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NEUROSTEROID, NATURAL AND ANABOLIC STEROIDS: PHYSIOLOGICAL, IMMUNOLOGICAL AND HISTOPATHOLOGICAL STUDY ON HYPERLIPIDAEMIC ALBINO RATS

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ABSTRACT

Neurosteroids are steroids that include endogenous steroids that the nervous system produces, and they function as neurotransmitters or neuromodulators. steroid hormones are chiefly produced in the adrenal glands and have a pivotal role in the regulation of many physiological actions in the body. An anabolic steroid, which is an artificial compound, has similar effects to testosterone. This study aimed at distinguishing between the roles of neurosteroid, natural steroid, and anabolic synthetic steroids by investigating the effects of some physiological, immunological, and histopathological on various target organs such as the Kidney, liver and spleen in hyperlipidemic rats. In order to achieve these aims, we randomly divided 50 male albino rats into five equal groups. The first group, which was fed on standard diet and injected subcutaneously with 0.5 ml of normal saline, was used as the control group, while the second group, which served as the hyperlipidemic control group was fed a high fat diet. The third group, hyperlipidemic rats, were orally administrated with DHEA (as a neurosteroid, 17.2mg/kg/day), the fourth group, hyperlipidemic rats, were subcutaneously injected with hydrocortisone (as a natural steroid, 26.1mg/kg/day). Finally, the fifth group of hyperlipidemic rats were intramuscularly injected with Sustanon (as an anabolic steroid, 66.9 mg/kg/week). The study has found that hyperlipidemic rats showed hematological parameters and interleukin IL-2 improvements with DHEA, fasting blood sugar and body weight with Sustanon and a lipid profile with both hydrocortisone and Sustanon, Renal function was almost deteriorated in all treated groups, and finally there were various alterations in the histopathological examination of kidney, liver and spleen. Finally, the study has come up with the following conclusions: DHEA administration can improve immunity and ameliorate tissue damage in the spleen. Hydrocortisone may improve the lipid profile, though it has negative effects on immunity and tissue health. Sustanon has positive effects on blood glucose and lipid profile; however, its effects on immunity are not clear enough.

KEYWORDS: Dehydroepiandrosterone, Hydrocortisone, Sustanon and Hyperlipidemia.

1. INTRODUCTION

Hyperlipidemia is the term use to refer to excessively high levels of lipids or lipoproteins in the blood as a result of defective fat metabolism or function. The excessive elevation causes severe consequences, which frequently result in atherosclerosis and other diseases like cardiovascular disease, peripheral vascular disease, and brain strokes. Atherosclerosis develops as a result of the accumulation of lipids (mainly cholesterol) in the walls of the arteries, which contracts the blood vessels and impairs blood flow. Rates of morbidity and mortality increased in the presence of other common associated conditions as hypertension, diabetes mellitus, and renal disorders (Naser *et al*., 2021; Yao *et al*., 2020).

Steroid hormones are mainly synthesized in the adrenal cortex, sex glands, and placenta, which are derived from cholesterol (Holst *et al*., 2004). Major endocrine system processes are regulated by these hormones, as well as stress management. They are produced and released by the adrenal glands in response to pituitary adrenocorticotropic hormone, and regulated by hypothalamic corticotropic releasing hormone. Steroids regulate various biological processes and tissues in vertebrates, particularly those related to metabolism, reproduction, production, inflammation, and cognition (Henley *et al*., 2005; Ramamoorthy & Cidlowski, 2016; Samuel *et al*., 2017).

Hydrocortisone is a rapid and short acting glucocorticoid that is used for the treatment of adrenal insufficiency and inflammatory

conditions. As it shares a molecular structure with cortisol, hydrocortisone is the substance that most closely resembles the human adrenal hormone and contains both glucocorticoid and mineralocorticoid effects (Khera *et al*., 2021). It also, has a pivotal role in the glucose, protein, and fat metabolism of the body. Its medical significance arises from its anti-inflammatory, anti-allergic, and immune-suppressive roles in the body (Chourpiliadis & Aeddula, 2022).

Dehydroepiandrosterone (DHEA) is produced by the adrenal cortex and synthesized from pregnenolone and is further metabolized to androstenedione, testosterone, and estrogens (Aoki & Terauchi, 2018). Additionally, it can be synthesized in the central and peripheral nervous system (Jahn *et al*., 2010). Moreover, DHEA is regarded as a neurosteroid due to its impact on the brain's neurotransmitter receptors. DHEA and its sulfated derivative (DHEAS) are multifunctional steroids with a variety of physiological functions, different mental effects and the immune systems (Quinn *et al*., 2018).

Commonly known as anabolic steroids, anabolic-androgenic steroids (AASs), are a large group of molecules that include endogenously produced androgens, such as testosterone, as well as synthetically manufactured as their derivatives. AAS anabolic properties have been widely used for therapeutic purposes (Albano *et al*., 2021). Sustanon (Su) is an oil-based injectable anabolic-androgenic steroid hormone that generally contains four distinct testosterone esters. Sustanon releases testosterone continuously into the blood for a period of three to four weeks, maintaining a constant testosterone level. A number of lines of evidence have shown that testosterone therapy might improve glucose level (Arazi *et al*., 2017; Gianatti *et al*., 2014).

The current study aims to investigate the physiological, immunological and histopathological effects between the neurosteroid, natural steroid and anabolic synthetic steroids on various target organs such as kidneys, liver and spleen in hyperlipidemic rats.

2. MATERIALS AND METHODS

2.1. Animal and housing

The experiment for this study was carried out in the department of biology, College of Science, University of Duhok taking into consideration ethical and a standard laboratory conditions. Albino rats were placed and bred in ventilated polypropylene cages with diameters (30×25×17cm) and permitted to free access to water and standard diet under 24ºC with equal light and dark period. The animals were acclimated to the laboratory conditions for 10 days then mixed for breeding. For the experimental study, adult male rats weighing between 150 and 200g (8-10 weeks age) were used (Guillén, 2017).

2.2. Standard diet

For each one kilogram (kg), a standard diet was constructed as follows: Wheat (665.5g), soy (256.2g), sunflower oil (43.5g), limestone (14.9g), Ca2PO4 (6.4g), salt (6.3g), lysine (2.4g), methionine (1.5g), enzymes (0.8g), choline chloride (0.6g), vitamins (0.58g), and trace elements (0.50g) (Pellizzon & Ricci, 2020).

2.3. Preparation of high fat (high cholesterol) diet

High fat diet was prepared for each 1kg by adding 5g cholesterol powder, 3g bile salt, 10 ml coconut oil, 250 ml cooking oil and 25 gm cow brain added to a standard rat diet. After two weeks, the serum lipid profile was examined from the animals fed on high fat diet. The blood samples were collected from the heart. The lipid profile parameters showed an elevation in these animals.

2.4. Providing and preparation of the steroids drug:

DHEA medication is used as a neurosteroid (50 mg pills / PHARMACY Laboratories s.c. Poland). The pills were grounded up and dispersed into normal saline before being given to the animals orally every day for six weeks at a dose of 17.2 mg/kg. As a natural steroid, hydrocortisone (100 mg/Hidrokortizone. Hemofarm A.D. Serbia) was dissolved in its own buffer and prepared for daily subcutaneous injection at a dose of 26.1 mg/kg into the animals for a period of six weeks. Finally, as an anabolic steroid, the Sustanon medication (250 mg/EVER Pharmajena GmbH, Germany) comprises testosterone esters (testosterone propionate, phenylpropionate, isocaproate, and decanoate). The medication had been prepared for usage and administered intramuscularly once a week at a dose of (66.9 mg/kg) for intervals of six weeks. Body weight was recorded in the first and second treatments daily, while in the last treatment was recorded weekly.

2.5. Experimental Design:

Five equal groups of fifty male albino rats were randomly assigned and treated for 6 weeks as follows:

1. Control group: Normal rats were fed on standard diet injected 0.5 ml normal saline (0.9%) subcutaneously and served as a control group.

2. HL Control group: Normal rats were fed on high fat (high cholesterol) diet and served as a hyperlipidemic control group.

3. HL DHEA group: Hyperlipidemic rats were injected orally (gavage) with DHEA (as a neurosteroid) drug. (17.2 mg/ kg rat /day).

4. HL Hydro group: Hyperlipidemic rats were injected with hydrocortisone (as a natural steroid) subcutaneously with a dose of (26.1 mg/ kg rat /day).

5. HL Testo group: Hyperlipidemic rats were injected with testosterone (as an anabolic steroid) (66.9 mg/kg rat / week) intramuscularly.

2.6. Estimation of hematological and biochemical parameters

After the experiment was accomplished, food was withheld from animals but they had free access to water for overnight. After being given a diethyl ether anesthetic (Scharlab S, L, Spain), blood samples were obtained directly by heart puncture. 2 ml of blood was inserted into EDTA tubes (Arzer Grande-Italy) in order to determine the hematological parameters using the automated hematological analyzer (Medonic, Sweden). To assess the results of the biochemical tests such as FBS, serum lipids, electrolytes, serum proteins, renal and liver function tests, the remaining blood samples were centrifuged for 15 minutes at 4000 rpm after being placed in gel tubes (Arzer Grande-Italy) for 30 minutes. The mentioned tests were estimated by Cobas 600 (C501) automated chemistry analyzer (Roche/Germany).

2.7. Estimation of IL-2 and IL- 6

Serum level of Il-2 and IL-6 were determined by enzyme -linked immunosorbent assay apparatus (BioTeckUSA) according to the instruction of the kit's manufacturing company (BT LAB – China).

2.8. Histopathological study

After the animals have been dissected, immediately after being removed, the kidney, liver, and spleen organs were washed with tab water and preserved in 10% formalin. Thin sections (4 µM) were stained with Hematoxylin and Eosin (H&E) by using Auto Staining Apparatus (Leica/Germany), after the paraffin blocks were prepared. The mounted slides were examined by using a light microscope (Motic/China), and a specialist camera (Anmo/Taiwan) was used to take the pointed field (Vitošević *et al*., 2018).

2.9. Statistical Analysis

Microsoft Excel 2016 was used for data analysis, as well as GraphPad Prism 5 (California- USA) was used for variance (ANOVA) analysis followed by Tukey test. The Results were expressed as mean ± standard errors and P-values <0.05 were considered as a statistically significant (Husni Abdulla *et al*., 2021).

3. RESULTS

The results have clarified the effects of neurosteroids, natural and anabolic steroids on hyperlipidemic rats. Hematological parameters, fasting blood sugar (FBS), lipid profile, urea, creatinine, uric acid, electrolyte, serum calcium, liver enzymes, serum proteins, interleukin 2 (IL-2), interleukin 6 (IL-6) and histological examination of kidney, liver and spleen were examined. The values represent mean ± standard error.

3.1. Hematological parameters

WBCs count showed highly significant reduction ($p<0.001$) in the control group of hyperlipidemic (HL) rats. While the other hematological parameters had no significant changes compared with normal control group.

WBCs count significantly reduced ($p<0.01$) in HL hydrocortisone treated animals (Figure 1-A), whereas, granulocytes showed significant elevation (Figure 1-B). MHC highly significant reduced ($p<0.001$) in HL DHEA treated group, also, in HL testosterone treated group significantly decreased ($p<0.01$). On the other hand, no significant variations appeared in the other hematological parameters compared with HL control groups (table 1).

Table (1): The effects of neurosteroid, natural and anabolic steroids on hematological parameters.

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
WBCs (x106/mm3)	10.74 ± 0.33	8.09 ± 0.36 ***	9.01 ± 0.26	6.64 ± 0.20 **	7.61 ± 0.25
Granulocytes %	14.79 ± 1.13	17.21 ± 1.61	18.55 ± 2.14	24.92 ± 1.67 *	15.54 ± 1.43
Lymphocytes %	73.42 ± 1.47	69.96 ± 1.55	71.48 ± 1.41	65.64 ± 0.91	72.88 ± 1.05
Monocytes %	9.95 ± 0.44	9.84 ± 0.60	7.97 ± 0.62	7.74 ± 0.70	9.18 ± 0.69
RBCs ($x10^6/mm^3$)	7.764 ± 0.14	7.906 ± 0.22	8.178 ± 0.07	8.028 ± 0.15	8.322 ± 0.09
Hb (g/dl)	15.06 ± 0.20	15.63 ± 0.45	15.53 ± 0.16	15.59 ± 0.29	15.87 ± 0.20
PCV (%)	44.19 ± 0.99	42.79 ± 1.41	42.53 ± 0.51	43.26 ± 0.74	43.46 ± 0.59
MCV (fl)	53.84 ± 0.71	54.00 ± 0.65	51.97 ± 0.26	53.54 ± 0.16	52.22 ± 0.31
MCH (pg)	19.41 ± 0.10	19.73 ± 0.06	19.06 ± 0.18 ***	19.43 ± 0.05	19.19 ± 0.07 **
MCHC (g/dl)	35.91 ± 0.38	36.59 ± 0.29	36.54 ± 0.16	36.39 ± 0.16	36.80 ± 0.17
Platelets ($/mm^3$)	578.4 ± 20.37	639.0 ± 12.96	569.7 ± 14.46	586.6 ± 13.06	626.5 ± 15.34

Value expressed mean ± SE * Significant at p<0.05 ** Significant at p<0.01 *** significant at p <0.001.

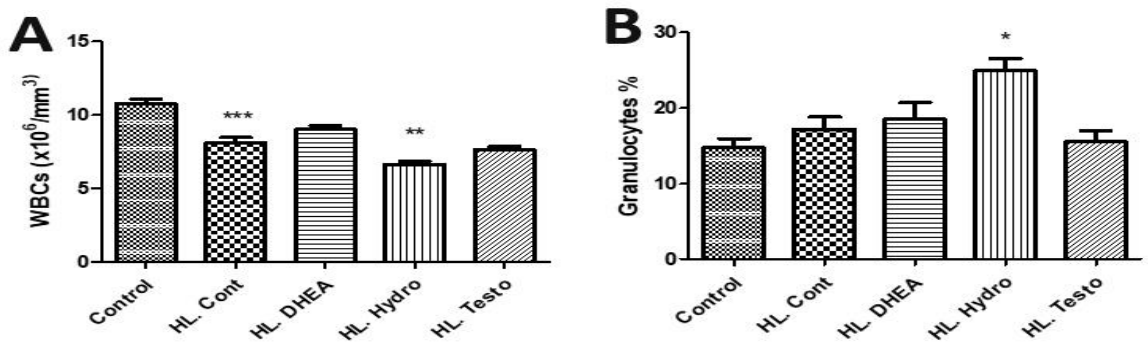


Fig. (1): The effect of neurosteroid, natural steroid and anabolic steroid on total **A**-WBCs count. **B**-Granulocytes%.

3.2. Blood glucose and lipid profile

Cholesterol, triglyceride (TG), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) showed high significant increase (p<0.001) in HL control group, whereas fasting blood glucose and high-density lipoprotein (HDL) showed no significant change in comparison with normal control group.

Fasting blood glucose and total cholesterol showed highly significant increase (p<0.001) in HL hydrocortisone treated group. As well as, total cholesterol, triglyceride, LDL and VLDL showed significant increase in HL DHEA treated group (p<0.001) and (p<0.01) respectively. Whereas, cholesterol, VLDV and HDL significantly decreased (p<0.001) and (p<0.05) in HL hydrocortisone and testosterone treated group (table 2) (Figure 2).

Table (2): The effects of neurosteroid, natural and anabolic steroids on FBS and serum lipids level

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
Glucose (mg/dl)	101.6 ± 2.38	120.7 ± 4.33	123.7 ± 3.14	156.0 ± 4.19 ***	113.0 ± 2.16
Cholesterol (mg/dl)	69.06 ± 2.32	143.8 ± 5.40 ***	182.3 ± 3.21 ***	119.0 ± 1.86 ***	131.5 ± 1.37
TG (mg/dl)	86.41 ± 5.04	127.8 ± 6.06 ***	152.6 ± 1.52 **	115.3 ± 1.73	123.1 ± 4.93
HDL (mg/dl)	38.00 ± 1.03	42.11 ± 1.72	39.00 ± 0.78	38.70 ± 0.88	36.50 ± 0.89 *
LDL (mg/dl)	18.24 ± 0.90	72.11 ± 2.6 ***	85.60 ± 1.34 ***	65.90 ± 1.15	61.80 ± 1.31 ***
VLDL (mg/dl)	17.17 ± 0.90	25.56 ± 1.21 ***	30.52 ± 0.30 **	23.06 ± 0.34	24.62 ± 0.98

Value expressed mean ± SE * Significant at p<0.05 ** Significant at p<0.01 * significant at p <0.001.**

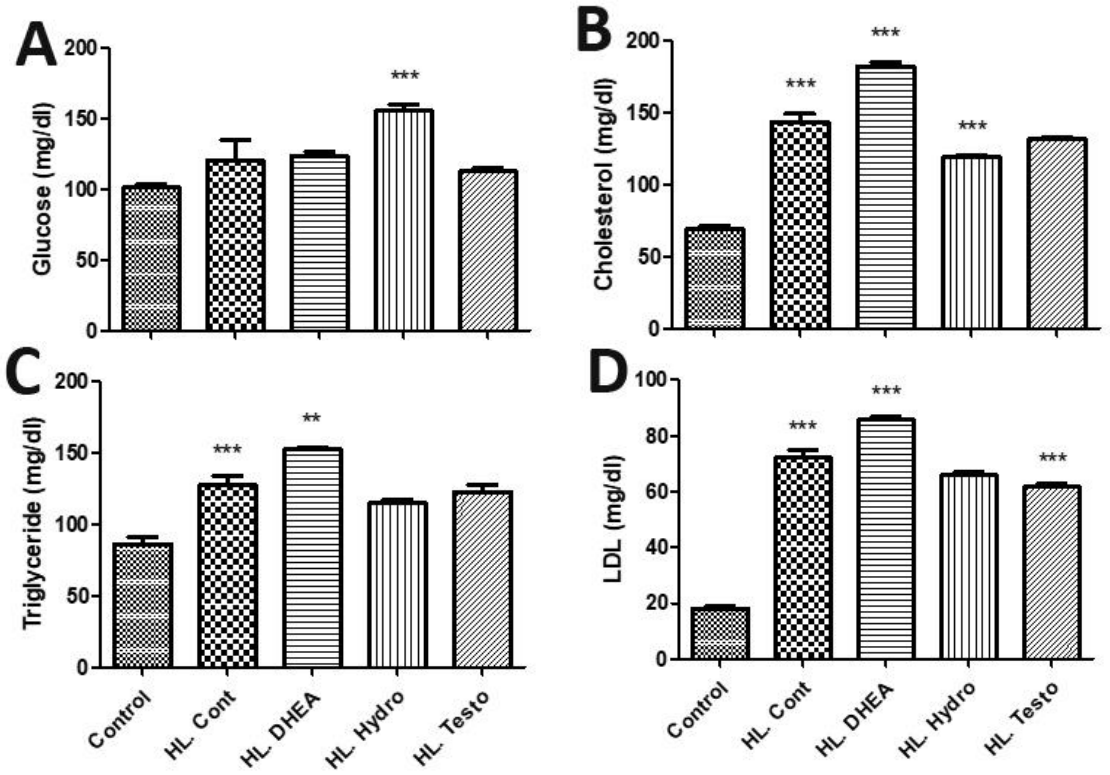


Fig. (2): The effect of neurosteroid, natural steroid and anabolic steroid on **A-**Blood glucose. **B-**Cholesterol**. C-** Triglyceride. **D-** LDL.

3.3. Urea, creatinine, electrolyte and serum calcium

Blood urea and creatinine showed highly significant elevation (p<0.001) in HL DHEA treated group, as well as, blood urea, creatinine and uric acid significantly increased (p<0.05) in HL hydrocortisone treated animals., while HL testosterone treated groups showed significant reduction (p<0.05) in blood urea compared with HL control group (table 3) (Figure 3).

Table (3): The effects of neurosteroid, natural and anabolic steroids on urea, creatinine, uric acid, serum electrolyte and calcium.

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
Urea (mg/dl)	17.04 ± 0.37	15.74 ± 0.69	19.50 ± 0.49 ***	17.97 ± 0.20 *	13.53 ± 0.28 *
Creatinine (mg/dl)	0.3247 ± 0.013	0.2756 ± 0.014	0.5460 ± 0.038 ***	0.3810 ± 0.023 *	0.3280 ± 0.018
Uric acid (mg/d)	2.429 ± 0.11	1.863 ± 0.19	2.160 ± 0.094	2.510 ± 0.12 *	1.540 ± 0.11
Na (mmol/L)	128.2 ± 2.49	134.0 ± 1.55	139.7 ± 0.59	138.1 ± 1.91	136.5 ± 1.86
Cl (mmol/L)	89.18 ± 2.49	92.89 ± 1.14	100.7 ± 0.81	99.70 ± 1.26	96.70 ± 1.36
K (mmol/L)	4.824 ± 0.26	4.744 ± 0.22	5.400 ± 0.14	4.390 ± 0.13	4.340 ± 0.085
Ca (mg/dl)	9.659 ± 0.16	9.133 ± 0.26	9.140 ± 0.13	8.870 ± 0.12	8.460 ± 0.097

Value expressed mean ± SE * Significant at p<0.05 ** Significant at p<0.01 *** significant at p <0.001.

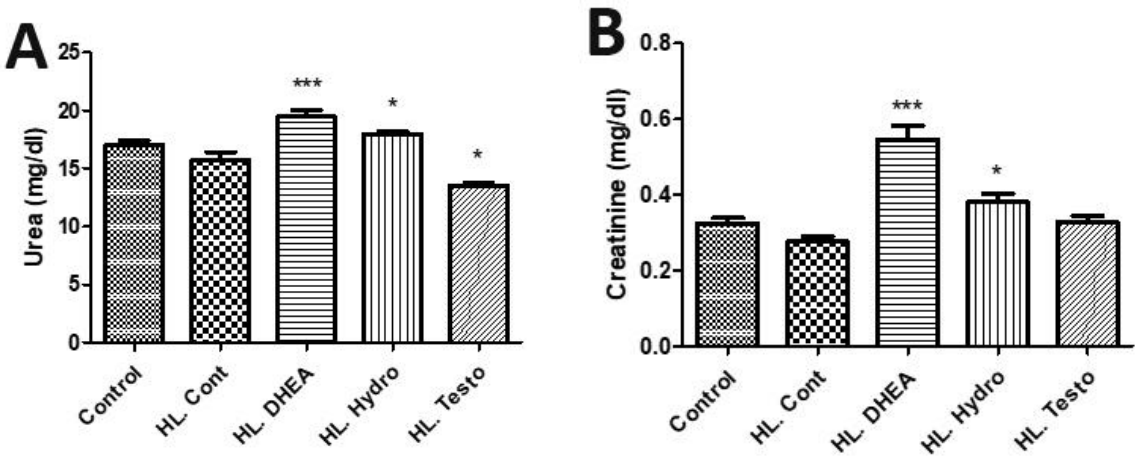


Fig. (3): The effect of neurosteroid, natural steroid and anabolic steroid on **A-**Blood Urea. **B-**Serum Creatinine.

3.4. Liver enzymes and serum proteins

Alkaline phosphatase (ALP) showed highly significant decrease (p<0.001), while total protein and albumin significantly increased (p<0.01) and (p<0.001) respectively in HL control group compared with control group.

ALP highly significant increased (p<0.001) in HL treated with DHEA. On the other hand, HL testosterone treated group revealed significant increase in ALP and globulin levels (p<0.001 and p<0.01) respectively. No significant changes were observed in other parameters compared with HL control group (table 4) (Figure 4).

Table (4): The effects of neurosteroid, natural and anabolic steroids on liver function parameters and serum proteins.

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
AST (GOT) IU/L	113.5 ± 3.14	121.6 ± 10.16	132.1 ± 9.47	141.2 ± 10.91	125.2 ± 3.88
ALT (GPT) IU/L	44.65 ± 1.03	41.67 ± 4.29	38.50 ± 1.10	37.10 ± 1.46	36.60 ± 1.57
ALP IU/L	350.5 ± 5.95	271.9 ± 6.13 ***	336.7 ± 6.11 ***	295.1 ± 8.61	444 ± 6.61 ***
Total Protein (g/dl)	5.400 ± 0.10	6.264 ± 0.14 **	5.830 ± 0.11	5.815 ± 0.054	6.564 ± 0.13
Albumin (g/dl)	2.82 ± 0.11	3.597 ± 0.11 ***	3.182 ± 0.10	3.471 ± 0.08	3.253 ± 0.07
Globulin (g/dl)	2.801 ± 0.07	2.668 ± 0.19	2.575 ± 0.11	2.308 ± 0.10	3.311 ± 0.12 **

Value expressed mean ± SE * Significant at p<0.05 ** Significant at p<0.01 *** significant at p <0.001.

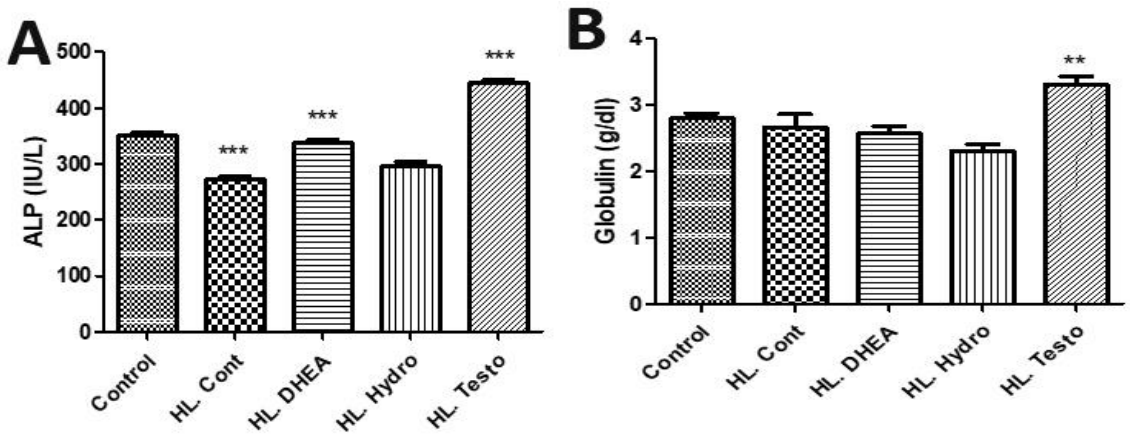


Fig. (4): The effect of neurosteroid, natural steroid and anabolic steroid on **A**-Alkaline phosphatase. **B**-Globulin.

3.5. IL-2 and IL-6

IL-2 and IL-6 showed insignificant variations in HL control group among the control group. Whereas IL-2 significantly increased (p<0.01). Although, IL-6 showed highly significant decrease (p<0.001) in HL treated groups with DHEA and hydrocortisone compared with HL control group (table 5) (Figure 5).

Table (5): The effects of neurosteroid, natural and anabolic steroids on IL-2 and IL-6

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
IL-2 (ng/dl)	20.63 ± 1.46	19.96 ± 1.17	29.39 ± 2.27 **	17.03 ± 1.25	18.82 ± 0.99
IL-6 (ng/dl)	6.64 ± 0.39	7.96 ± 0.20	5.62 ± 0.37 ***	5.96 ± 0.26 ***	8.56 ± 0.27

Value expressed mean ± SE * Significant at p<0.05 ** Significant at p<0.01 *** significant at p <0.001.

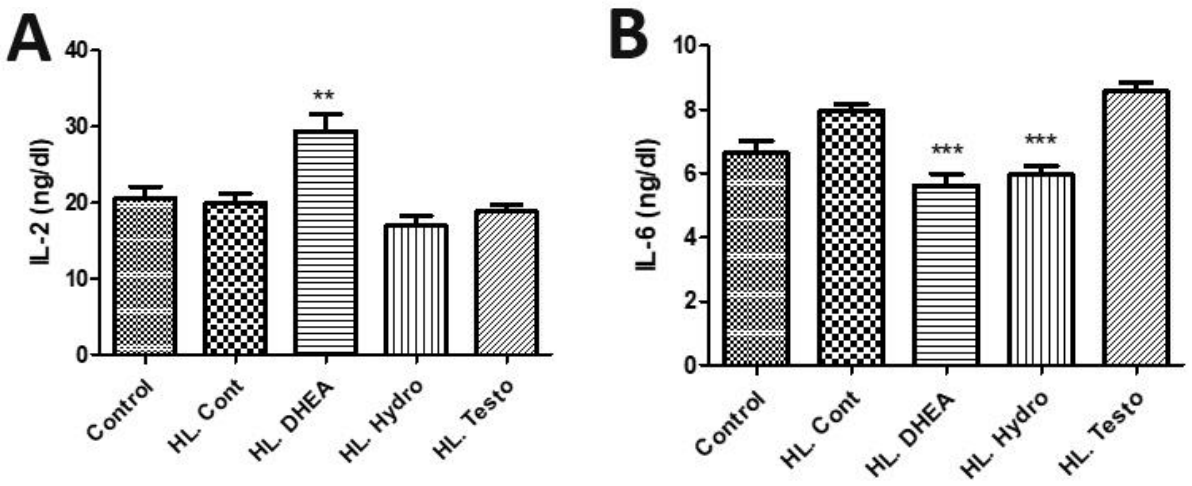


Fig. (5): The effect of neurosteroid, natural steroid and anabolic steroid on **A-**IL-2. **B-** IL-6.

3.6. Body Weight

Body weight changes revealed highly significant increase ($p<0.001$) in HL control group compared with control group. On the other hand, no significant changes recorded in all treated groups compared with HL control group (table 6) (Figure 6).

Table (6): The effects of neurosteroid, natural and anabolic steroids on Body Weight

Parameters	Control	HL. Control	HL. DHEA	HL. Hydro	HL. Testo
First Day (g)	168.2 ± 3.33	157.6 ± 2.34	164.0 ± 4.1	163.4 ± 4.99	161.9 ± 2.643
Last Day (g)	266.4 ± 5.02	345.8 ± 9.49 ***	366.4 ± 3.91	327.2 ± 6.06	329.5 ± 6.6
Weight changes (g)	98.20 ± 2.37	188.2 ± 10.85 ***	202.4 ± 6.54	163.8 ± 5.48	167.6 ± 6.87

Value expressed mean ± SE * Significant at $p<0.05$ ** Significant at $p<0.01$ *** significant at $p<0.001$.

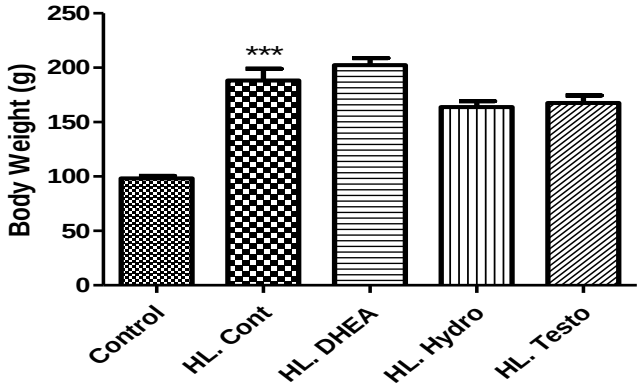


Fig. (6): The effect of neurosteroid, natural steroid and anabolic steroid on Body weight.

3.7. Histopathological examination of kidney, liver and spleen of hyperlipidemic rats

3.7.1. Kidney

Kidney sections showed almost normal cell architecture appearances of glomeruli and renal tubules in control group. Whilst, several histopathological damages were exposed with HL control group includes glomerulus atrophy of renal corpuscle, increase in Bowman's space, moderate and mild congestion, necrosis in both

proximal and distal convoluted tubules with accumulation amount of white adipose connective tissue proper in kidney capsule. Furthermore, HL DHEA treated group also showed several histopathological disturbances such as comprehended moderate necrosis in parietal layer of Bowman's capsule, congestion, hemorrhage, necrosis in renal tubules. Mild atrophy in renal corpuscle and increase in Bowman's space, congestion, necrosis and different stages of nucleus death of cuboidal cells of proximal and distal convoluted tubules were presented in HL group treated with hydrocortisone. Furthermore, semi- normal architecture, different death stages in renal tubular cuboidal cells and renal capsule provided with amount of white adipose connective tissue proper, were also shown in HL testosterone treated rats (Figure 7).

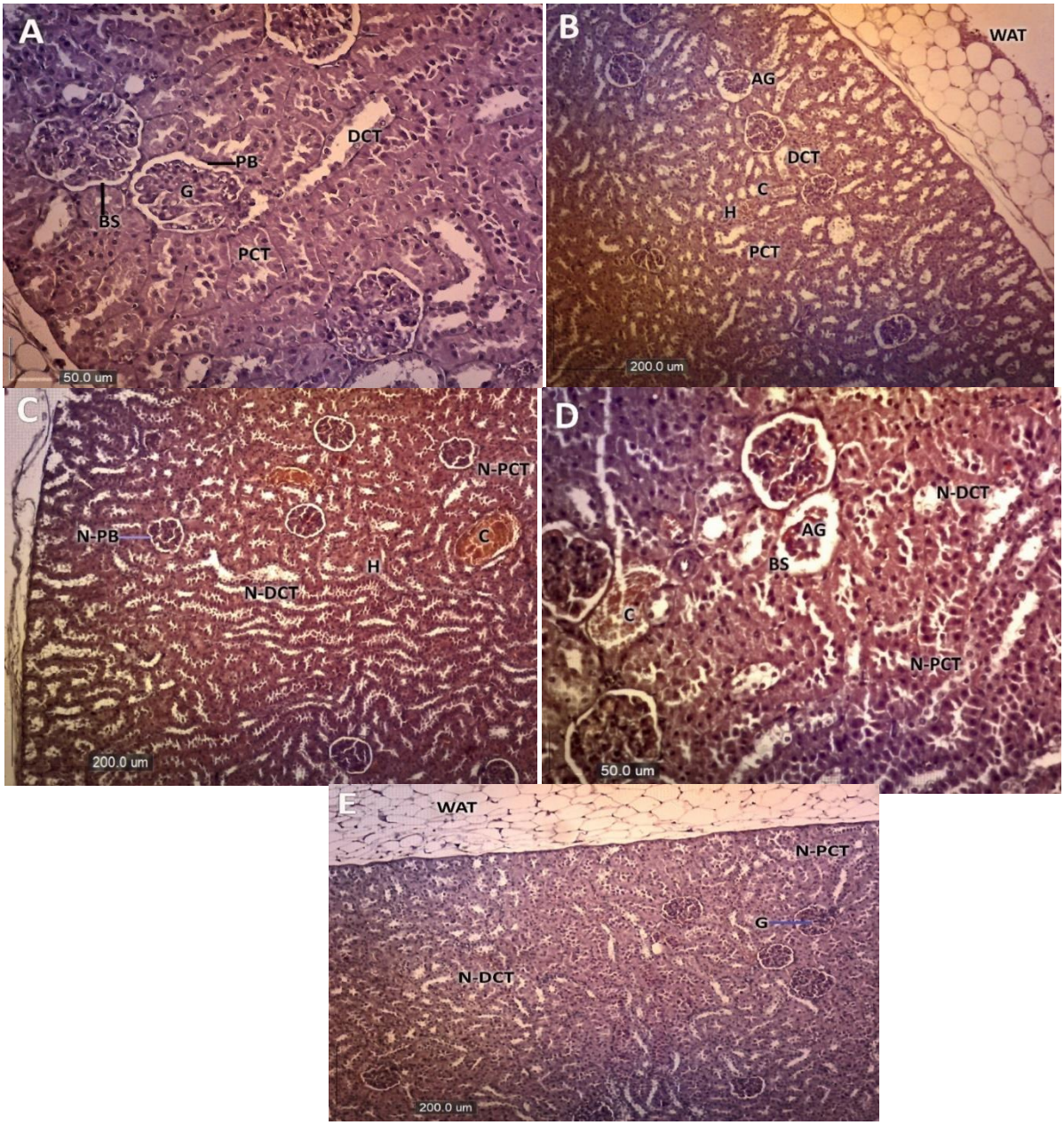
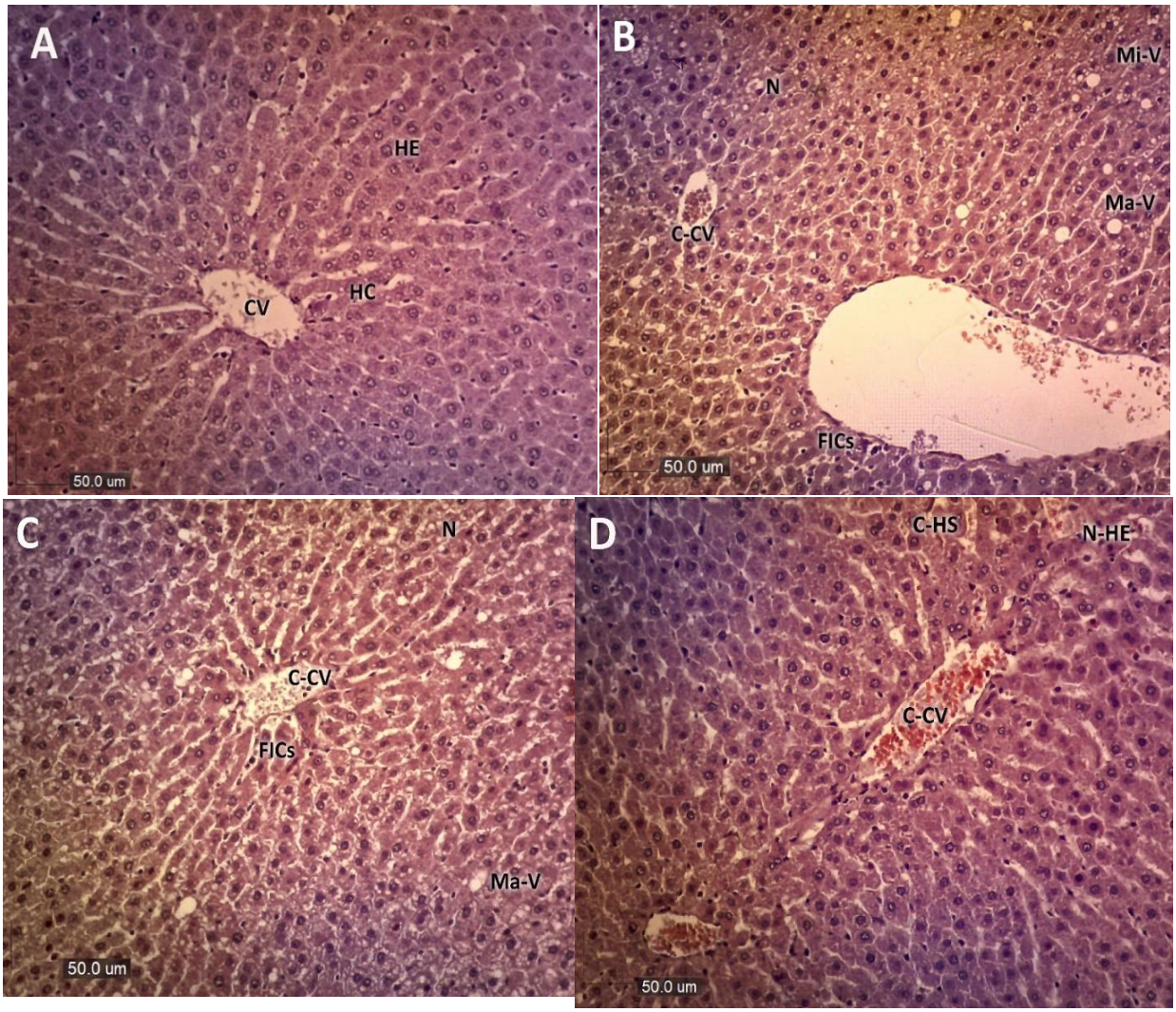


Fig. (7): Cross section of kidney (H&E): **A- Control group (10x):** Showing normal glomeruli (G), with normal proximal & distal convoluted tubules (PCT & DCT). **B- HL control group (4x):** Hemorrhage (H), congestion (C), atrophy in glomerulus (AG) & white adipose tissue (WAT). **C- HL DHEA group (4x):** Hemorrhage (H), congestion (C), necrosis in Bowman's capsule parietal layer (N-PB) & necrosis in both renal tubules (N-PCT & N-DCT). **D- HL hydrocortisone group (10x):** AG, C, N-PCT & N-DCT. and **E- HL testosterone group (4x):** WAT, N-PCT & N-DCT.

3.7.2. Liver

The liver structure, as in the control group, was observed to have a normal-sized central vein, a clear appearance of hepatocytes with a large and central nucleus, and hepatic cord was noticeable. HL control group exposure several histological changes as congestion in hepatic central vein, different changes in the nucleus of hepatocytes, vacuole in hepatocytic cytoplasm, micro and macro vascular fatty deposition, necrosis and moderate filtration of inflammatory cells (leukocytes). HL DHEA treated animals showed congestion, hepatocytic necrosis, micro and macro vascular fatty deposition, necrosis, moderate filtration of inflammatory cells (leukocytes) and different nucleus damages in hepatocytes. Furthermore, HL hydrocortisone treated group exposed numerous histopathological changes as congestion in central vein and hepatic sinusoid with normal architecture of hepatic cord, necrosis of hepatocytes with different stages of nucleus death. On the other hand, HL treated animal with testosterone showed different histopathological damages comprise micro and macro vascular fatty deposition, necrosis, moderate filtration of inflammatory cells (leukocytes) on general liver architecture, swelling shape of hepatocytes with number of small vacuoles in the cytoplasm, different stages of hepatocytic nucleus, filtration of inflammatory cells (leukocytes) and mild congestion appears in central vein lumen (Figure 8).



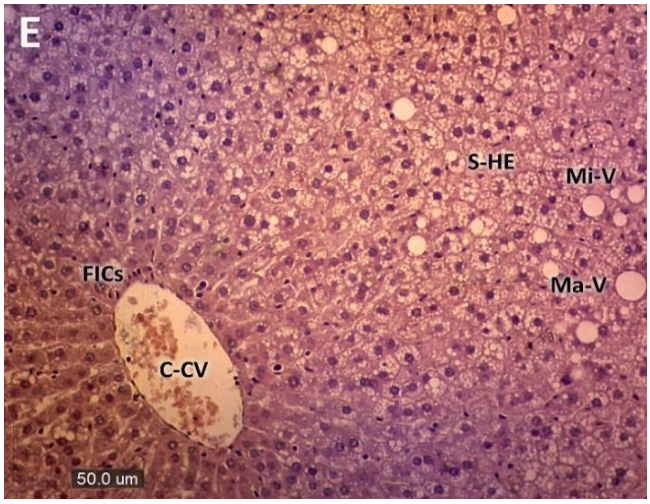
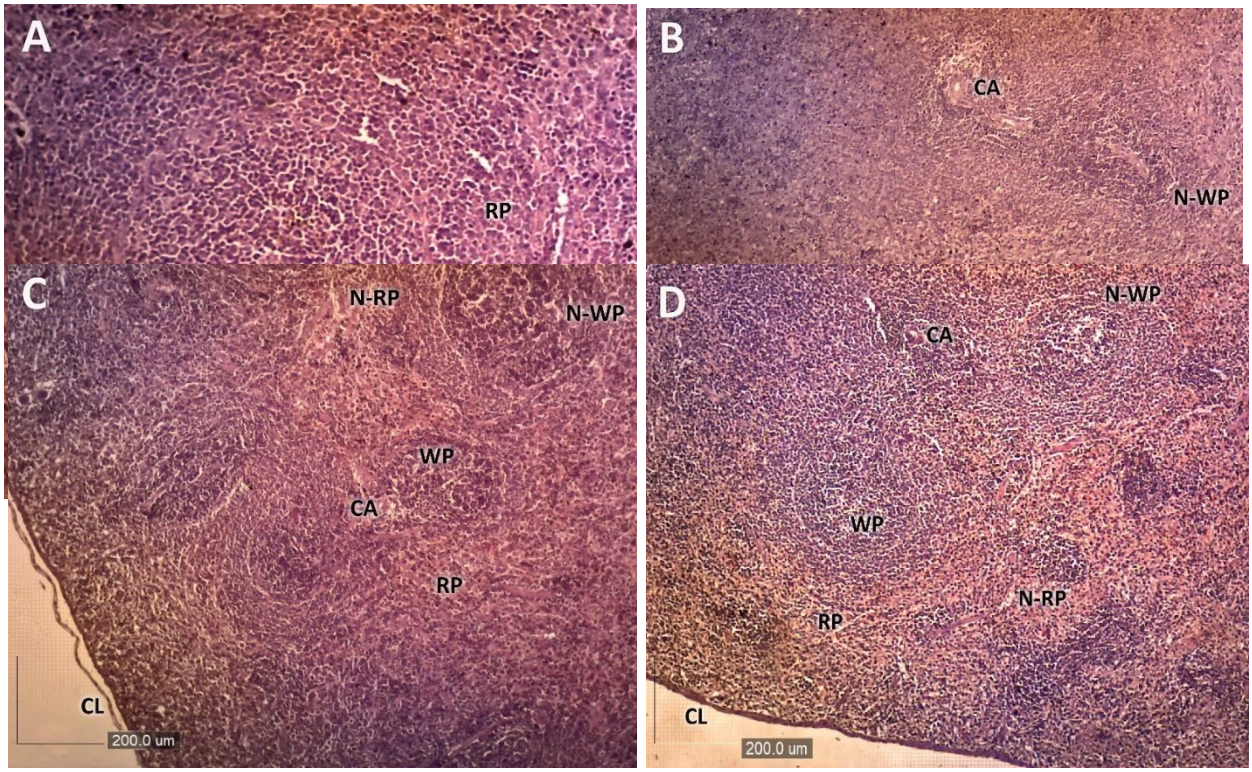


Fig. (8): Cross section of liver (H&E): **A- Control group (10x):** Showing normal central vein (CV), hepatic cord (HC) & hepatocytes (HE). **B- HL control group (10x):** Congestion in central vein (C-CV), necrosis (N), micro- vacuoles (Mi-V), macro- vacuoles (Ma-V) & filtration of inflammatory cells (FICs). **C- HL DHEA group (10x):** C-CV, Mi-V, Ma-V & FICs. **D- HL hydrocortisone group (10x):** Congestion in hepatic sinusoid (C-HS), hepatocytic necrosis (N-HE) & C-CV. and **E- HL testosterone group (10x):** Swelling of hepatocytes (S-HE), C-CV, Mi-V, Ma-V & FICs.

3.7.3. Spleen

The normal control group displayed typical spleen architecture, containing regular white and red pulp appearance and a discernible central arteriole. Numerous histopathological changes like necrosis in both white and red pulps, moderate reduction in white pulp size and mild fibrin deposition in central arteriole were shown in HL control group, while in HL DHEA treated group white pulp appeared in different size with moderate necrosis in both white and red pulps. Also, moderate reduction in white pulp size and red pulp suffered from moderate separation with mild necrosis in red and while pulps were seen in both HL rats treated with hydrocortisone and testosterone (Figure 9).



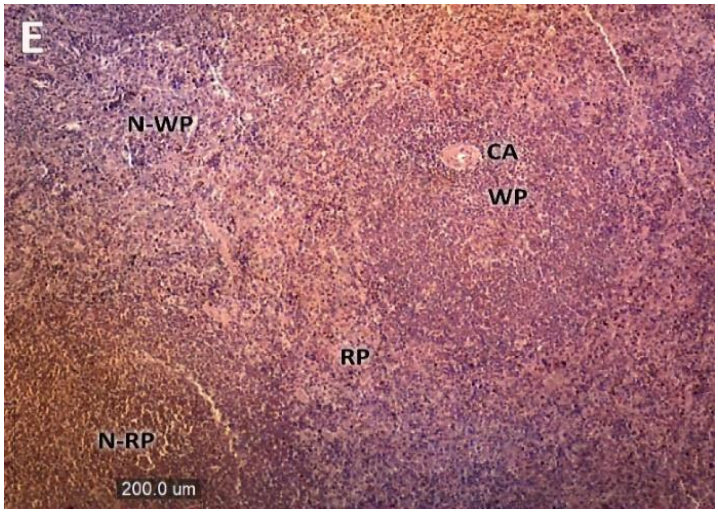


Fig. (9): Cross section of spleen (H&E): **A- Control group (10x):** Showing normal white pulp (WP), red pulp (RP) & central arteriole (CA). **B- HL control group (4x):** CA, white pulp necrosis (N-WP), red pulp necrosis (N-RP) & capsule (CL). **C- HL DHEA group (4x):** WP, RP, CA, N-WP, N-RP & CL. **D- HL hydrocortisone group (4x):** WP, RP, CA, N-WP, N-RP & CL and **E- HL testosterone group (4x):** CA with fibrinoid degeneration, WP, RP, N-WP & N-RP.

4. DISCUSSION

Hyperlipidemia is considered as a disorder that is characterized by high levels of lipids in the blood though they play important roles in the metabolic processes of the body, while hyperlipidemia is a major risk factor for cardiovascular disease, stroke, type II diabetes mellitus and microvascular diseases (Verma, 2016).

The purpose of this study is to examine the physiological, immunological and histopathological comparisons between the effects of neurosteroid, natural steroid and anabolic synthetic steroid on various target organs such as the kidney, liver and spleen in hyperlipidemic induced rats. Circulating steroid hormones, including DHEA and DHEA-Sulfated can cross the blood-brain barrier freely and can be converted in the brain to neurosteroids in several regions, including the cortex, the hippocampus and the amygdala. Moreover, DHEA together with DHEA-S showed anti-glucocorticoid and neuroprotective activities (Misiak *et al*., 2018). Also, there is evidence that DHEA-S, which is termed neurosteroids, is synthesized in the glial cells of rodent brains, and can be made and act locally (Pham *et al*, 2000). Glucocorticoids (GCs) are steroid hormones which are widely used for the treatment of inflammation, autoimmune diseases and cancer, exerting their broad physiological and therapeutic effects (Timmermans *et al*., 2019). Anabolic androgenic steroids are synthetic derivatives of the male hormone (testosterone) to maximize anabolic and minimize androgenic effects (Evans, 2004; Traish, 2014).

The comparison between hyperlipidemic (HL) control and normal control rats showed a significant reduction in WBCs count, low WBCs count are related with high lipids (Lai *et al*., 2019). Harsløf *et al* (2021), suggested a reverse relation between WBCs count and HDL concentration, showing the ability of HDL to suppress proliferation of hematopoietic stem, progenitor cells and myeloid proliferation.

The differences between steroid hormones treated groups showed that WBCs count were significantly reduced, while granulocytes was significantly elevated in HL hydrocortisone treated animals, whereas no significant changes in HL DHEA and testosterone treated groups were seen. Hydrocortisone had an inhibitory effect on WBCs and decreased their numbers, the reduction could be due to the effect of glucocorticoids by inhibiting leukocyte circulation and the access of leukocytes to the site of inflammation (Al-Maliki *et al*., 2018; Stahn & Buttgereit, 2008). Glucocorticoids might have important effects, inducing neutrophilia by the inhibiting of neutrophil adhesion to endothelial cells. This effect reduces

the trapping of neutrophils in the inflamed region (Alan & Alan, 2018).

Ziogas *et al* (2020) demonstrated that DHEA can restore the inflammation by decreasing endothelial expression, thereby inhibiting leukocyte recruitment leading to inflammation. Albano *et al* (2021) suggested the correspondence effect of high dose of AASs to glucocorticoids which might explain the clinical reduction of WBC numbers in HL testosterone group. Total cholesterol, triglyceride, LDL and VLDL showed high significant increase in HL control group compared with control group, might be through the influence of high fat diet provided to the animals. Glucose level increased significantly in HL hydrocortisone, the pathophysiology of glucocorticoid-induced diabetes caused by increased insulin resistance, reduced glucose uptake in muscle and adipose tissue (Alan & Alan, 2018). Furthermore, it has been shown that glucocorticoids alter the function of pancreatic beta cells through decreasing GLUT2 and glucokinase receptor expression at the same time, increasing the activity of glucose-6-phosphate dehydrogenase (Tamez-Pérez *et al*., 2015).

DHEA treated group exposed a hyperlipidemic symptom and significant increase in body weight. DHEA administration showed significant increase in cholesterol and triglycerides, these results agree with Mahmoud *et al* (2018), who reported a high dose of DHEA administration showed significant increase in hepatic weight, cholesterol, and triglycerides contents compared to those of normal dose of DHEA. Also, treatment of DHEA showed changes in serum lipids; an increase in serum triglyceride and cholesterol in rats fed on high cholesterol diet. Moreover, high dose of DHEA was associated with high serum lipids, might be due to cholesterol derived from DHEA biosynthesis (Jiménez *et al*., 2019). Additionally, administration of high dose of DHEA showed an obvious elevation in body weight, which might be resulted from obesity inducing hypogonadism as body weight increases and leads to hyperlipidemia (Fernandez *et al*., 2019). Safwat *et al* (2022), also reported the DHEA administration increased serum lipids and body weight in orchiectomized rats. Contrary Qin *et al* (2020), reported that DHEA supplementation did not changed total cholesterol and triglyceride levels. Our results were in contrary to the beneficial role of DHEA with lipids, which found that DHEA decrease serum apolipoprotein A, considering to be beneficial for cardiovascular diseases (Labrie, 2010). HL hydrocortisone treated rats showed significant reduction in total cholesterol level. Chronic exposure to exogenous glucocorticoids is a secondary cause of hyperlipidemia. But the degree of lipid abnormalities in different clinical conditions is quite variable; all possible changes in lipid profile included (Alan & Alan, 2018). Glucocorticoids are well known to reduce overall body mass, probably by promoting muscle proteolysis and by depressing growth hormone-insulin like growth factor (GH–IGF-1) axis (Shpilberg *et al*., 2012). Testosterone administration that decreases intraabdominal and intermuscular adipose tissue stores might be expected to have a beneficial effect on insulin sensitivity (Woodhouse *et al*., 2004). As well as, the decrease in fat mass was also accompanied by a decrease in plasma glucose concentration and an increase in insulin resistance (Emmelot-Vonk *et al*., 2008).

Blood urea and serum creatinine levels showed significant elevation in HL DHEA and hydrocortisone treated groups. Whereas, blood urea was significantly reduced with HL testosterone administrated compared with HL control group. DHEA administration significantly increased blood urea and serum creatinine levels as complications of glomerular and renal tubules injuries which were obvious in renal tissues (Forghani *et al*., 2023). Also, DHEA can increase oxidative stress in the kidneys that leads to reduction in glomerular filtration rate (GFR) and increase in blood urea and creatinine level (Jahn *et al*., 2011). Furthermore, glucocorticoids can cause an elevation in both blood urea and serum creatinine levels through increasing proteins breakdown, reduction in GFR and inducing renal injury (Kraut & Madias, 2017). High dose of anabolic androgenic testosterone (Sustanon) resulted in dramatic changes in the histology of nephrons, which may reflect kidney disorders and reduce ability to excrete nitrogenous compounds (Abd Hamza & Rashid, 2017).

Despite of insignificant change in uric acid with DHEA treated group, there was a positive association between DHEA and uric acid, which was observed clinically in both men and postmenopausal women (Wan *et al*., 2020). The elevation in uric acid was resulted from the effect of glucocorticoids lowering renal blood flow (Mangos *et al*., 2003). A previous study

found that serum uric acid was negatively correlated with SHBG (Sex hormone-binding globulin), these findings give possible explanations of the clinical reduction in uric acid level in HL testosterone treated rats (Cao *et al*., 2017).

The significant reduction in alkaline phosphatase (ALP) level in HL control group was not explainable, while previous studies suggested that elevation in ALP was associated with hyperlipidemia causing vascular disease and blood pressure (Wang *et al*., 2018). Total protein and albumin were significantly increased in HL control group. Albumin can transport cholesterol among various receptors, which in turn increases the movement of cholesterol following concentration gradients between the numerous cholesterol pools present in plasma and tissues (Yao *et al*., 2022).

HL DHEA and testosterone treated animal showed significant increase in ALP level which might be due to stimulation of osteoblasts production and reduction of urinary calcium excretion (Luo *et al*., 1997). Testosterone treatment significantly elevated blood alkaline phosphatase, but not aspartate aminotransferase or alanine aminotransferase (Sadowska-Krępa *et al*., 2020). The significant elevation in globulin level in HL testosterone treated group could be resulted from high testosterone sex hormone binding globulin (SHBG), which is produced in the liver and binds with circulating testosterone (Sinclair *et al*., 2015).

HL DHEA treated group was significantly elevated IL-2. On the other hand, in spite of HL hydrocortisone treated animals showed obvious clinical reduction, it turned out not to be statistically significant. Moreover, IL-6 in both HL DHEA and hydrocortisone treated rats were significantly decreased. DHEA increases the production of cytokines that promote white blood cell activity, also the inhibition of the production of cytokines is responsible for inflammation by affecting cytokine production, downing regulating inflammatory cytokines, elevating the regulation of the anti-inflammatory IL-2 synthesis, enhancing lymphocyte proliferation and increasing T cell (Gabai *et al*., 2020; Whitham *et al*., 2020). Glucocorticoids inhibit synthesis and secretion of inflammatory molecules, such as IL-2 and IL-6 by affecting posttranslational events (Alan & Alan, 2018). Also, glucocorticoids inhibit cytokine production by macrophages and T cell, thus decrease the normal proliferation of B cell. They may also act directly on B cell to inhibit antibody synthesis and in high concentration may even kill B cell (Amar *et al*., 2013).

The clinical condition of hyperlipidemia can have negative effects on various important organs, including the kidneys, liver and spleen. A previous study has manifested that kidney lipid metabolism was interfered by hyperlipidemia (Salim *et al*., 2018). Arisha *et al*. (2022), reported a several renal histopathological alterations including degeneration in renal corpuscles and renal tubules, dilation in Bowman's space and hemorrhage in rats fed with high cholesterol diet (HCD), caused by enzymatic activation associated with both metabolic and oxidative effects. Koubaa-Ghorbel *et al*. (2020), found that animals fed on high cholesterol diet (HCD) had significant hemorrhage, necrotic renal tubular cells and reduction in kidney function that could be attributed to a deficiency in the permeability and stability of cell membranes. Hyperlipidemia leads to several liver damages without severely affecting liver function. Also, the accumulation of lipid in tissue may lead to increase of nitro-oxidative stress in several organs including liver (Csonka *et al*., 2017). Steatosis, obesity, insulin resistance and glucose intolerance were resulted from high-fat diet, the progression of steatohepatitis to fibrosis and hepatocellular carcinoma mostly associated with high dietary cholesterol (Zhang *et al*., 2021). Destructed cell's membrane caused by the free radicals and lipid oxidation creates several conditions, including necrosis, congestion, hemorrhage and multiple intracytoplasmic vacuoles described as macro and micro-vesicular steatosis (Iswari *et al*., 2020). Histological examinations have revealed an increase in spleen size, hemorrhage and necrosis. Asghar *et al*. (2021), established a link between obesity and immune dysfunction by increasing spleen size as disease progression and immune response consequence. Also, TNF-α was elevated with high fat diet consumption, the elevation of TNF-α due to the effect of high fat diet may be attributed to the balance impairment of inflammation and anti-inflammation in the spleen (Feng *et al*., 2021).

DHEA administration to experimental animals caused acute damages to renal tissue including congestion, hemorrhage and necrosis in both proximal and distal tubules. Moreover, treated rats with DHEA increase the expression of transforming growth factor beta 1 (TGF- β 1), which may lead to increase oxidative stress

levels in the renal tissue and GFR reduction (Jahn *et al*., 2011). In parallel with our results, Forghani *et al.* (2023) reported a significant increase in plasma urea and creatinine levels, which is an indication of renal injury. High dose of hydrocortisone causes a dilation in renal tubules and renal injury including congestion, hemorrhage and necrosis in both proximal and distal tubules (Al-Muswie, 2017). Furthermore, glucocorticoids administration could be a part in the development of numerous tissue organs as kidney, liver and lungs (Hammadi Jasim *et al*., 2022). Both proximal and distal tubules marked a histopathological affection with anabolic steroid treated animals included irregular cellular lining pattern and necrotic nuclei and detachment of brush border in proximal tubules, which might be attributed to reduction in cellular ATP and mitochondrial damage (Isaac, 2019). Obesity is considered as one of the factors that causes development of liver steatosis. Treated rats with high dose of DHEA can cause a hypertrophied hepatocytes due to lipid accumulation and development of lipid droplets and might affect G6Pase gene expression and decrease hepatic glucose liberation which may direct it to lipogenesis pathway, resulted in accumulation of hepatic fat (Mahmoud *et al*., 2018). Stimulation of hepatic gluconeogenesis and increase of glycogen deposition due to glucocorticoids administration might lead to several histopathological damages as hepatic cells degeneration. Also, Arachidonic acid and prostaglandin, which typically function as antiaggregant agents were inhibited by glucocorticoid can cause sinusoidal dilatation, necrosis and hepatic congestion (Noel, 2013).

Anabolic androgenic steroids (AASs) utilization might cause several histopathological changes including; mild to severe vascular congestion, fatty degeneration and congestion in hepatic sinusoid with infiltration of inflammatory cells through significant elevation of collagen fibers deposition and may result in fibrosis and hepatic tissue congestion (Nucci *et al*., 2017; Yonis *et al*., 2021). DHEA has a positive immunologic effect by increasing the suppression of pro-inflammatory cytokines and restoring the splenocytes proliferative capacity. It has been suggested that DHEA directly improves monocytes and lymphocytes through high affinity DHEA-specific receptors in humans, as well as in experimental animals (Rearte *et al*., 2014). Long term administration of hydrocortisone increases the transport of fatty acids to the cells instead of glucose and use it as a source of energy and might cause splenic tissue destruction with the appearance of small lymphocytes. Also, it may lead to numerous histopathological changes to several organs such spleen (Al-Muswie, 2017). Supraphysiological administration of AASs could elevate oxidative stress and reveal several histopathological changes of spleen such as degeneration, fibrosis, necrosis in white and red pulps, hyperplasia of red pulp, widening the white pulp and congestion, which were revealed in anabolic testosterone treated group. Moreover, AASs may have an impact on splenocytes, splenic macrophages and immune responses (Al-alwany *et al*., 2016).

5. CONCLUSION

The results of the current study have revealed that DHEA has a positive effect on immunity as it improves the levels of IL-2, which is a vital cytokine for immune response. Nevertheless, it is of importance to know that DHEA also exhibits negative impact on lipid profile, renal function and body weight. These results suggest though DHEA could improve immune function, its possible side effects on weight and lipid metabolism have to be carefully taken into consideration. Contrarily, it has been found that both hydrocortisone and Sustanon had damaging effects on immunity because they decreased WBC count and IL-2 levels, which indicates a negative impact on the ability of the body to give an effective immune response /reaction. Nonetheless, it is crucial to note that these substances have shown positive effects on both lipid profile and total body weight. It has also found that Sustanon improves both blood sugar and lipid levels, which could be of benefit to those who suffer from certain metabolic disorders. However, it had negative effects on renal function tests, which suggest that caution and monitoring are to be carefully considered on testosterone supplementation. In nutshell, though DHEA has shown potential in enhancing immune function by improving IL-2, its negative impact on lipid profile and body weigh has to be considered. However, hydrocortisone and Sustanon, could have positive effects on lipid profile and weight management though they are associated with other possible problems or disadvantages. Thus, further investigation is of importance in order to better understand the

longstanding implications and consider the perils and merits of such interventions.

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ستیرۆیدەکانی دەمار، سروشتی و ئەنابۆلیک: لێکۆڵینەوەی فیزیۆلۆژی، بەرگری و بافتزانی لەسەر مشکی ئەلبینۆی زیاد چەوری خوێن

پوختە

نێرۆستیرۆیدەکان بریتین لە ستیرۆیدەکان کە ستیرۆیدەکانی ناوخۆیی لەخۆدەگرن کە سیستەمی دەمار بەرهەمی دەهێنێت، و وەک گواستەرە دەماریییەکان یان گۆڕینی دەمارەکان کاردەکەن. هۆرمۆنە ستیرۆیدەکان بە شێوەیەکی سەرەکی لە ڕێژنەکانی ئەدرنالدا بەرهەم دەهێنرێن و ڕۆڵێکی سەرەکییان هەیە لە ڕێکخستنی زۆرێک لە کردارە فیزیۆلۆژییەکان لە جەستەدا. ستیرۆیدی ئەنابۆلیک کە پێکهاتەیەکی دەستکردە، کاریگەری هاوشێوەی هۆرمۆنی تێستۆستیرۆنی هەیە.

ئەم توێژینەوەیە ئامانجی جیاکردنەوەی ڕۆڵی نیورۆستیرۆید و ستیرۆیدی سروشتی و ستیرۆیدە دروستکراوەکانی ئەنابۆلیک بوو لەڕێگەی لێکۆڵینەوە لە کاریگەرییەکانی هەندێک لە ئەندامە فیزیۆلۆژی و بەرگری و بافتناسییەکان لەسەر ئەندامە ئامانجدارە جیاوازەکانی وەک گورچیلە و جگەر و سپڵ لە مشکی زیادبوونی چەوریدا.

بۆ ئەوەی ئەم ئامانجانە بەدەست بهێنین، ئێمە بە شێوەیەکی هەڕەمەکی 50 مشکی نێری ئەلبینۆمان دابەش کرد بۆ پێنج گروپی یەکسان. گروپی یەکەم کە بە خۆراکی ستاندارد خۆراکیان پێدرا و لە ژێر پێستەوە بە 0.5 مل خوێی ئاسایی دەرزییان لێدرا وەک گروپی کۆنترۆڵ بەکارهێنران، لە کاتێکدا گروپی دووەم کە وەک گروپی کۆنترۆڵکردنی زیادبوونی چەوری کاریان کردووە بە خۆراکی چەوری بەرز خۆراکیان پێدرا. گروپی سێیەم، مشکی زیادبوونی چەوری، بە شێوەی زارەکی بە DHEA (وەک نیورۆستیرۆید، 17.2 میلیگرام/کیلۆگرام/ڕۆژ) بەکارهێنران، گروپی چوارەم، مشکی زیادبوونی چەوری، لە ژێر پێستەوە بە دەرزی هایدرۆکۆرتیزۆن (وەک ستیرۆیدی سروشتی، 26.1 میلیگرام/کیلۆگرام/ڕۆژ)یان پێدرا. . لە کۆتاییدا، مشکە چەورییە بەرزەکانی گروپی پێنجەم لە ڕێگەی ماسولکەوە دەرزی سوستانۆنیان پێدرا (وەک ستیرۆیدێکی ئەنابۆلیک، 66.9 میلیگرام/کیلۆگرام/هەفتە).

توێژینەوەکە دەریخستووە کە مشکی بەرزبوونەوەی چەوری پارامێتەرەکانی خوێن و باشتربوونی ئینتەرلوکین IL-2 لەگەڵ DHEA، شەکری خوێنی بەڕۆژووبوون و کێشی جەستەیان بە سوستانۆن، پرۆفایلی چەوری لەگەڵ هەردوو هایدرۆکۆرتیزۆن و سوستانۆن، کارکردنی گورچیلە نزیک بوو لە تێکچوون لە هەموو گروپە چارەسەرکراوەکاندا، لە کۆتاییدا هەبوون گۆڕانکاری جۆراوجۆر لە پشکنینی هیستۆپاتۆلۆژی گورچیلە، جگەر و سپڵ.

لە کۆتاییدا توێژینەوەکە ئەم ئەنجامانەی خوارەوەی هێناوەتە ئاراوە: بەڕێوەبردنی DHEA دەتوانێت بەرگری باشتر بکات و تێکچوونی شانەکانی سپڵ باشتر بکات. ڕەنگە هایدرۆکۆرتیزۆن پرۆفایلی چەوری باشتر بکات، هەرچەندە کاریگەری نەرێنی لەسەر بەرگری و تەندروستی شانەکان هەیە. سوستانۆن کاریگەری ئەرێنی لەسەر گلوکۆزی خوێن و پرۆفایلی چەوری هەیە، لەگەڵ ئەوەشدا کاریگەرییەکانی لەسەر بەرگری بەس ڕوون نییە.

الستيرويدات العصبية والطبيعية والمصنعة: دراسة فسيولوجية ومناعية ونسيجية على الجرذان الألبينية المصابة بفرط شحميات الدم.

الخلاصة

الستيرويدات العصبية هي المنشطات التي تشمل الستيرويدات الداخلية التي ينتجها الجهاز العصبي ، وهي تعمل كناقلات عصبية أو محورات عصبية. يتم إنتاج الهرمونات الستيرويدية بشكل رئيسي في الغدد الكظرية ولها دور حيوي في تنظيم العديد من الفعاليات الفسيولوجية في الجسم. الستيرويد المنشطة ، وهو مركب اصطناعي ، له تأثيرات مماثلة لهرمون التستوستيرون.

.هدفت هذه الدراسة إلى التمييز بين دور الستيرويدات العصبية والستيرويد الطبيعي والستيرويدات الابتنائية الاصطناعية من خلال التحقق من تأثيرات بعض الفسيولوجية والمناعة والتشريح المرضي على الأعضاء المستهدفة المختلفة مثل الكلى والكبد والطحال في الفئران المصابة بفرط شحميات الدم.

من أجل تحقيق هذه الأهداف ، قمنا بشكل عشوائي بتقسيم **50** من الجرذان البيضاء إلى خمس مجموعات متساوية. تم استخدام المجموعة الأولى التي تم تغذيتها على نظام غذائي قياسي وحقنها تحت الجلد بـ **0.5** مل من محلول ملحي عادي كمجموعة ضابطة ، بينما تم استخدام المجموعة الثانية ، والتي كانت بمثابة مجموعة ضابطة لفرط شحميات الدم ، على نظام غذائي عالي الدهون. المجموعة الثالثة ، الجرذان المصابة بفرط شحميات الدم ، تم إعطاؤها عن طريق الفم باستخدام **DHEA** (كعلاج عصبي ، **17.2** مجم / كجم / يوم) ، المجموعة الرابعة ، جرذان مفرطة الشحميات ، تم حقنها تحت الجلد بالهيدروكورتيزون (على هيئة ستيرويد طبيعي ، **26.1** مجم / كجم / يوم) . أخيرًا ، تم حقن المجموعة الخامسة من الجرذان المصابة بفرط شحميات الدم عن طريق الحقن العضلي باستخدام سوستانون (على شكل ستيرويد ابتنائي ، **66.9** مجم / كجم / أسبوع).

توصلت الدراسة إلى أن الفئران التي تعاني من فرط شحميات الدم أظهرت تحسنًا في مستويات الدم وتحسنات إنترلوكين **IL-2** مع **DHEA** ، وسكر الدم الصائم ووزن الجسم مع **Sustanon** ، وملف الدهون مع كل من الهيدروكورتيزون والسوستانون ، وقد تدهورت وظائف الكلى تقريبًا في جميع المجموعات المعالجة ، وأخيراً كان هناك تغييرات مختلفة في الفحص المرضي للكلى والكبد والطحال.

أخيرًا ، توصلت الدراسة إلى الاستنتاجات التالية: يمكن لإدارة **DHEA** تحسين المناعة وتخفيف تلف الأنسجة في الطحال. قد يحسن الهيدروكورتيزون من الدهون ، على الرغم من آثاره السلبية على المناعة وصحة الأنسجة. للسوستانون تأثيرات إيجابية على مستوى الجلوكوز والدهون في الدم ، ومع ذلك ، فإن آثاره على المناعة ليست واضحة بما فيه الكفاية.

الكلمات الدالة: ديهيدرو إيبياندروستيرون والهايدروكورتيز والسوستانون داء فرط شحميات الدم.