BIOCHEMICAL AND HISTOPATHOLOGICAL ASPECTS OF NANDROLONE DECANOATE NEPHROTOXICITY AND POTENTIAL IMPACT OF ALPHA LIPOIC ACID

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ABSTRACT

Background: One of the widely abused anabolic-androgenic steroids worldwide is nandrolone decanoate (ND). **Objectives:** This work aimed to study whether alpha lipoic acid (ALA) treatment could modulate ND-induced renal dysfunction. **Materials & methods**: forty adult albino rats were divided into four groups. 1st group served as negative control; 2nd group received ALA (100 mg/kg orally by gastric gavage daily); 3rd group received ND in 28 mg/kg BW intra-peritoneal injection once weekly; 4th group received the dose of ND along with ALA (in the previous doses); all for eight weeks. **Results**: administration of nandrolone decanoate induced significant increase in serum urea and creatinine. Significant increase in lipid peroxidation malondialdehyde (MDA) and pro-inflammatory cytokines (TNF-α) together with significant reduction of the antioxidant Glutathione peroxidase (GPx) activities and the anti-inflammatory interleukin (IL-4) in kidney tissues were also recorded. Histopathological evidence of renal tissue injury was detected. Co-administration of ALA along with ND ameliorated the effects mentioned above. **Conclusion:** According to this study, the administration of ALA can provide a protective role, through its anti-inflammatory and antioxidant effects, against ND-induced renal toxicity.

Keywords: *Nandrolone* decanoate, *Oxidative Stress, alpha lipoic acid, IL-4*, TNFα

INTRODUCTION

Anabolic androgenic steroids (AAS) have been considered testosterone synthetic cholesterol derivatives, which are therapeutically consumed with many catabolic chronic cases and in other states as hypogonadism, breast cancer and anaemia (**Achar et al., 2010).**

AAS are widely abused for their cosmetic and beautifying intents among bodybuilders and athletes. AAS are thought to promote athletic performance **(Breuner, 2014).**

Nandrolone decanoate (ND) is an AAS that provokes its anabolic effect via protein synthesis, muscle growth and enhancement of erythropoiesis (**Mottram and George, 2000)**.

On the other hand, the abuse of ND produced critical irreversible organ injury, diminished fertility and hypogonadism due to the subsidence of the hypothalamic-pituitary-testicular endocrinal pathway. ND also induced cardiovascular diseases as cardiomyopathy, arrhythmias, atherosclerosis and hypertension. Hepatic cancers, behavioural and psychiatric disturbances were also reported (**Maravelias et al., 2005)**.

AAS led to renal functional changes like rising serum creatinine, blood urea nitrogen and uric acid. Acute renal failure was detected by antecedent studies (**Juhn, 2003)**.

A case of acute renal failure and hemolytic anaemia with 2ry malignant hypertension was reported in a patient with AAS use and associated with vigorous anaerobic exercise (**Merino García et al., 2018)**.

These adverse effects were suspected to be through varied mechanisms such as boosting the renin-angiotensin-aldosterone pathway, promoting the release of endothelin and ROS with over-production of pro-apoptotic substances such as TGF-β1 and pro-fibrotic substances and inflammatory cytokines such as TNF-α, IL-1b

and IL-6. Therefore, TNF-α may be implicated in ND-induced renal injury **(Patil et al., 2016).**

Lipoic acid (LA), an inbred antioxidant formed in the mitochondria of the liver and various tissues, produces a beneficial impact on parameters of oxidative stress **(Dudek et al., 2013)**.

Furthermore, it was found that the administration of alpha lipoic acid (ALA) caused regression of histopathological lesions in extracted rat kidneys (**Ayhan et al., 2014)**.

MATERIALS AND METHODS

A-Chemicals:

1- Nandrolone decanoate (ND):

ND has a trade name (Nandurabolin). It was obtained from El- Nile pharmaceutical company in Egypt in the form of an ampoule 25 mg.

2- Alpha- Lipoic acid; (ALA) (Thioctic acid)*:* It was obtained as Thiotacid® tablets from EVA pharma for pharmaceuticals and Medical Appliances, Egypt. The tablet consists of 300 mg of ALA.

B- Animals and Experimental Design:

Forty adult male albino rats (180–200 g) were obtained from Zagazig University, Faculty of Medicine, the animal house. Before the inception of the experiment, all rats were kept for 14 days to fit them into the new ambience, to preclude diseased animals and to assure physical well-being. Food was given equally to all rats, and water was presented in separate clean utensils.

Our study proceeded under the basic information given by the Institutional Research Board for the use and care of experimental animals with ethical approval number; **ZU-IACUC/3/F/122/2022.**

Indiscriminate and equal grouping of the rats was done into four groups (10 rats/ group). Groups were put in separate cages:

– **Group I** (-ve control group): healthy rats were used to put the standard parameters under no specific treatment. The rats received distilled water and were fed with normal rodent pellets.

- Group II (ALA group): each rat was given ALA 100 mg/kg dissolved in sterile distilled water orally via gastric gavage daily for eight weeks **(Balkis Budin et al., 2009).**

- Group III (ND group): each rat received 28 mg/kg ND (1/20 of LD50) through intraperitoneal injection once weekly for eight weeks. LD50 of ND is more prominent than 566 mg/kg body weight (**Drugs in Japan, 1982**).

– Group IV (ND + ALA): each rat received 28 mg/kg body weight ND through intraperitoneal injection once weekly for eight weeks and received ALA (100 mg/kg) dissolved in sterile distilled water orally by gastric gavage daily for eight weeks.

Twenty-four hours after the experimental period was completed, we took the samples of blood from the retro-orbital plexus of all rats after being anaesthetized to estimate serum creatinine and urea levels. After that, rats were sacrificed and the kidneys' specimens were taken.

After being washed with ice cold normal saline, the kidneys were divided into two parts, one was homogenized in 5-10 mL cold buffer (phosphate buffer (pH, 7.4) per gram tissue, using a tissue homogenizer. The supernatant was collected at 4^{o}C after centrifugation for 15 min at 4,000 rpm. It was used for estimation of malondialdehyde (MDA) level, glutathione peroxidase (GPX) activity, TNF α and IL-4 levels. The other part underwent fixation in 10% formalin for further histopathological studies.

C- Methods

1- Histopathological Examination:

Specimens were prepared as 5-μm paraffin sections after fixation of kidney tissues in 10% formalin saline solution and then stained with hematoxylin and eosin (H & E) as stated by **Bancroft and Layton (2008).**

2- Biochemical Analysis*:*

1. Serum urea & creatinine:

Serum urea (mg/dl) was assayed following **Orsonneau *et al*. (1992)**, while serum creatinine (mg/dl) was assayed according to colourimetric method proposed by the method of **(Fossati et al., 1983).**

2. Kidney Tissue Oxidative Stress Parameters:

- MDA level (nmol/ g tissue): we used the supernatants to detect the MDA level **(Jain et al., 1989)**. MDA was assayed by the colourimetric procedure of **Ohkawa et al. (1979)**.

- GPx activity: we used the supernatants to detect the Gpx activity according to the pamphlet of Bio-diagnostic kits employing colourimetric method of **Paglia and Valentine (1967)**.

3. TNF-α and IL-4:

ELISA was used to reveal the tissue levels of TNF-α using the kit of rat TNF-α immunoassay (BioSource International, Inc. Camarillo, California, USA) following the manufacturer's references. A micro-titer plate reader, able to detect at 450 nm (Sunrise, Austria), was employed (**New et al., 1998**).

IL-4 levels in the tissues were detected by solid phase ELISA using the rat IL-4 kit (Ray Biotech, Norcross, USA) and a micro-titer plate reader at 450 nm. **(Nolan et al., 2005)**

- Statistical Analysis

Regarding statistical analysis, we used SPSS 13.0 for the windows program. Data were represented as means ± SD. Analysis of variance (ANOVA) was used to compare the statistical significances by measuring the biochemical results means differences, and Tukey's test was used to calculate the groups' differences. At $p<0.05$, significant differences were valued.

RESULTS

- Histopathological Findings:

The normal histological pattern was observed in sections taken from both the control and ALA group using the light microscopic examination. A well-defined renal corpuscles and Bowman's spaces were detected. The renal tubules were lined by normal epithelium (**Fig. 1).** On the other hand, pathological lesions in renal tissues were seen in sections from ND treated group in the form of marked congestions in capillaries and perivascular cellular infiltrations. Atrophy of the glomerulus, focal cytoplasmic congestion and degenerative changes in the proximal and distal convoluted tubules were detected **(Fig. 2).** Upon treatment with ALA, the histopathological changes regained their regular pattern with no apparent inflammation or congestion **(Fig. 3).**

- Biochemical Results

I- Kidney Function Tests:

- levels of urea and creatinine (Table 1)

Mean values of serum urea and creatinine in the negative control group and ALA-treated group were not significantly different.

On the other hand, the levels elevated significantly upon treatment with ND (group III) ($p<0.001$) relative to the -ve and ALA groups. In contrast, the levels improved significantly ($p<0.05$) upon treatment with ALA added to ND treatment (group IV).

II- Kidney Tissue Oxidative Stress Parameters (Table 2):

ND treatment made MDA to be elevated significantly simultaneously with a significant depression of the antioxidant (GPx activity) in kidney tissue. On the other hand, ALA significantly depressed the kidney tissue MDA (lipid peroxidation product) and recovered the drooping in the GPx activity (antioxidant defence).

III- Kidney TNF-α and IL-4 (Table 3):

ND administration significantly increased TNF-α content in kidney tissue and suppressed the anti-inflammatory IL- 4. Upon the co-administration of ALA, there was a significant reduction in TNF-α and a significant increment in kidney IL-4 contents.

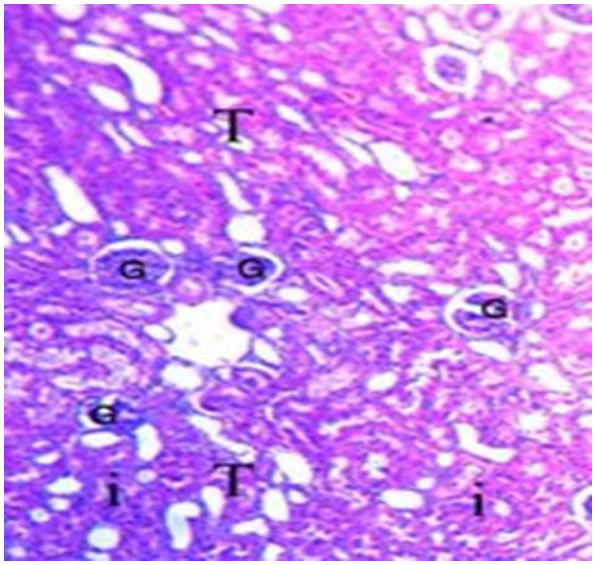
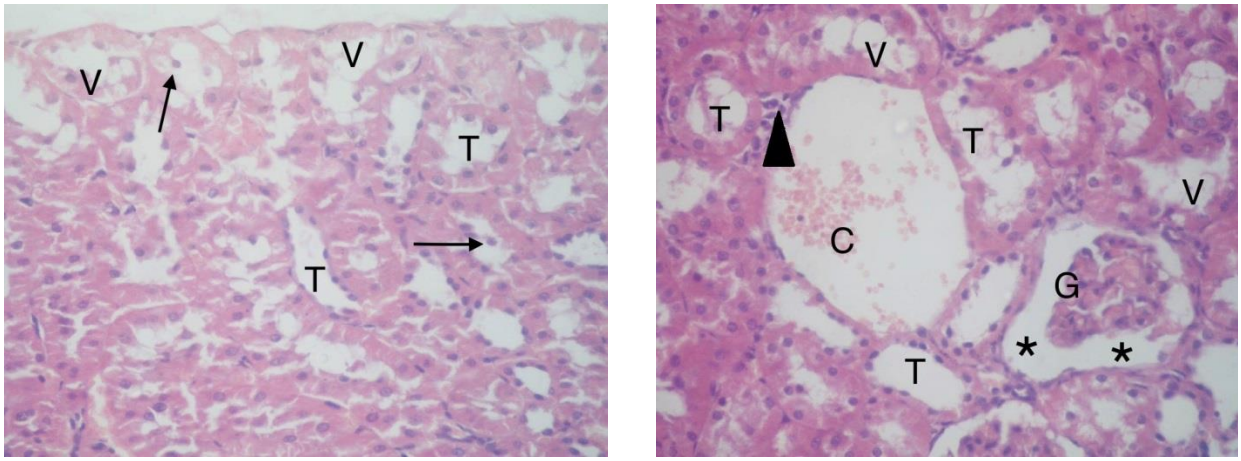
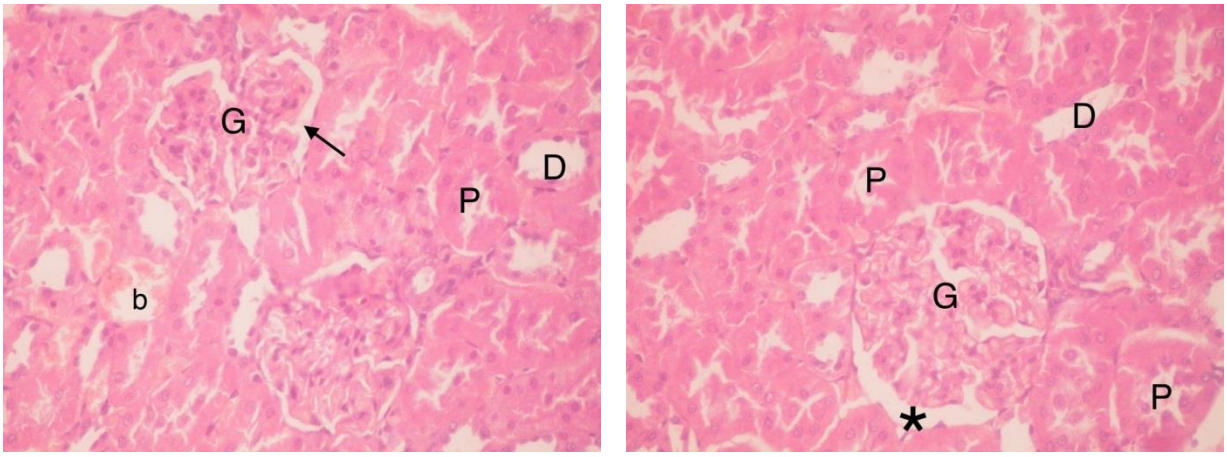


Figure (1): A photomicrograph of sections of rat kidney from control group showing normal architecture with normal renal corpuscle and glomeruli (G) with a well-defined and bowmans space. The renal tubules are lined by regular epithelium (T) **(H & E X 200)**.



a) **b)**

Figure (2) (a & b): A photomicrograph of sections of rat kidney from ND treated group showing distortion and dilatation of tubules (T) with darkly stained and many exfoliated nuclei (arrow) , marked vacuolations (V), atrophic glomerulus was seen (G) with excessive widening of the bowman's space (*****). Many inflammatory cells (arrow head) and congestion (**C**) were observed **(H & E X 400)**.



a **b**

Figure (3) (a & b): A photomicrograph of sections of rat kidney from DN & ALA treated group showing nearly normal distal (D) and proximal (p) convoluted tubules with less congestion in the blood vessels (b). glomeruli (G) were nearly within normal histoarchitecture with normal (arrow) or less dilated bowman's space **(*) (H& E X 400).**

Table (1): Comparison in terms of mean + SD regarding urea & creatinine in group-I (negative control), group-II (ALA-treated), group-III (ND-treated), and group V (combined ALA & ND) after 8 weeks of the study, n= 10

Parameter	**Studied Groups (X+ SD)**					
	Group I	Group II	Group III	Group IV	**F**	**P**
Urea (mg/dl)	5.2±1.13	5.6±1.32	8.1±2.4 [a,b]	5.9±1.5 [c]	6.12	0.002*
Creatinine (mg/dl)	0.58±0.14	0.56±0.15	0.87±0.21 [a,b]	0.63±0.17 [c]	7.11	<0.001**

SD: standard deviation, F: ANOVA test, *: Significant (P<0.05) **: Highly significant (P<0.001), Post hoc: Tukey's test, a: Significant as compared to Group I, b: Significant as compared to Group II, c: Significant versus Group III.

Table (2): Comparison in terms of mean + SD regarding malondialdehyde (MDA) & Glutathione peroxidase (GPx) in group-I (negative control), group-II (ALA-treated), group-III (ND-treated), and group V (combined ALA & ND) after 8 weeks of the study, n= 10

Parameter	**Studied Groups (X+ SD)**				**F**	**P**
	Group I	Group II	Group III	Group IV		
MDA (nmol/g)	42.17±7.14	45.46±6.84	124.18±15.27 [a,b]	51.63±7.61 [c]	157.08	<0.001**
GPx (ng/ mgm tissue)	160.37±34.10	164.17±40.55	18.46±3.66 [a,b]	148.34±35.67[c]	47.64	<0.001**

SD: standard deviation, F: ANOVA test, *: Significant (P<0.05) **: Highly significant (P<0.001), Post hoc: Tukey's test, a: Significant as compared to Group I, b: Significant as compared to Group II, c: Significant versus Group III.

Table (3): Comparison in terms of mean + SD regarding interleukin-4 (IL4) & tumor necrosis factor-alpha (TNF-α) in group-I (negative control), group-II (ALA-treated), group-III (ND-treated), and group V (combined ALA & ND) after 8 weeks of the study, n= 10

Parameter	Studied Groups (X+ SD)				F	P
	Group I	Group II	Group III	Group IV		
Renal IL-4 (pg/mg protein)	21.8±3.47	22.04 ± 3.72	8.12±1.84 [a,b]	19.31±3.01 [c]	45.21	<0.001**
TNF-α (pg/mg protein)	1.99±0.32	2.04±0.40	10.67±2.94 [a,b]	3.70±1.13 [c]	66.81	<0.001**

SD: standard deviation, F: ANOVA test, *: Significant (P<0.05) **: Highly significant (P<0.001), Post hoc: Tukey's test, a: Significant as compared to Group I, b: Significant as compared to Group II, c: Significant versus Group III

DISCUSSION

ND is a synthetic derivative of the male testosterone hormone, which has been modulated to promote their anabolic added to their androgenic activity (**Shahidi, 2001).**

ND is among the most commonly used supplements by athletes, and it can impact the kidney in variable ways. It can worsen or even initiate acute renal and chronic renal damage through glomerular injury, glomerular hyperfiltration, hypercalcemia and apoptosis **(Nieschlag and Vorona, 2015).**

The current study showed that ND administration for eight weeks induced histopathological alterations in the renal tissues. These alterations included apparent congestion in capillaries with perivascular cellular inflammatory infiltration. Atrophy of the glomerulus, marked cytoplasmic vacuolations and degenerative changes in the proximal and distal convoluted tubules were also demonstrated, along with disturbed renal functions with elevated urea and creatinine.

These histopathological findings corresponded to the findings of **Takashashi et al. (2004)** and **Ebeye et al. (2016),** that stated the pathological changes in the rat kidney, like tubular degeneration, glomerulosclerosis, glomerular oedema and foci of congestion following intake of extra doses of ND.

On the other hand, this was in agreement with another study that postulated the impacts of a related anabolic androgenic steroid, testosterone undecanoate (TU), treatment on the degeneration of the kidney in 25% of the animals treated with TU **(Shabir et al., 2015; Bento-Silva et al., 2010)**.

According to the biochemical analysis of the current study, serum urea and creatinine significantly elevated upon ND administration.

Harrington et al. (2011) stated that the use of anabolic steroids regularly, either orally or parenterally, resulted in elevated serum urea and creatinine along with reduced haemoglobin levels. They recorded that the patient developed intrinsic kidney parenchymal injury and needed hemodialysis for this end-stage kidney disease**.**

A dose-dependent correlation was reported between the treatment with exogenous dihydrotestosterone and the progression of glomerulosclerosis, tubule-interstitial fibrosis and albuminuria in rats (**Xu et al., 2009).**

We researched the oxidative stress impact and the apoptotic reaction caused by ND in the renal tissues. We found that long-term treatment with ND for extended periods enhanced oxidative damage in the rat kidneys.

The current study showed an increment in lipid peroxidation (malondialdehyde) and pro-inflammatory cytokines (TNF-α) significantly simultaneously with a significant drooping of renal tissue antioxidant GPx activities and IL-4 (anti-inflammatory interleukin).

It was reported that animals treated with nandrolone revealed disruption in redox homeostasis in various organs such as the liver, heart and kidneys (**Daher et al., 2018)**.

Evidence supported that ND could easily interrupt the redox homeostasis of the kidney, heart and liver tissues of rats **(Frankenfeld et al., 2014)**, and elevated activities of cytochrome p-450 in the liver and tissues of ND-induced mice could be indications for the tissue level alterations caused by anabolic steroids **(Acharjee and Mahanta, 2009).**

It is well known that cytokines are vital proteins accountable for cell-to-cell connection. They promote cellular interaction between cells of the body systems and the immune system. There are two diverse forms of it: anti-inflammatory and pro-inflammatory cytokines. Pro-inflammatory cytokines like IL-12, TNF-α and IL-2 stimulate inflammatory responses that are repressed by anti-inflammatory cytokines like IL-4, IL-10 or IL-13 **(Dinarello, 2000; Opal and DePalo, 2000).**

TNF-α interceded harm of ND in renal cells as it may have a dual function in the stimulation of the apoptosis pathway, either extrinsic or intrinsic (**Riezzo et al., 2014).**

Supra-physiological dose of ND enhanced the liberation of interleukin-1beta in addition to TNF-α in the cultures of peripheral blood lymphocytes of humans. The cytotoxic cytokine, TNF-α, is responsible for the initiation of cellular apoptosis and liberation of cytochrome C through the disruption of the mitochondrial membrane (**Misseri et al., 2005)**.

Apoptosis is considered a participating operator in developing fibrosis of kidney tissues. It can be initiated through numerous inflammatory cytokines. Apoptosis from androgen can be prompted by triggering a caspase-dependent apoptotic pathway in the cells of renal tubules. On the other hand, testosterone may be encompassed in the liberation of pro-inflammatory cytokines like IL-1b, IL-6 and TNF-α. The release of such cytokines can lead to an inflammation of the renal tissues and a progression of chronic kidney disease **(Verzola et al., 2009).**

Previous research has proved the beneficial role of antioxidants, as co-enzyme Q against ND-induced organ toxicities **(Ali et al., 2018).**

In the current study, the protective role of ALA against ND-induced kidney insult can be explained by different perspectives.

ALA is an efficient antioxidant; it can beat radicals easily and does not display any serious side effects. ALA includes sulfur composed of two thiol groups; therefore, it plays its role as a cofactor for multiple mitochondrial enzymes by catalyzing the α-ketoacid (**Gorąca et al., 2011)**.

Moreover, the antioxidant features of ALA are likely due to its metal chelating action, its competence to ROS directly scavenging and its capability to rejuvenate and interact with other antioxidants, including vitamin C and vitamin E and glutathione **(Singh and Jialal, 2008).**

A different preference of ALA is its capability to go through all body parts due to its dual solubility both in water and in fat. On account of ALA distinctive features, it is competent to enter certain parts of the cell that most other antioxidants can't reach **(Segall et al., 2004).**

Previous research proved the role of ALA as an antioxidant agent against many toxins. It antagonized the hepatotoxic effect of ricin **(Wahdan and Sarhan, 2016).**

The therapeutic prospect of ALA has been elucidated in diverse defects associated with oxidative stress and inflammation in variable organs like the kidney **(Kang et al., 2009).**

ALA treatment decreased TNFR1 expression and induced suppression of TNF-α and IL-6 (**Zhang et al., 2011)**.

Supplementation with ALA can suppress inflammatory markers by getting out of free radicals and suppressing the processes of transduction of pro-inflammatory redox-sensitive signal that include translocation of nuclear factor kappa B, resulting in reduced cytotoxic cytokines and other free radicals **(Wong et al., 2001).**

On the other hand, ALA treatment recovers cellular antioxidant capability and phases 2 enzymes like glutathione reductase, glutathione-S-transferase, reduced glutathione, and catalase **(Cao et al., 2003).** Added to the previous, ALA can block serine kinases (e.g., IKKβ) stimulation to depress inflammatory cytokines **(Evans et al., 2005).**

ALA can prohibit TNF-α provoked kappa B kinase stimulation (**Zhang and Frei, 2001)**.

ALA raised IL-4 markedly that was essential for controlling autoimmune inflammation in the cells. **(Ponomarev et al., 2007).**

ALA nearly restored healthy glomeruli. Also, normal proximal and distal convoluted tubules were observed with ALA treatment. It was confirmed by reduced tubular dilation and regenerated tubular epithelium in ALA-treated rats (**Şehirli et al., 2008).**

Together in vitro and in vivo experiments stated that ALA decreased serum levels of blood urea nitrogen and serum creatinine, diminished MDA and ROS levels added to mitigation of the severity of renal damage (tubular dilatation, tubular cell necrosis, haemorrhage and cytoplasmic vacuolation) **(Koga et al., 2012).**

CONCLUSION

According to the results of the study, administration of ND in a dose of 1/20 of the LD_{50} for eight weeks resulted in a renal insult at the histopathological and biochemical levels in adult albino rats. ALA was a product that, when administered concomitantly with ND, alleviated the manifestations of renal insult.

RECOMMENDATION

- There is a requirement for more research to study the impacts of ALA on ND-induced various organ toxicities.
- It is necessary to perform more studies on ND-toxicity and the impact of ALA on it over various periods.

Conflict of interest

The authors declare that they have no competing interests.

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REFERENCES

Achar, S.; Rostamian, A., and Narayan, S.M. (2010): Cardiac and metabolic effects of anabolic androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions and rhythm. Am. J. Cardiol., 106: 893–901.

Acharjee, B.K., and Mahanta, R. (2009): Enhanced hepatic and kidney cytochrome p-450 activities in nandrolone decanoate treated albino mice. Drug Metab. Lett., 3:120-124.

Ali, D. M.; Labib, D.A.A., and Mohamed, M.M.N. (2018): the protective role of coenzyme q10 against nandrolone decanoate-induced cardiotoxicity in rats: biochemical, genetic, histological and immunohistochemical study. Egypt J. Forensic Sci. Appli. Toxicol., 18 (1): 19 – 34.

Ayhan, M.; Guney, E; Atile, N. S.; Serter, M., and Meteoglu, I. (2014): preventive effects of alpha-lipoic acid on diabetic nephropathy in a rat model. Acta medica Mediterranean, 30(6): 1221-1225

Balkis Budin, S.; Louis, S.R.; Abu Bakar, M.; Radzi, M.; Osman, K.; Das, S., and Mohamed, J. (2009): Effect of alpha lipoic acid on oxidative stress and vascular wall of diabetic rats. Romanian Journal of Morphology and Embryology, 50(1):23-30.

Bancroft, J.D., and Gamble, M. (2008): Theory and practice of histological techniques: Elsevier Health Sciences.

Bento-Silva, M.T.; Martins, M.; Torres-Leal, F.L.; Barros, T.L., and Carvalho, I. (2010): Effects of administering testosterone undecanoate in rats subjected to physical exercise: effects on the estrous cycle, motor behavior and morphology of the liver and kidney. Braz. J. Pharm. Sci., 46:79-89.

Breuner, C.C. (2014): Performance-enhancing substances. Adolesc. Med. State Art. Rev.; 25(1):113-125.

Cao, Z.; Tsang, M.; Zhao, H., and Li, Y. (2003): Induction of endogenous antioxidants and phase 2 enzymes by alpha-lipoic acid in rat cardiac H9C2 cells: protection against

oxidative injury. Biochem. Biophys. Res. Commun., 310:979–85.

Daher, E.F.; Fernandes, P. H.; Meneses, G.C.; Bezerra, G.F.; Ferreira, L.S., and Viana, G.A. (2018): Novel kidney injury biomarkers among anabolic androgenic steroids users – evidence of subclinical kidney disease. Asian J. Sports Med., 9(1): e65540. DOI: 10.5812/asjsm.65540

Dinarello, C.A. (2000): Proinflammatory Cytokines. Chest, 118 :503-508. doi: 10.1378/chest.118.2.503.

Drugs in Japan, Ethical Drugs (1982): Vol. 6, Yakugyo Jiho Co., Ltd., Tokyo, Japan, pp: 541.

Dudek, M.; Bilska-Wilkosz, A. and Knutelska, J. (2013): "Are anti-inflammatory properties of lipoic acid associated with the formation of hydrogen sulfide?" Pharmacological Reports, 65(4): 1018–1024.

Ebeye, O. A.; Ekundina, V.O., and Osahon, R.I. (2016): Histomorphological effect of nandrolone decanoate on the hepatorenal tissues of adult wistar rat exposed physical activity. European journal of pharmaceutical and medical research ,3(5), 285-289.

Evans, J.L.; Maddux, B.A., and Goldfine, I.D. (2005): The molecular basis for oxidative stress-induced insulin resistance. Antioxid. Redox. Signal., 7:1040–1052.

Fossati, P.; Prencipe, L., and Berti, G. (1983): Enzymic creatinine assay: A new colorimetric method based on hydrogen peroxide measurement. Clin. Chem., 29:1494–1496.

Frankenfeld, S.P.; de Oliveira, L.P.; Ignacio, D.L.; Coelho, R.G.; Mattos, M.N., and Ferreira, A.C. (2014): Nandrolone decanoate inhibits gluconeogenesis and decreases fasting glucose in wistar male rats. J. Endocrinol., 220:143-153.

Gorąca, A.; Huk-Kolega, H.; Piechota, A.; Kleniewska, P.; Ciejka, E., and Skibska, B. (2011): "Lipoic acid—biological activity and therapeutic potential," Pharmacological Reports, 63(4): 849–858.

Harrington, P.; Ali, G., and Chan, A. (2011): The development of focal segmental glomerulosclerosis secondary to anabolic steroid abuse. BMJ Case Rep., 2011: bcr0720114531. doi:10.1136/bcr.07.2011.4531

Jain, S.K.; McVie, R.; Duett, J.; Herbst, J.J. (1989): "Erythrocyte membrane lipid peroxidation and glycosylated hemoglobin in diabetes". Diabetes, 38: 1539-1543.

Juhn, M.S. (2003): Popular sports supplements and ergogenic aids. Sports Med., 33: 921-939.

Kang, K.P.; Kim, K.H.; Jung, Y.J.; Lee, A. S.; Lee, S.; Lee, S.Y.; Jang, K.Y.; Sung, M.G.; Park, S. K., and Kim, W. (2009): Alpha-lipoic acid attenuates cisplatin-induced acute kidney injury in mice by suppressing renal inflammation. Nephrology Dialysis Transplantation, 24(10): 3012-3020.

Koga, H.; Hagiwara, S.; Kusaka, J.; Goto, K.; Uchino, T.; Shingu, C.; Kai, S., and Noguchi, T. (2012): New α-lipoic acid derivative, DHL-HisZn, ameliorates renal ischemia-reperfusion injury in rats. Journal of Surgical Research, 174(2): 352-358.

Maravelias, C.; Dona, A.; Stefanidou, M., and Spiliopoulou, C. (2005): Adverse effects of anabolic steroids in athletes A constant threat. Toxicol. Lett., 158:167–175.

Misseri, R.; Meldrum, D. R.; Dinarello, C. A.; Dagher, P.; Hile, K. L.; Rink, R. C., and Meldrum, K.K. (2005): TNF-alpha mediates obstruction-induced renal tubular cell apoptosis and proapoptotic signaling. Am. J. Physiol. Renal Physiol., 288 (2): F406–F411. doi: 10.1152/ajprenal.00099.2004.

Merino García, E.; Borrego Utiel, F.J.; Martínez Arcos, M.Á.; Borrego Hinojosa , J., and Pérez Del Barrio, M. P. (2018): Kidney damage due to the use of anabolic

androgenic steroids and practice of bodybuilding. Nefrologia, 38(1): 101-103.

Mottram, D.R. and George, A.J. (2000): Anabolic steroids. Best Pract. Res. Clin. Endocrinol. Metab., 14:55–69.

New, D.R.; Maggirwar, S.B.; Epstein, L.G.; Dewhurst, S., and Gelbard, H.A. (1998): HIV-1 Tat induces neuronal death via tumor necrosis factor-alpha and activation of non-N-methyl-d-aspartate receptors by a NF kappa B-independent mechanism. J. Biol. Chem.; 273:17852–8.

Nieschlag, E. and Vorona, E. (2015): Doping with anabolic androgenic steroids (AAS): adverse effects on non-reproductive organs and functions. Rev. Endocr. Metab. Disord., 16: 199-211.

Nolan, Y.; Maher, F.O.; Martin, D.S.; Clarke, R.M.; Brady, M.T., and Bolton, A.E. (2005): Role ofinterleukin-4 in regulation of age-related inflammatory changes in the hippocampus. J. Biol. Chem., 280: 9354–62.

Ohkawa, H.; Ohishi, N., and Yagi, K. (1979): Assay for lipid peroxidation in animal tissues by thiobarbituric acid reaction. Annals of Biochemistry., 95: 351–358.

Opal, S.M. and DePalo, V.A. (2000): Anti-inflammatory cytokines, Chest: 117; 1162-1172.

Orsonneau, J.; Massoubre, C.; Cabanes, M., and Lustenberger, P. (1992): Simple and sensitive determination of urea in serum and urine. Clin. Chem., 38(5): 619-623.

Paglia, D. E.; Valentine, W. N. (1967): Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. Journal of Laboratory and Clinical Medicine, 70 (1):158-169. PMid:6066618.

Patil, C.N.; Wallace, K.; LaMarca, B.D.; Moulana, M.; Lopez-Ruiz, A., and Soljancic,A. (2016): Low-dose testosterone protects against renal ischemia-reperfusion injury by increasing renal IL-10-to-TNF-α ratio and attenuating T-cell infiltration. Am J Physiol. Renal Physiol., 311: F395-F403.

Ponomarev, E. D.; Maresz, K.; Tan, Y., and Dittel, B. N. (2007): CNS-derived interleukin-4 is essential for the regulation of autoimmune inflammation and induces a state of alternative activation in microglial cells. J. Neurosci. 27, 10714–10721

Riezzo, I.; Turillazzi, E.; Bello, S. ;Cantatore, S.; Cerretani, D.; Di Paolo, M.; Ida Fiaschi, A.; Frati, P.; Neri, M.; Pedretti, M. and Fineschi, V. (2014): Chronic nandrolone administration promotes oxidative stress, induction of pro-inflammatory cytokine and TNF-α mediated apoptosis in the kidneys of CD1 treated mice. Toxicol. Appl. Pharmacol. Oct., 280(1): 97-106.

Segall, A.; Sosa, M., and Alami, A. (2004): "Stability study of lipoic acid in the presence of vitamins A and E in o/w emulsions for cosmetic application," Journal of Cosmetic Science, 55 (5): 449–461.

Şehirli, Ö., Şener, E.; Çetinel, S.; Yüksel, M.; Gedik, N., and Şener, G. (2008): α-lipoic acid protects against renal ischemia–reperfusion injury in rats. Clinical and experimental pharmacology and physiology, 35(3): 249-255.

Shabir, N.; Malik, H.; Sajjad, S., and Abbas, M.N. (2015): Effect of Nandrolone Decanoate, Boldenone Undecylenate on Renal Status of Rabbits. Global Veterinarian, 14: 432-438.

Shahidi, N.T. (2001): A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. Clin. Ther.; 23(9):1355-90.

Singh, U. and Jialal, I. (2008): "Alpha-lipoic acid supplementation and diabetes," Nutrition Reviews, 66 (11): 646–657.

SPSS, Chicago, IL, USA, 2009.

Takashashi, M.; Tatsugi, Y., and Kohno, T. (2004): "Endocrinological and patrhological

effects of anabolic-androgenic steroid in male rats". Endocrine Journal., 51(4): 425-434.

Verzola, D.; Villaggio, B.; Procopio, V.; Gandolfo, M.; Gianiorio, F.; Famà, A.; Tosetti, F.; Traverso, P.; Deferrari, G. and Garibotto ,G. (2009): Androgen-mediated apoptosis of kidney tubule cells: role of c-Jun amino terminal kinase. Biochem. Biophys. Res. Commun., 387:531–6.

Wahdan, A. A. and Sarhan, N. (2016): possible protective effect of alpha lipoic acid against ricin induced hepatotoxicity in adult male albino rats. Egypt J. Forensic Sci. Appli. Toxicol., 16 (2): 209 – 221.

Wong, A.; Dukic-Stefanovic, S., Gasic-Milenkovic, J.; Schinzel, R, Wiesinger ,H. and Riederer, P. (2001): Anti-inflammatory antioxidants attenuate the expression of inducible nitric oxide synthase mediated by advanced glycation end products in murine microglia. Eur J Neurosci., 14:1961–7.

Xu, Q.; Prabhu, A.; Xu, S.; Manigrasso, M.B., and Maric, C. (2009): Dose-dependent effects of dihydrotestosterone in the streptozotocin-induced diabetic rat kidney. Am. J. Physiol. Ren. Physiol., 297: F307–15.

Zhang, W.J. and Frei, B. (2001): Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells. FASEB J., 15:2423–32.

Zhang, Y.; Han, P.; Wu, N.; He, B.; Lu,Y. and Li, S. (2011): Amelioration of lipid abnormalities by alpha-lipoic acid through antioxidative and anti-inflammatory effects. Obesity (Silver Spring), 19:1647–1653.

الملخص العربى

الجوانب البيوكيميائية والهستوباثولوجية للتسمم الكلوى للناندرولون ديكانوات والتأثير المحتمل لحمض ألفا ليبويك

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يعد الناندرولون ديكانوات واحد من المنشطات الاندروجينيية البنائة والتى يساء استخدامها على نطاق واسع في جميع أنحاء العالم . يهدف هذا العمل إلى دراسة ما إذا كان علاج حمض ألفا ليبويك (ALA) يمكن أن يعدل الخلل الكلوي الناجم عن الناندرولون ديكانوات. تم تقسيم ٤٠ جرذًا ألبينو بالغًا إلى ٤ مجموعات. كانت المجموعة الأولى بمثابة المجموعة الضابطة السلبية ؛ تلقت المجموعة الثانية 100 مجم / كجم من حمض ألفا ليبويك عن طريق الفم يوميًا ؛ تلقت المجموعة الثالثة الناندرولون ديكانوات ٢٨ مجم / كجم من وزن الجسم بالحقن البريتونى مرة واحدة في الأسبوع. تلقت المجموعة الرابعة جرعة الناندرولون ديكانوات مع حمض ألفا ليبويك (كما في الجرعات السابقة) ؛ كل ذلك لمدة ٨ أسابيع. تسبب تناول الناندرولون ديكانوات في زيادة معنوية في مستويات اليوريا والكرياتينين في الدم. كما تم تسجيل زيادة كبيرة في مادة مالونديالديهيد الدهنية (MDA) والسيتوكينات المؤيدة للالتهابات (TNF-α) مع انخفاض كبير في أنشطة مضادات الأكسدة GPx والإنترلوكين المضاد للالتهابات (IL-4) في أنسجة الكلى. كان هناك دليل نسيجي على إصابة أنسجة الكلى. وتحسنت التأثيرات المذكورة أعلاه فى المجموعة الرابعة . ووفقًا لنتائج هذه الدراسة ، يمكن أن يوفر تناول ALA دورًا وقائيًا ، من خلال آثاره المضادة للالتهابات ومضادات الأكسدة ، ضد التسمم الكلوي الناجم عن الناندرولون ديكانوات.