

Role of alpha lipoic acid in protecting testes of adult rats from lead toxicity

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Abstract

The current study was conducted to investigate the role of alpha lipoic acid (ALA) against testicular toxicity- induced by lead acetate (PbAc) in rats. Four groups of adult Wistar albino rats (8 for each) were intubated daily for 56 days as follows; control (C) received distilled water; lead acetate at dose of 5mg/kg b.w (T1); ALA at dose of 60mg/kg b.w (T2) and group T3 received both of PbAc + ALA at the same doses of above. Blood samples were collected at 0, 28 and 56 day of the experiment, then the sera were collected for determination of testosterone (T) and follicular stimulating hormone (FSH). At the end of the experiment, body weight, testes weight and epididymal sperm parameters was studied. Furthermore, histo-morphometric and histopathological study changes were examined. The results revealed a significant decrease in testes weight to body weight ratio, serum testosterone, sperm concentration and motility, diameters of seminiferous tubules, height of seminiferous epithelia and number of Leydig cells, moreover the results showed a significant increase in serum FSH, dead sperm and abnormal sperm morphology in group T1 when compared with the other groups. Comparing to lead acetate treated rats, group T3 showed an improvement at the level of the studied parameters, accompanied with mild congestion in the interstitial tissue with a marked developing proliferation of spermatogenic cells, as well as presence of mature spermatozoa in the seminiferous tubules. In conclusion, subchronic exposure of rats to lead acetate showed an amelioration of all reproductive parameters near to normal values due to the antioxidant effects of ALA and the histological changes of the testes confirmed such change in serum parameters and the beneficial role of ALA.

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Introduction

Globally, it is well established that main hazard to environmental health is by lead toxicity in animals and all ages of humankind particularly children with long-term exposure at very low levels and animals (1). Occupational and environmental exposure to lead was increased several folds resulting in the wide range of applications in industries, cosmetics, folk remedies, drugs and medicine (2). One major manifestation of accumulation of lead in the cells is attributed to induce oxidative stress that causing loss the

integrity of the cell membrane, mitochondrial dysfunction, deoxyribonucleic acid (DNA) damage, apoptosis and antioxidant defense systems of cells (3) via increased production of reactive oxygen species (ROS) which may be contributed to an increase in lipid peroxidation (LPO) level (4), moreover, the disorder of mitochondrial enzymes with a dropped antioxidants level by lead toxicity in spermatozoa resulting in alterations in sperm motility, acrosomal morphology, semen quality and increased tail anomalies (5). It has been observed that lead causes a decline in fertility via decreasing in the level of testosterone, moreover dropping in

testosterone production in rats was reported as well (6) after exposure to lead. Many potential adverse effects on the male reproductive system were being caused by exposure to lead including oligozoospermia, asthenozoospermia, libido reduction, sperm DNA damage, prostate gland abnormal function and serum testosterone alteration (7,8). Alpha lipoic acid (ALA) is a water and lipid soluble universal antioxidant, has a property that allows concentrating in cellular and extracellular environments. ALA is a dithiol compound enzymatically synthesized from octanoic acid in the mitochondria. The functions of ALA are a cofactor in several mitochondrial enzymes that involved in energy production (9). Concerning the male reproduction, many studies suggests that ALA has a key role to protect the testes and its functions against a broad spectrum of toxicant insults, where oxidative stress is a part of the underlying etiology (10,11). However, the role of alpha lipoic acid on testicular toxicity-induced by lead acetate in the rat model, however, has not been addressed previously. Therefore, this study was designed to elucidate the protective effects of ALA in ameliorating testicular dysfunction induced by lead mediated its antioxidant properties.

Materials and methods

Animals, housing and experimental design

Thirty-two adult male albino Wister rats were used in this study (13-15 weeks old and weighed 190-220 gram) from December 2018 to February 2019. The rats were housed in plastic cages $70 \times 50 \times 15 \text{ cm}^3$ at $20\text{-}22^\circ\text{C}$, humidity 50% - 56% and 12 hours' light-dark period in an animal house of College of Veterinary Medicine/University of Baghdad. Rats were acclimatized for 15 days, then were randomly divided into 4 equal groups and each intubated daily for 56 days as follows: Group (C) intubated distilled water and served as control; group T1 was intubated 5mg/Kg B.W. of lead acetate trihydrate (Sigma-Aldrich Chemicals Co., St. Louis, USA) dissolved in distilled water; group T2 was intubated 60mg/Kg B.W. of ALA (10) and group T3 was intubated 5mg/Kg B.W of lead acetate and 60 mg/Kg of ALA. Fasting blood samples were collected by cardiac puncture technique by using a non-heparinized gel tube at 0, 28, and 56 days, serum was isolated into Eppendorf tubes and kept at -20°C for estimation of serum testosterone and FSH levels by using testosterone and FSH kits (Monobind Inc. USA) using ELISA technique according to (12,13). At the assigned time, the animals were fasted overnight, anesthetized and weighted. After sacrifice, the right and left testes were separated from the adjacent epididymis and removed from the animal body. Both left and right testes were weighed to measure the testicular weight to body weight ratio. The right testes were sectioned transversally, and specimens from the middle part were taken, then immediately fixed in freshly prepared 10% neutral formaldehyde. Then, sections were prepared in thickness 5-6 μ and stained with hematoxylin and

eosin (H&E) according to (14) for morphometrical and histopathological studies including, diameter of seminiferous tubules, highest of seminiferous epithelium and Leydig's cell count (15). From left testis, suspended epididymal sperm was prepared to study epididymal sperm picture including, sperm concentration, abnormal morphology, motility and dead and life sperm (16,17).

Statistical analysis

Data was performed using SAS. One and Two Ways Analysis of Variance (ANOVA) and Least Significant Differences (LSD) were used to determine significant differences $P \leq 0.05$ (18).

Results

Lead acetate- treated group showed a significant ($P \leq 0.05$) decrease in testicular weight to body weight ratio as compared with the control and T3 groups, whereas, a significant increase in this parameter was observed in T2 and T3 treated groups as compared with the group T1 (figure-1A). Serum testosterone concentration decreased significantly ($P \leq 0.05$) in group T1 and T3 after 28 and 56 days of treatment compared with the control and T2 groups (figure -1B), however, utilization of ALA to lead acetate treated rats caused a moderate significant ($P < 0.05$) increase in the testosterone concentration in group T3 compared with T1 group. Whereas, group T2 revealed a highly significant ($P \leq 0.05$) increase in testosterone level as compared with the other groups. Conversely, the current examinations demonstrated a significant ($P \leq 0.05$) increase in serum FSH concentration in groups T1 and T3 at two treatment periods compared with control and T2 groups (figure -1C). In addition, a significantly increase in serum FSH of rats in groups T1 and T3 was observed after 28 and 56 days of the experiment compared with pretreated period. The data in figure-2A-D recorded a significant ($P \leq 0.05$) changes in the percentage of dead sperm and abnormal morphology, characterized with hammered head, coiled tail, bent tail, and broken head with a significant decrease in motility and concentration of sperm in T1 and T3 as compared to control and T2 groups. Comparing with the control, a significant ($P \leq 0.05$) increase in sperm motility and concentration was observed in group T2. Statistical analysis showed there was a significant ($P \leq 0.05$) decrease in diameter of seminiferous tubules, highest of seminiferous epithelium and number of Leydig's cells in group T1 as compared with the other experimental groups (figure-2E-G). However, it was to be found a non- significant ($P \geq 0.05$) differences in these parameters between control and group T2 when compared between each other. Following treatment of rats with lead acetate and ALA showed a significant ($P \leq 0.05$) increased in these parameters as compared with group T3, which reflecting the antioxidant properties of ALA against PbAc on these parameters.

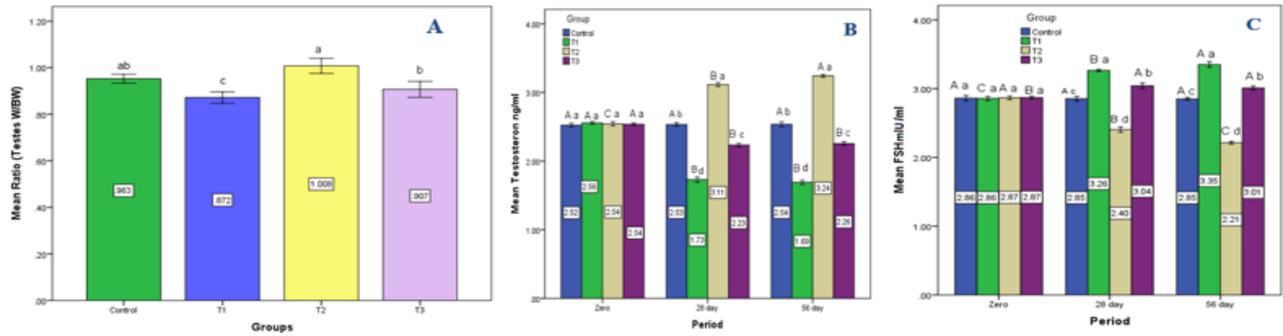


Figure 1: shows the effect of lead acetate and alpha lipoic acid or both on (A) testes weight / body weight ratio (B) serum testosterone and (C) follicular stimulating hormone concentration in adult male rats. Values are expressed as mean \pm SE. n=5. C: Control received distilled water. T1: Rats received 5mg/kg B.W PbAc. T2: Rats received 60mg/kg B.W of ALA. T3: Rats received 5mg/kg B.W of PbAc and 60mg/kg B.W of ALA. Different small letters mean significantly ($P \leq 0.05$) different between groups. Different capital letters mean significantly ($P \leq 0.05$) different within the time.

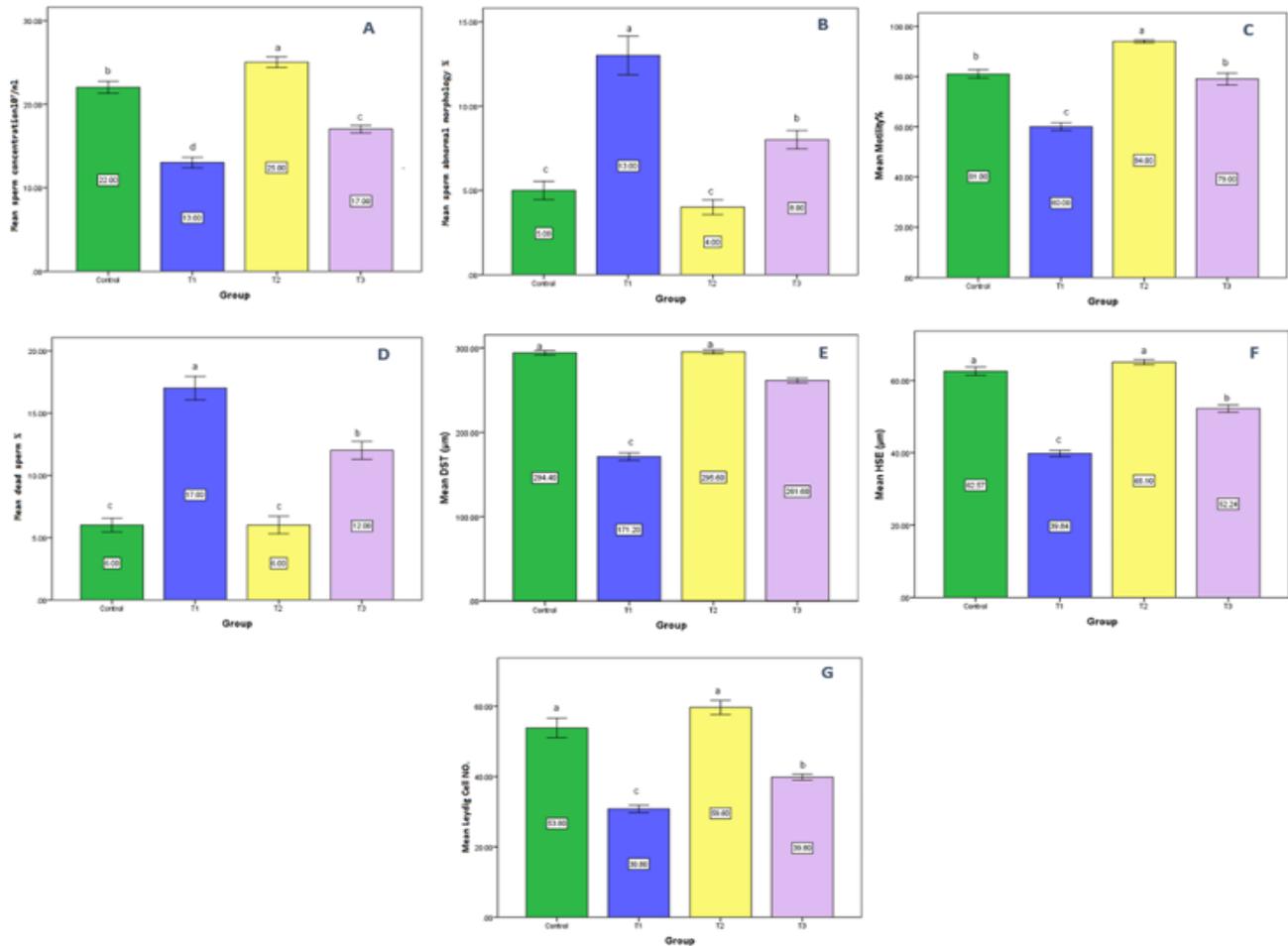


Figure 2: Shows the effect of lead acetate and alpha lipoic acid or both on sperm evaluation (A) concentration, (B) abnormal morphology, (C) motility, (D) dead sperm, (E) diameter of seminiferous tubules, (F) highest of seminiferous epithelium and (G) number of Leydigs cells in adult male rats for 56 day. Values are expressed as mean \pm SE. n=5. C: Control Group, T1: Rats received 5mg/kg B.W PbAc. T2: Rats received 60mg/kg B.W of ALA. T3: Rats received 5mg/kg B.W of PbAc and 60mg/kg B.W of ALA. Different small letters mean significantly different ($P \leq 0.05$) between groups.

Microscopic examination of testicular sections of the control group showed the normal histological architecture with normal seminiferous tubules, regular basement membrane with different stages of spermatogenic cells and spermatozoa filled the center of seminiferous tubules (Figure 3 and 4). Whereas, group T1 (lead acetate-treated group) showed marked changes in testicular histology characterized by reduce in diameter with complete absence of spermatozoa, together with great increase of interstitial space and marked reduction of Leydigs cells (Figure 5). Other sections manifested various degree of degeneration, necrosis of germinal epithelium, disruption of ST epithelial with presence of interstitial edema and atrophied or absence of Leydigs cells, also some of ST filled with eosinophilic edematous associated with hemorrhage and apoptotic cells was observed (Figure 6-10). Group T3 (lead acetate and ALA-treated group) showed a tendency towards a return to normalcy characterized by moderate to marked developing proliferation of spermatogenic cells with a number of Sertoli cells together with moderate interstitial edema containing number of Leydigs cells (Figure 11), furthermore, presence of mature spermatozoa was noticed in the lumen of seminiferous tubules (Figure 12). However, normal spermatogenesis with well intact tubular basement membrane and spermatogenic cells was observed in group T2, that was identical to the control group (Figure 13 and 14).

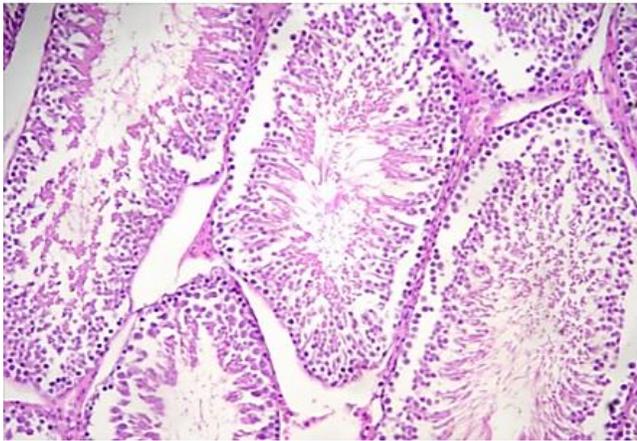


Figure 3: Section in testes of control rats with normal architecture of seminiferous tubules (ST) and Leydig cells (H&E stain 10X).

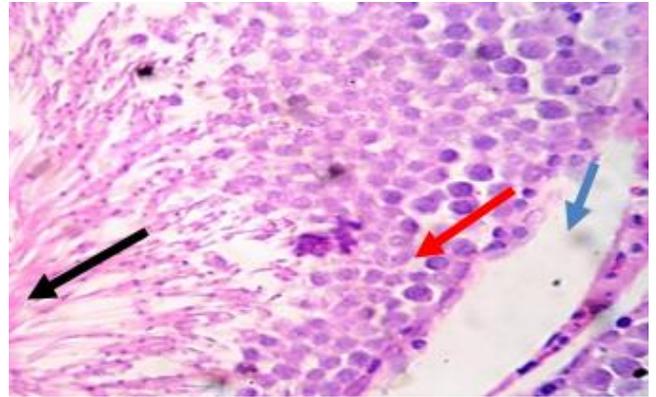


Figure 4: Section in testes of control rats with different stages of spermatogenic cells; spermatogonia blue arrow, spermatocyte red arrow and spermatid black arrow (H&E stain 40X).

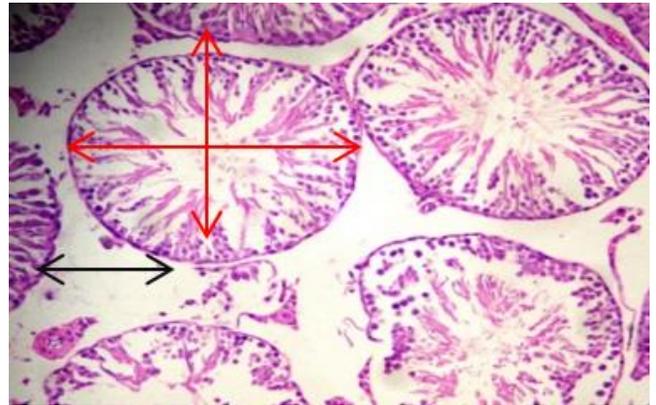


Figure 5: Section in testis of group T1 revealed reduction in diameter of seminiferous tubules four headed red arrow and increase interstitial space double-headed black arrow (H&E stain 110X).

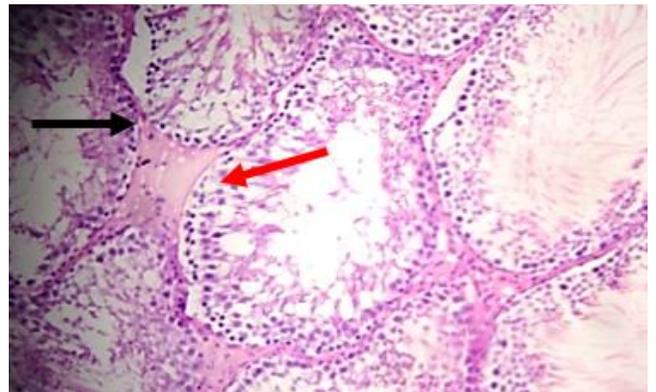


Figure 6: Section in testis of group T1 shows interstitial edema black arrow and ST vacuole red arrow (H&E stain 10X).

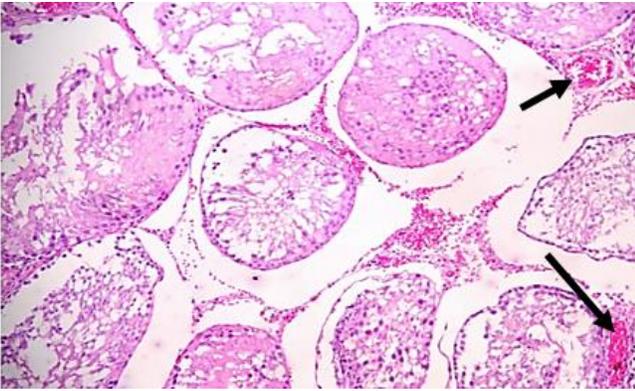


Figure 7: Section in testis of group T1 shows vascular congestion of interstitial space black arrow (H&E stain 10X).

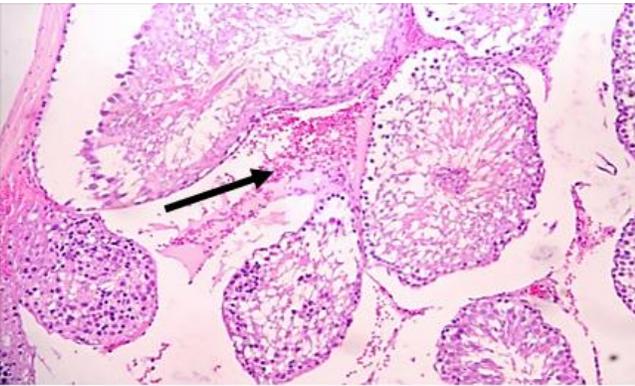


Figure 8: Section in testis of group T1 shows interstitial hemorrhage with edema black arrow (H&E stain 10X).

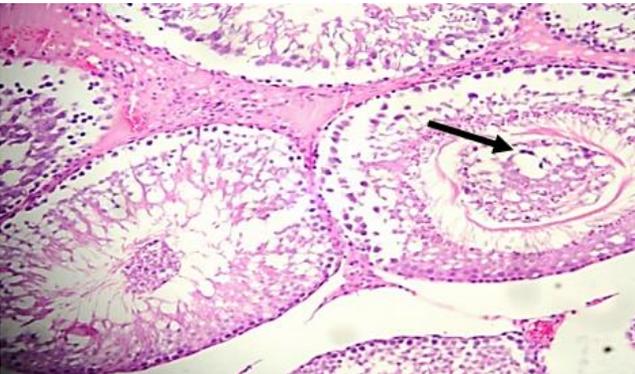


Figure 9: Section in testis of group T1 shows vacuolation with sloughed tubular epithelium and major edema (H&E stain 40X) .

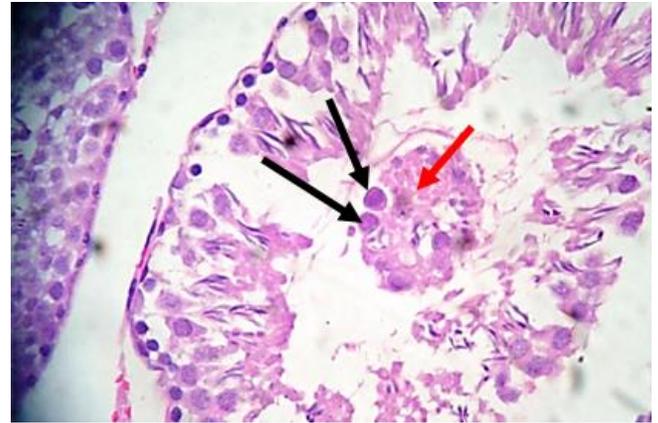


Figure 10: Section in testis of group T1 shows apoptotic cells black arrow with necrotic spermatid in the center of ST red arrow (H&E stain 40X).

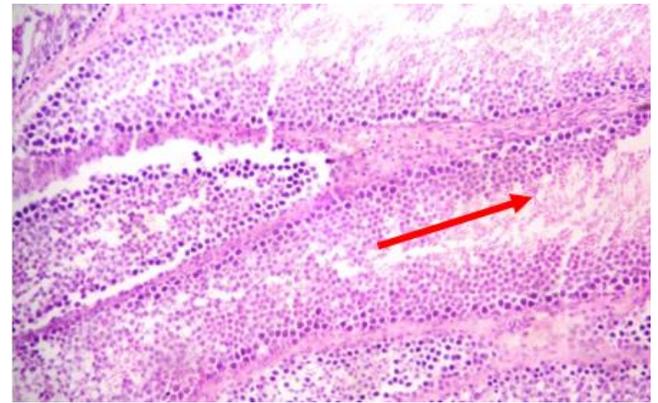


Figure 11: Section in testis of group T2 shows normal architecture of ST with narrow lumen red arrow and prominence leydig cells (H&E stain 10X).

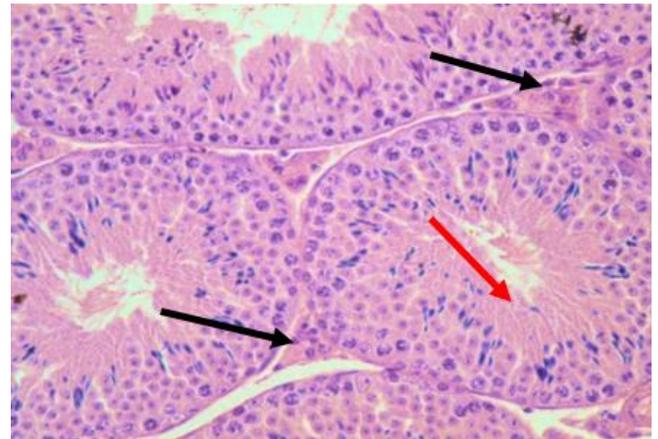


Figure 12: Section in testis of group T2 shows normal architecture of ST and lumen filled with sperm red arrow and prominence leydig cells black arrow (H&E stain 40X) .

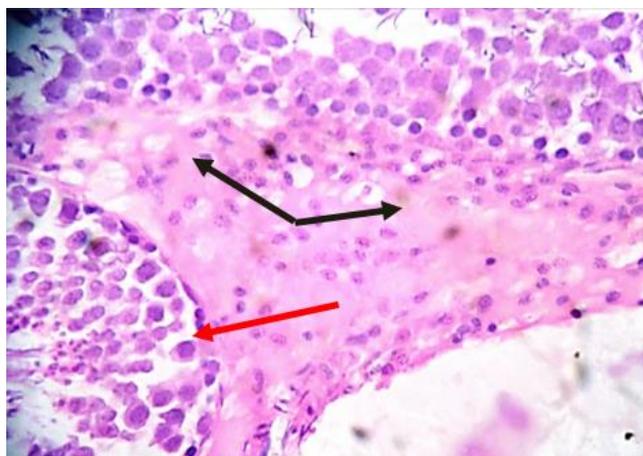


Figure 13: Section in testis of group T3 shows Leydig cell embedded in the edematous fluids in black arrow and normal sertoli cell red arrow (H&E stain 40X).

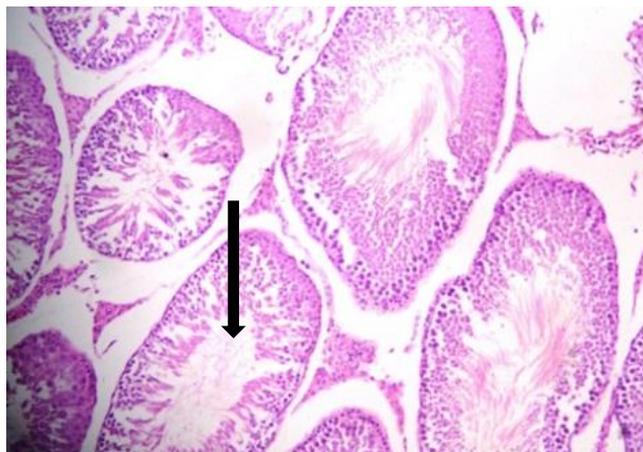


Figure 14: Section in testis of group T3 shows mature spermatozoa in the lumen of ST black arrow (H&E stain 10X).

Discussion

Current results showed a significant decrease in testicular weight/ body weight ratio in group T1 compared with other treated groups, this could be explained due to induced oxidative stress. These results were in agreement with a number of studies (11,19). Some studies reported that an elevation in serum and testicular oxidative damage in rats exposed to lead causing decrease in the number of Leydig cells, germ cells and inhibition/or impairment of spermatogenesis, may be due to induced apoptosis (20,21). Studies have also showed that the decrease in testicular weight is attributed to reduce in testicular size with degeneration, necrosis, thickened of basement membrane and scanty of Leydig's cells (22).

Administration of ALA led to increase this ratio levels in the T2 group, also it could be increased this ratio in the groups T3 that was exposed to lead compared with the control levels, may be attributed to a potential antioxidant properties of ALA in overwhelm the adverse effect of lead (23) via inhibiting the generation of hydroxy radicals that attack sulphur-containing antioxidants to sustain the levels of protein thiols and modulate tissue endogenous antioxidants (24). Lead has been found to cause a significant decrease in testosterone hormone concentration through the experimental periods in T1 group, this result was consistent with that recorded by Wahab *et al.*, (25). A decreased in testosterone could be resulted by the effect of lead acetate on the axial of hypophysis-pituitary-testes and/or by decreasing in the activity of testicular steroidogenic enzymes, such as 3-beta-hydroxysteroid dehydrogenase (3β -HSD), 17-beta-hydroxy dehydrogenase (17β -HSD) resulted to Sertoli and Leydig cells insufficiency causes testicular damage and decrease in testosterone synthesis (6,8). Moreover, we have observed an increase in FSH concentration in lead acetate treated group. This result was agreement with (8). High concentration of serum FSH is consider to be reliable indicator of seminiferous tubule damage and associated with oligospermia (26) with inhibin B overproduction suggesting an impairment of spermatogenesis (7). Earlier study showed change in FSH concentration among the workers whom exposed to low and high level of lead (27), but (28) has found non-significant correlation between sex hormones concentration with blood lead level in workers of battery factory. Accordingly, the results of the current study support the idea that related to the primary effect of lead on testicular tissue in short-term with low doses, revealed that subclinical testicular damage with low testosterone and increase in FSH level. Whereas, the secondary effect of lead appears as a hypothalamic or pituitary disturbance at high doses with different periods of exposure take place (29).

Analysis of semen parameters allows clinicians to make an almost perfect diagnosis of oxidative stress (30). Current results reflect the potential deleterious effects of lead acetate on spermatozoal parameters. These results were going in line with the other studies (31,32). Furthermore, a decrease in serum testosterone and increase in FSH concentrations could be induced some alterations in spermatogenesis and steroids biosynthesis that affected on sperm quality and male fertility (33). The low production of ROS by spermatozoa at physiological levels is essential for spermiogenesis, capacitation, acrosome reaction and sperm-oocyte fusion (34). Whereas, unbalanced in oxidant/antioxidant status with the increase formation of LPO (35) associated with destruction of sperm plasma membrane, losing integrity of mitochondrial membrane and sperm DNA damage leading to infertility (34). Co-treatment of lead with ALA shows a significant improvement in sperm parameters may be due the potential antioxidant properties of ALA through its ability to scavenge FRs in aqueous and non-aqueous phases (36) and

its ability to synthesized robust shield surrounding the sperm cell membrane (23). In our study, histopathological alterations in lead treated rats characterized with degenerative changes was observed in lead acetate treated rats due to negatively effects on male reproductive system. These results were similar with other studies (19,37). Such changes due to oxidative stress-induced by lead attributed to protein interaction mechanisms and induced programing cell death associated with decline in testosterone hormone (38) as well as, supposed that cytoskeleton dysfunction might inhibit the synthesis and/or transport LH receptors, these results correlated with (6). Supplementation of both lead and ALA for 56 day caused rearrangement of histopathological changes of the testes near to normal against lead acetate and restored their activity. These effects are consistent to (39). Also we observed that ALA treated rats manifested an improvement in functions of the testes. ALA giving protection via its action on intracellular, extracellular and at the membrane level, hence it is regulating the metabolism, increased availability of mitochondrial co-enzymes and improvement of protection of free radicals to eventually leading to the reduction in the incidence of mitochondrial dysfunction and then sufficient amount of ATP production (40).

Conclusion

The novel findings of this study are that the subchronic administration of ALA attenuates lead acetate toxicity, improvement of hormonal profile, decreases the testicular and body oxidative damage in rats.

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Conflict of interest

No conflicts of interests are declared by authors for the contents in the manuscript.

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دور حمض ألفا ليبويك في حماية الخصى من سمية خلات الرصاص المستحدثة في الجرذان البالغة

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الخلاصة

لقد أجريت الدراسة الحالية للتحقق من دور حمض ألفا ليبويك في الحماية من تسمم الخصى المستحدثة بخلات الرصاص في الجرذان البالغة. تم استخدام أربع مجاميع من ذكور الجرذان البالغة (٨ لكل منها) و عوملت لمدة ٥٦ يوماً على النحو التالي؛ السيطرة أعطيت الماء المقطر؛ خللات الرصاص بجرعة ٥ ملغم / كغم من وزن الجسم للمجموعة الأولى؛ حمض ألفا ليبويك بجرعة ٦٠ ملغم / كغم من وزن الجسم للمجموعة الثانية؛ أما المجموعة الثالثة فقد أعطيت كل من خللات الرصاص وحمض ألفا ليبويك بنفس الجرعة السابقة. جمعت عينات الدم للفترات ٠ و ٢٨ و ٥٦ يوماً من التجربة، ثم تم جمع مصل الدم لتقدير هرمون التستوستيرون والهرمون المحفز للجريبات. في نهاية التجربة، تمت دراسة وزن الجسم، وزن الخصية ومعايير الحيوانات المنوية للبربخ. علاوة على ذلك، تم فحص التغيرات النسيجية المورفومترية والنسيجية المرضية. كشفت النتائج أن هناك انخفاضاً معنوياً في هرمون التستوستيرون في مصل الدم، نسبة وزن الخصى إلى وزن الجسم، تركيز وحركة الحيوانات المنوية، وأقطار الأنابيب المنوية، وارتفاع ظهارة المنوية وعدد خلايا لايدج، كما أظهرت النتائج زيادة كبيرة في هرمون محفز الجريبات المصل، والحيوانات المنوية الميتة والتشكل غير الطبيعي للحيوانات المنوية في المجموعة الأولى مقارنة مع الفئران المعالجة بخلات الرصاص. أظهرت المجموعة الثالثة تحسناً على مستوى المعايير المدروسة مصحوبة باحتقان خفيف في النسيج الخلالي مع تكاثر ملحوظ في نمو الخلايا المنوية، وكذلك وجود الحيوانات المنوية الناضجة في النبيبات المنوية. نستنتج من ذلك أن المعاملة بحمض ألفا ليبويك خفف من التسمم تحت المزمّن بخلات الرصاص في خصى الجرذان المعاملة بهما وأكدت التغيرات النسيجية للخصيتين هذا التغيير في معايير المصل والدور المفيد لحمض ألفا ليبويك.