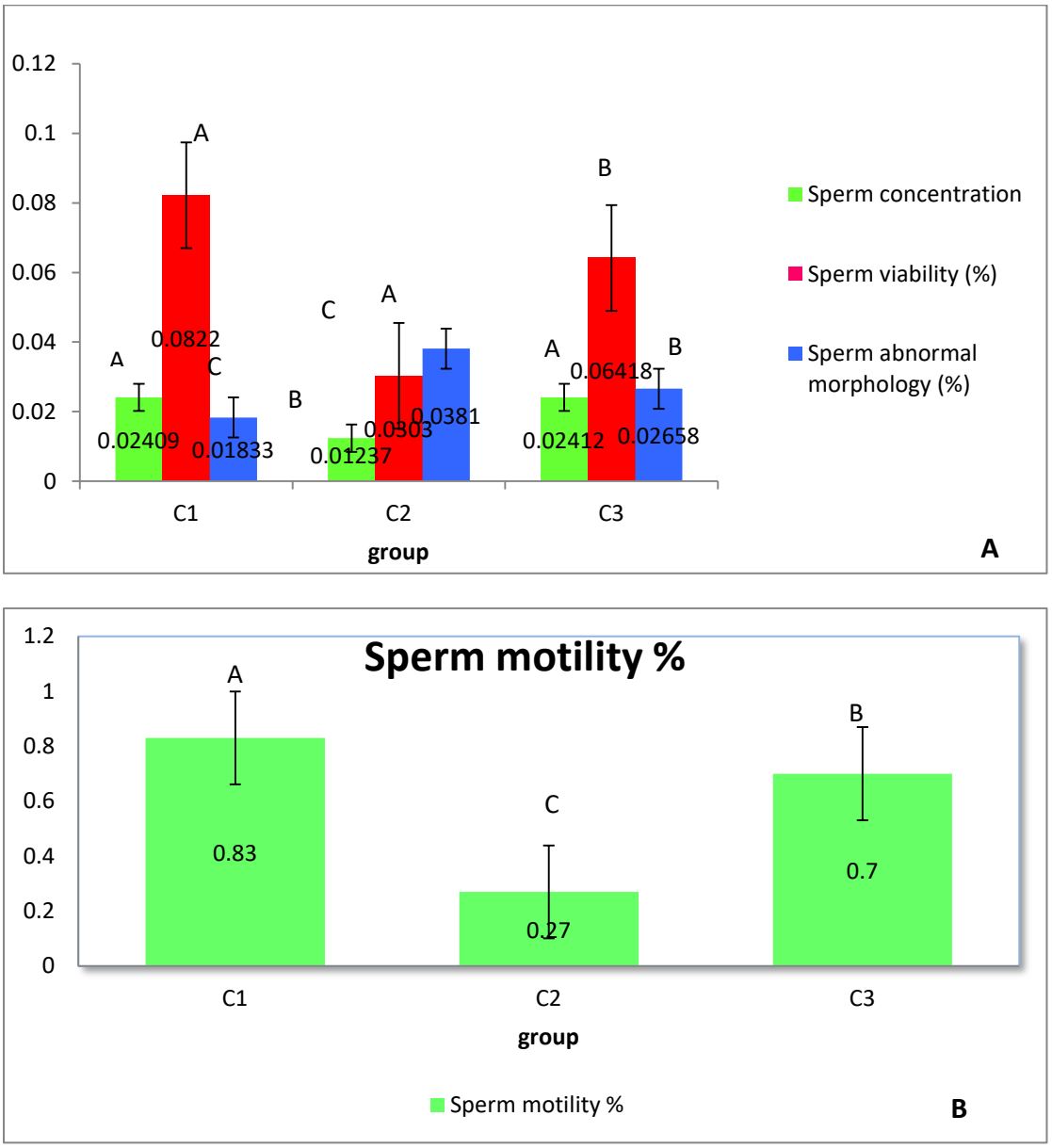


**Figure. ( 2 ): (A) Effect of LC on sperm parameters (B) sperm motility of male rats treated with cimetidine. For details see figure 1**

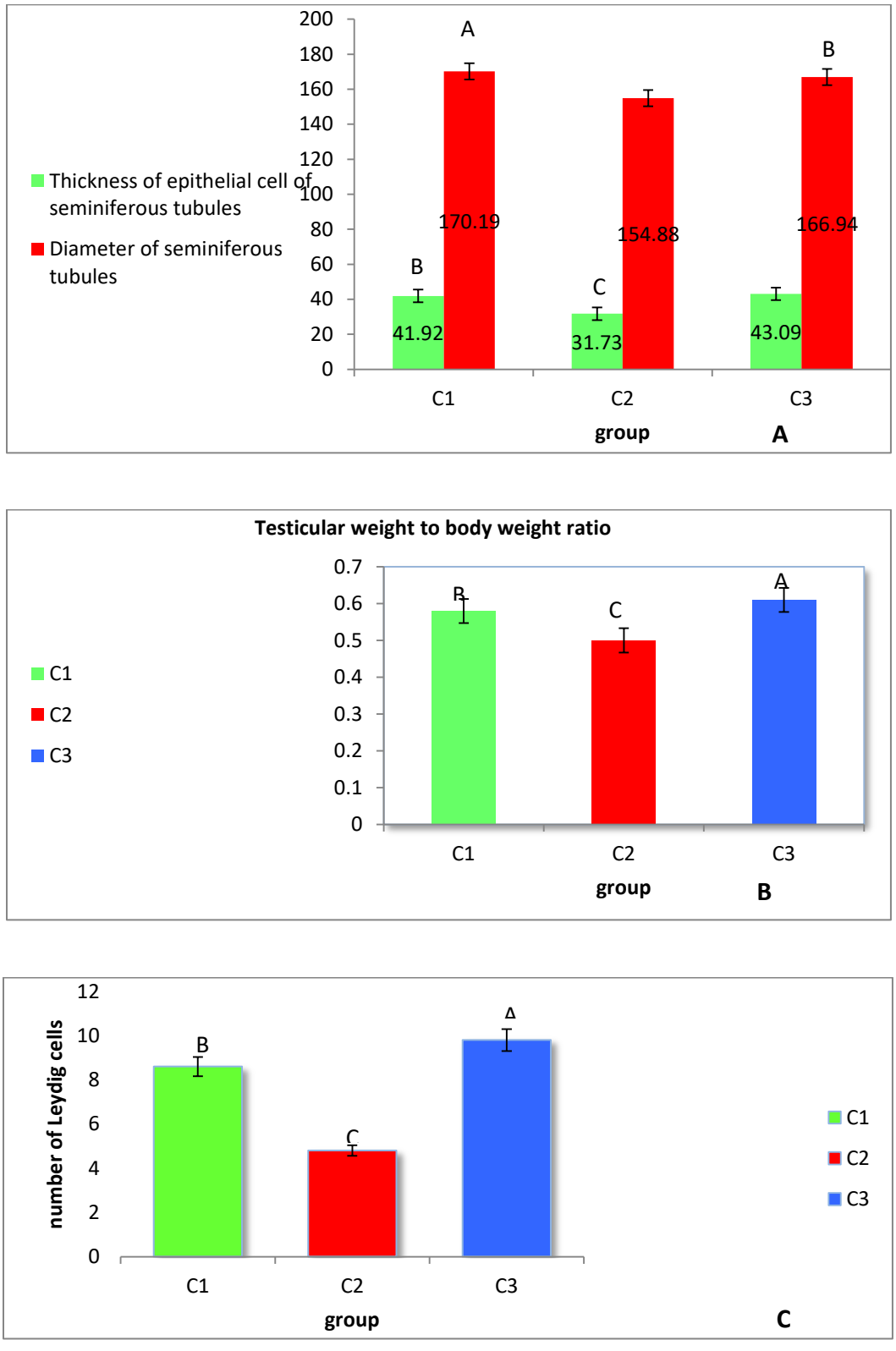


**Figure. ( 3 ): (A) Effect of LC on thickness& diameter of seminiferous tubules, (B) ratio of testicular weight to body weight , (C) number of Leydig's cells on male rats treated with cimetidine .**

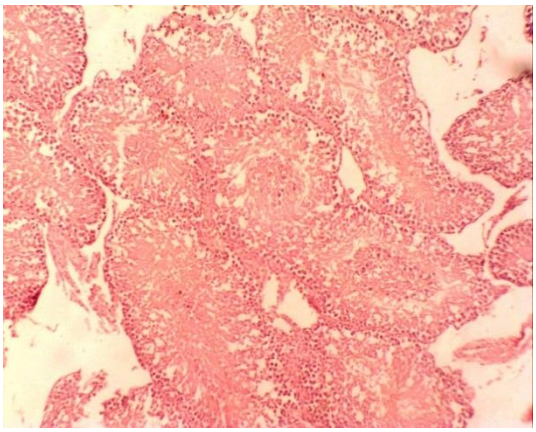

Figure 4: Rat testis of a control group. ( H &E stain 10 X )

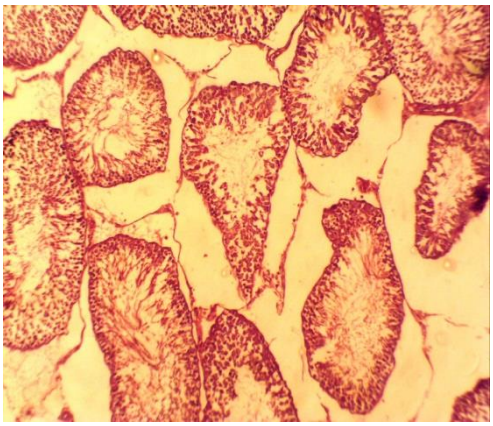

Figure 5: Rat testis of group C2 treated with cimetidine exhibit vacuolation and absence Leydig's cells ( H &E stain 10X ).

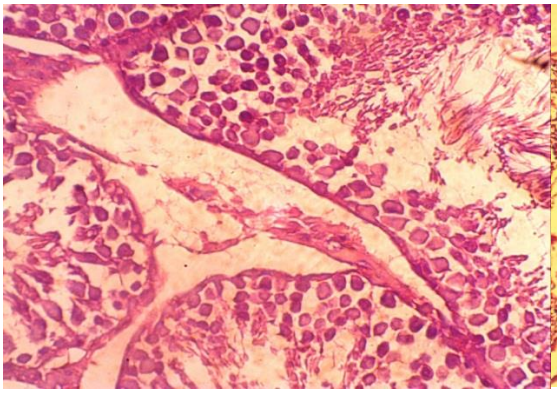

Figure. 6: Rat testis of group C2 treated with cimetidine note:- Leydig cell not present ( H &E stain 40 X ).

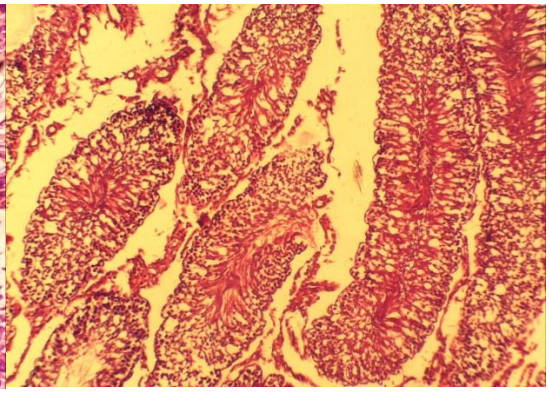

Figure. 7: Rat testis of group C3 treated with cimetidine plus LC. exhibit multiplication of Leydig's cells ( H &E stain 10 X ).

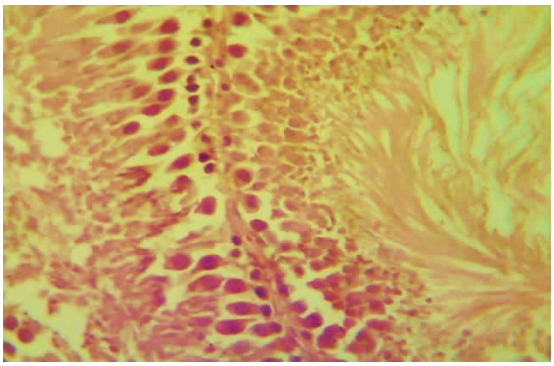

**Figure.8:Rat testis of group C3 , normal arrangement of seminiferous tubules (H&E stain 40X )**

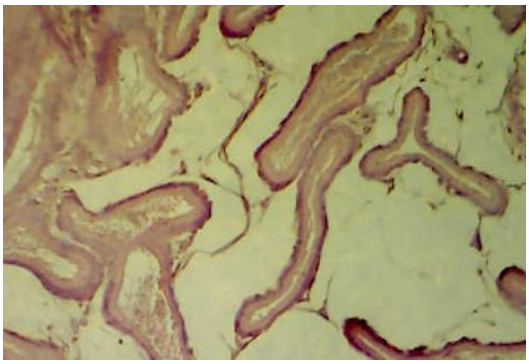

**Figure.9: Rat epididymis group C2 , deformity structure (H&E stain10X).**

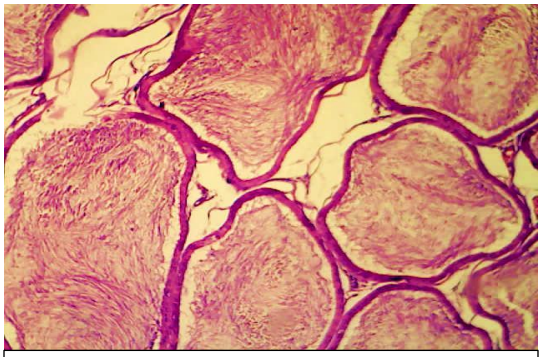

**Figure.10: Rat epididymis group C3 shows the normal structure (H&E stain10X).**

According to the findings of this study, administering male rats cimetidine (150 mg/kg i.p.) caused impaired sperm quality as well as a decline in the number of Leydig's cells and the levels of testosterone, follicle-stimulating hormone, and luteinizing hormone in comparison to the other groups. Other studies have reported elevated LH and testosterone levels in male patients (Peden et al.,1981, Wang et al ., 1982). Cimetidine inhibited FSH and LH in the blood, which induced signals for testosterone hormone synthesis. Suppression of these signals, which is caused by a serum reduction in testosterone levels, shows reproductive dysfunction, cell death, and apoptosis (LIU et al., 2018). The decrease in testosterone levels in rats treated with cimetidine could be attributable to decreased use of cholesterol by Leydig cells since the elevated cholesterol level impairs the function of the Leydig cells. On the other hand, the result exhibited that the LC caused a significant increment in hormones in rats treated with cimetidine concurrently with LC (C3) group. Increased hormonal levels in rats could be attributed to the hormonal profile's positive effect hich indicates the LC's positive effect in the treatment of reproductive dysfunction ( Al_Shammari and Alsaid, 2020 ) . Increase in testosterone biosynthesis as a result of either an increasing number and activity of Leydig's cells (the study findings revealed a significant increase Leydig's cells number (group C3) figure (7) and/or an increase in the sensitivity of LH receptors on Leydig's cells resulting in an increase in steroid biosynthesis and testosterone concentration in seminiferous tubules cavities (Agarwal et al., 2018), could be a possible mechanism of the LC on the Leydig cells. L-carnitine, however, reduced this effect in rats and returned testosterone levels to values close to control. (Masi et al., 2003; El-Sayed et al.,

2005). According to published research on L-carnitine, acetyl L- carnitine protects against declines in dopamine and testosterone, as well as other stress markers. These observations are substantiated by Rani and Panneerselvam (2002), who revealed that increasing antioxidants with LC had a neuroprotective effect on the brain in rats. LC also has antioxidant effects that protect sperm membranes from harmful ROS and may serve as roosters to preserve sperm membranes, extending sperm life and enhancing male fertility (Neuman *et al*., 2002).

The present study showed that cimetidine has a harmful effect on all sperm parameters (count, abnormal morphology, viability, and motility). This research showed that Leydig cell steroidogenesis was

influenced by cimetidine, leading to a decrease in te stosterone hormone resulting in low sperm counts.

A study of levels of testosterone in adult rats revealed significant age-related declines in these levels. On the other hand, the release of spermatids from Sertoli cells (called spermiation) needs both testosterone and FSH (Pineda and Dooley, 2003), thus, the increase of FSH, LH, and testosterone by LC can in some way promote mitosis and meiosis, which may stimulate sperm cell concentration (El-Sherbini et al.,2017 ). Increasing the testicular weight of rats which confirms the correlations between testicular weight and sperm concentration may also be the product of the increase in this parameter. In the cimetidine treated group, an increase of abnormal sperm morphology may be attributed to the oxidative stress, induced by cimetidine. A high level of ROS is also associated with poor sperm morphology in human seminal plasma (Venkatesh et al., 2009).

In group C3, The current study found a significant decrement in sperm abnormal morphology compared to C2 could be due to the effects of LC as a scavenging mechanism. Besides, increasing FSH and testosterone in the LC group(C3) improved male fertility by decreasing abnormal sperm morphology and preserving normal sperm shape, in addition, testosterone is important in facilitating the progression of round spermatids to elongated spermatid, this increment of testosterone may lead to a decrease in abnormal sperm morphology (Neuman et al., 2002).

Cimetidine causes a decrease in testosterone. This decrease in testosterone may lower the production of fructose in the secretion of the epididymis and decrease sperm viability and motility. The result of this study found that LC increased testosterone levels; this hormone regulated epididymal secretion; played an important role in sperm maturation & survival; and also that the hormonal requirements for sperm survival in cauda epididdymidis for fructose production may result in increased sperm viability and motility (Banihani et al., 2014).

In rats receiving cimetidine, seminiferous tubular diameter and thickness were found to be significantly reduced due to oxidative stress, causing damage to the testicular tissue (Sasso-Cerri et al., 2001). Therefore, a decline in these parameters may indicate defective spermatogenesis as evidenced by sperm reduction parameters. On the other hand, LC has attenuated the reduction of seminiferous tubular diameter and thickness. In addition, LC acts as an antioxidant (El-Sherbini et al., 2017). This plays an important role in free radical scavenger produced by cimetidine, and the reduction of seminiferous tubular diameter and thickness may be attenuated.

According to the results of this study, a lower ratio of testicular weight to body weight in rats given cimetidine might be due to a lower concentration of serum testosterone. In previous studies, it was shown that cimetidine can affect the structures of the testis (França et al., 2000) and has led to the weight loss of the testis causing significant structural changes in the seminiferous tubules. In another study, cimetidine did not show any adverse effect on reproductive organs body and relative weight (LIU et al., 2018). Differences in dosage and administration route may be responsible for the variation. The maintenance of testicular weight and accessory reproductive glands is widely known to be dependent on testosterone levels. (Scholz et al.,2014 ). Therefore, the significant increase in testicular weight in rats treated with LC may be attributable to an increase in testosterone and/or FSH levels, or it may be the result of testosterone's anabolic activities contributing to an increase in body weight. (Somfai et al., 2011). In addition, testosterone may enhance the number and activity of somatic and germinal testicular cells, resulting in an increase in testicular weight (Al-Okaily and Al-Shammari , 2016). Thus, L-Carnitine administration in rats can prevent testicular damage and maintain hormonal profile from the negative effects of cimetidine.

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