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Original Article

Effect of Long-Term Treatment with Dexamethasone on the Liver and Kidney Histopathology, as well as Blood Biochemistry in Male Rabbits (*Lepus Cuniculus*)

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Abstract

Glucocorticoids have a wide range of pharmacological activities. Generally speaking, the steroid drugs, such as dexamethasone (DEX) can have severe side effects on the histology of different organs. In fact, glucocorticoids have been known as powerful medicines which can cure inflammation and work with the immune system to treat a wide range of health problems. Therefore, this study aimed to investigate the effects of DEX on the histological changes of the liver and kidney, as well as blood biochemical parameters. In total, 13 specific pathogen-free male *Lepus cuniculus* rabbits aged 8-10 months old, with a mean weight of 1.12±0.13 kg were randomly divided into three groups. Group I (n=3) did not receive DEX, and they only received saline solution as a placebo (control). In Group II (n=5), the animals received 0.25 mg DEX/kg body weight/day for a period of 56 days, and the animals in Group III (n=5) received 0.5 mg DEX/kg body weight/day for 56 days. Blood was aspirated from the rabbit's marginal ear vein. All blood samples were centrifuged at 3000×g for 10 min to separate serum samples. Blood lipids and trace elements (zinc, copper, calcium, and iron) were measured. The microscopical analyses of the liver and kidney tissues were performed through the observation of the histological changes in the tissues. The results showed a significant ($P \leq 0.05$) decrease in the body and organ weight, as well as serum concentrations for the trace elements. On the other hand, lipid profile showed a significant increase ($P \leq 0.05$) in cholesterol, triglycerides, and low-density lipoprotein. However, a significant decrease was recorded in high-density lipoprotein in both treated groups with DEX, compared to the control group. The results of the histological evaluation showed some degrees of degeneration, necrosis, cell vacuolation, and lymphocyte infiltration in the kidney and liver tissues in the treatment groups.

Keywords: Dexamethasone, Essential Mineral, Histology, Lipid Profile

1. Introduction

Dexamethasone (DEX) is a member of the glucocorticoid class of hormones. Furthermore, it is a corticosteroid indicated for allergic states, dermatologic diseases, endocrine disorders, gastrointestinal diseases, hematologic disorders, neoplastic diseases, nervous system, ophthalmic diseases, renal diseases, respiratory diseases, and rheumatic disorders. It is well-documented that the metabolism of most tissues is affected by glucocorticoids influencing several functions in tissue(s) which together produce a pattern of metabolic changes. Many glucocorticoids' main effects have consequently resulted from the stimulation of the synthesis of specific enzymes. To exhibit glucocorticoids effects, they penetrate the cell membrane and bind to receptor proteins. The hormone-

receptor complex binds in the cell nucleus, thereby influencing ribonucleic acid (RNA) and protein synthesis. Therefore, macromolecular synthesis may be required for even inhibitory or catabolic steroid actions. Other types of steroids may also act as glucocorticoids or antiglucocorticoids by interacting with the glucocorticoid receptors (1).

In several tissues, such as muscle, skin, and lymphoid, the catabolic actions of glucocorticoids resulted in a significant decrease in synthesis and an increase in the degradation of protein and RNA. Glucocorticoids inhibit glucose and amino acid uptake in many instances and enhance lipolysis in the adipose tissues. The inhibitory actions form a basis for glucocorticoid suppression of immunologic and inflammatory responses, wound healing, blood lymphocytes and eosinophils, as well as the bone matrix. In the liver, these steroids stimulate a number of enzymes and an increase in protein and glycogen content, while inhibiting only a few functions. There is an enhanced hepatic capacity for gluconeogenesis, which with substrate from catabolism elsewhere, results in increased glucose production. The integrated effects of glucocorticoids result in hyperglycemia, negative nitrogen balance, and fat loss. However, glucocorticoid actions are countered by other hormones, most notably insulin, which is stimulated in response to hyperglycemia, thereby partly reversing some of the metabolic changes. Glucocorticoids enhance or permit certain actions of other hormones. The latter usually stimulates the production of cyclic adenosine 3′,5′-monophosphate (cyclic AMP). In fact, the patterns of glucocorticoid and cyclic AMP actions in conserving glucose are generally parallel. As with cyclic AMP and other types of steroids, glucocorticoids may play a more important role in fetal cellular and tissue differentiation than previously appreciated (2).

In most cases, glucocorticoids are not used for their influences on glucose and protein metabolism; however, they are employed in higher doses since they are broadly anti-inflammatory (3), and their uses fit into several groups. Central nervous system disorders, immune suppression, cancer chemotherapy, shock, blood calcium reduction, as well as DEX also have some use in pregnancy termination in dogs (4-6). DEX is a chemical synthetic derivative of the glucocorticoid hydrocortisone, and it is used in the treatment of metabolic diseases (e.g., Ketosis) in ruminants and inflammatory diseases in a number of animal species; however, DEX is commonly used for several weeks or even months at a time to get a chronic process under control. It has an important role that the dose be tapered to an every third-day chart once the condition is controlled. The reason for this is that body will understand the presence of these hormones and do not produce any of its own. In time, the adrenal glands will atrophy so that when the medication is discontinued, the patient will be unable to respond to any stressful situation. An actual circulatory crisis can be the result. The use of the medication every other day allows the body's own adrenal glands to remain active (6). This study aimed to investigate the effects of oral administration of DEX on the profiles of blood biochemical parameters and histological states of the liver and kidney.

2. Materials and Methods

2.1. Animals

In total, 13 specific pathogen-free male *Lepus cuniculus* rabbits aged 8-10 months old, with a mean weight of 1.12±0.13 kg were used in the current study. The animals were confined in cages and kept with a meal and water in the Veterinary Medicine College of Basrah University, Iraq, at 30±2.3°C and under a 12-h light-dark cycle. The animals were acclimatized for one week and divided randomly into three groups. Group I (GI) (n=3) did not receive DEX, and they only received saline solution as a placebo (control). The animals in Group II (GII) (n=5) received 0.25 mg DEX/kg body weight/day for 56 days; moreover, Group III (G III) (n=5) received 0.5 mg DEX/kg body weight/day for 56 days. The animals were weighed every four days during the whole experiment (56 days).

2.2. Blood Sampling, Serum Lipids Measurements, and Trace Element Concentration

Blood was aspirated from the rabbit's marginal ear vein with Venoject (BD Life Sciences, Cockeysville, Md, USA) without any anticoagulants. All blood samples were centrifuged at 3000×g for 10 min. After centrifugation, the supernatant was carefully separated. The blood serum was stored in the refrigerator at -20°C until used. Blood lipid measurement (cholesterol, triglyceride, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) was conducted using a Chemistry Auto Analyzer (Boehringer Mannheim, Germany, Munich). Flame atomic absorption spectrometry was also used for the determination of the serum zinc, copper, calcium, and iron.

2.3. Organ Weight

At the last day of the experiment, all animals were euthanized with chloroform in close plastic cages. The animals were dissected, the liver and kidneys were isolated, and they were weighted in each group.

2.5. Histological Analyses

The microscopical analyses were made through the observation of the changes in the histological tissues of the liver and kidneys. For the microscopic analysis, at the end of the experiment (after 56 days), the animals were killed, and the fragments of the liver and kidneys were removed and fixed in 10% phosphate-buffered formalin. Furthermore, the specimens were dehydrated, cleared, infiltrated, and embedded in the paraffin wax. The blocking was cut using a rotary microtome. All sections were stained by Hematoxylin and Eosin staining (7).

2.6. Statistical Analysis

Data were analyzed in SPSS software (version 21), and the results were presented as means±SD and least significant difference using one-way ANOVA. A *P*-value of ≤ 0.05 was considered statistically significant.

3. Results and Discussion

3.1. Body and Organ Weight

The results (Tables 1 and 2) were a reversal of a significant decline ($P \leq 0.05$) in body weight after 56 days of treatment in the GII and GIII, compared to the control group. Moreover, the liver and kidney organs showed a significant increase ($P \leq 0.05$) in weight, compared to the controls after 56 days at the end of the experiment (Figures 1 and 2). The DEX had an effect on the carbohydrate and protein metabolism, which led to glycosuria and a decrease in anabolism (8). A decrease in body weight may be caused by damage in the thyroid gland and a decrease in blood zinc concentration after treating by DEX (9). The decrease in the body weight may be caused by the prevention of glucose entry of cells leading to the loss of weight after acute treatment with DEX (10). In a study conducted by Smith, Erasmus (11), the results showed that DEX could negatively affect the endocrine gland functions, and thereby, led to the functional failure of the cellular metabolism process, which was associated with weight loss. The DEX-induced reductions in bone mineral mass caused a significant reduction in body growth (12). However, DEX usually caused cortisone inhibition inside the body resulting in the inhibition of the body activity and food intake (13).

Table 1. Impact of dexamethasone doses on body weight (kg) of adult male rabbits during the experiment

Days	Bodyweight (Kg)		
	Control	Group II	Group III
1	1.15±0.110[a]	1.23±0.210[a]	1.17±0.190[a]
7	1.13±0.12[a]	1.20±0.11[a]	1.13±1.010[a]
14	1.18±0.210[a]	1.15±0.160[a]	1.08±0.085[a]
28	1.21±0.140[a]	1.01±0.070[b]	0.99±0.012[b]
56	1.28±0.098[a]	0.95±0.011[b]	0.87±0.014[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 2. Impact of dexamethasone doses on the organ weight (g) of adult male rabbits after the experiment (56 days)

Organ weight	Groups		
	Control	Group II	Group III
Kidney	0.71±0.023[a]	0.95±0.013[b]	1.19±0.041[c]
Liver	3.50±0.07[a]	4.18±0.031[b]	4.81±0.04[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

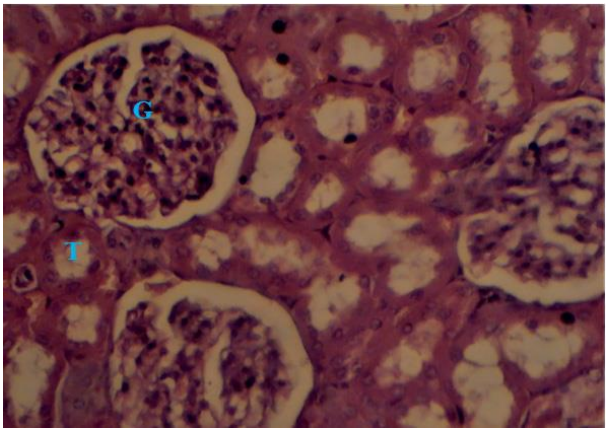

Figure 1. Section of the kidney in the control group showing normal glomeruli (G), normal proximal, and distal tubules (T) (H&E 400×)

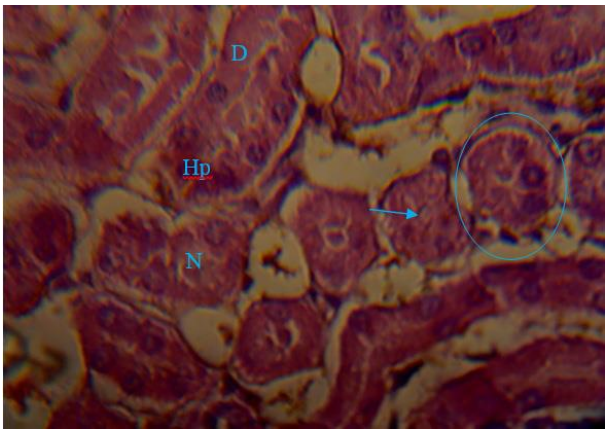

Figure 2. Section of the kidney in the GII (0.25 mg/kg/day); Dexamethasone administration for 56 days showing a hyper pigment (Hp), degeneration of tubular cells (D), necrosis of tubular cells (N), hypertrophied cells (circle), and lumen diminished in proximal tubules (arrow) (H&E 400×)

3.2. Profile of Serum Lipids

Table 3 illustrates the effect of daily oral administration of DEX (0.25 and 0.5 mg/kg body weight/day) on lipid profile among the male rabbit serum samples in the treatment groups. The recorded data from GII and GIII showed a significant increase ($P \leq 0.05$) in serum cholesterol. The highest values for cholesterol were shown at days 28 and 56 of the experiment, compared to the control. In addition, the triglyceride concentration in serum recorded a significant increase ($P \leq 0.05$) in the treatment groups (GII and GIII), compared to the control group. The highest values for triglyceride were shown on days 28 and 56 of the experiment, compared to the control (Table 4). Although the serum HDL showed a significant decrease ($P \leq 0.05$) in the treatment groups (GII and GIII), compared to the control group, the lowest values were recorded at days 28 and 56 of the experiment (Table 5).

On the other hand, the serum LDL concentration was apparently increased ($P \leq 0.05$) in the treatment groups (GII and GIII), compared to the controls, and the highest values were shown on days 28 and 56 of the experiment, compared to the control. Plonné, Schulze (14) mentioned that DEX caused an increase in lipid production by the liver cells and an increase in insulin resistance, which led to insulin disability and inhibited the action of enzymes that transported lipids into tissue cells. However, DEX may cause a decrease in mononuclear cells motility and inhibit the cholesterol analysis (15). Severino, Brizzi (2) showed an increase in blood cholesterol in the treated rabbits by DEX due to the inhibition of nitric oxide synthesis, which plays an important role in cholesterol regulation. DEX was scientifically proven to cause insulin resistance, which leads to a decrease in the insulin effect on the liver and fatty tissue, causing an increase in triglycerides and lipoprotein secretion in the blood (16).

DEX has the ability to stimulate the production and secretion of LDL, which is very rich in triglycerides

(14). It is concluded from different research results that DEX injection was a causative agent in increasing cholesterol, LDL, and triglyceride, as well as a reduction in HDL in blood serum (17). DEX showed a high ability to inhibit the catabolism of low protein and lipids (LDL) in the liver by blocking their receptors located on the surface of cell membranes (18).

Table 3. Impact of dexamethasone doses on the serum cholesterol concentration (mg/dl) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	77.4±2.1[a]	73.8±3.1[a]	74.1±1.9[a]
7	74.3±1.9[a]	86.9±2.4[b]	93.9±2.4[c]
14	70.9±3.1[a]	94.9±3.1[b]	101.7±3.1[b]
28	72.3±2.9[a]	95.3±2.6[b]	130.4±4.9[c]
56	76.1±3.2[a]	100.8±2.8[b]	146.8±5.6[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 4. Impact of dexamethasone doses on the serum triglyceride concentration (mg/dl) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	55.8±1.4[a]	58.9±2.1[a]	57.7±2.1[a]
7	57.1±2.1[a]	68.9±2.3[b]	78.9±2.7[c]
14	54.9±1.8[a]	77.4±3.1[b]	88.9±3.4[c]
28	58.9±1.9[a]	86.9±3.1[b]	101.2±4.2[c]
56	57.7±2.4[a]	94.7±3.4[b]	126.4±3.3[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 5. Impact of dexamethasone doses on the serum HDL (mg/dl) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	33.4±1.4[a]	34.7±1.3[a]	35.1±1.9[a]
7	34.9±1.7[a]	32.9±1.9[ab]	30.9±2.2[b]
14	36.3±2.01[a]	28.7±1.1[b]	25.7±2.4[b]
28	37.1±1.4[a]	25.8±2.1[b]	20.9±1.3[c]
56	35.5±1.5[a]	21.9±3.1[c]	20.1±1.7[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

3.3. Serum Trace Elements

The results showed a significant decrease in the serum zinc, copper, calcium, and iron levels in the treatment groups (GII and GIII) ($P \leq 0.05$) during the experiment, and lower values was recorded on days 28 and 56, compared to the control group (Tables 6-10). The lowest values were obtained at 5.01±0.13, 1.01±0.015, 4.55±0.34, and 6.51±0.63 for zinc, copper, calcium, and iron, respectively in the GIII, compared to the values of the GII and control groups. The results of a study conducted by Eid, Ebeid (4) confirmed that the oxidative stress had occurred after treatment with DEX, which negatively affected the functional activity of the oxidative enzymes due to a decrease in zinc concentration. Singh and Singha (19) revealed that the glucocorticoid induced stress and caused a decrease in zinc concentration. However, the response of the serum level of the copper may depend on the changes in the rate of synthesis of the serum copper-binding protein which is called ceruloplasmin, which causes rapid excretion with urine out of the body (20). Weiler, Wang (12) noted a significant decrease in calcium concentration in the blood after treatment with DEX. The results of the current study attribute that to DEX that causes a defect in the function of the intestines and kidneys to reabsorb calcium.

Lukert and Raisz (21) confirmed that DEX may reflect a reduction in calcium transport across the cellular membrane of enterocytes to the mesentery and cause a decrease in the calcium level in blood. The present study recorded a decrease in blood iron that was caused by oral DEX, which reflects the reason for producing and releasing cytokines, such as IL-1 and IL-6 (22). It may be due to the nutritional deficiency caused by a decrease in food intake due to the effect of DEX (23).

Table 6. Impact of dexamethasone doses on the serum LDL (mg/dl) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	7.8±0.51[a]	8.3±0.63[a]	7.8±0.71[a]
7	8.2±0.64[a]	10.45±0.85[b]	13.4±0.59[c]
14	7.7±0.48[a]	13.1±0.59[b]	18.9±1.3[c]
28	8.14±0.56[a]	16.8±0.71[b]	23.87±1.4[c]
56	8.05±0.71[a]	20.4±1.3[b]	28.9±1.1[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 7. Impact of dexamethasone on serum zinc concentration (µg/ml) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	13.4±0.63[a]	14.65±0.88[a]	13.9±0.81[a]
7	15.81±0.81[a]	11.38±0.55[b]	10.11±0.51[b]
14	14.4±0.19[a]	10.92±0.45[b]	7.71±0.32[c]
28	15.77±0.89[a]	7.45±0.56[b]	5.44±0.15[c]
56	14.66±0.61[a]	7.13±0.44[b]	5.01±0.13[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 8. Impact of dexamethasone on serum copper concentration (µg/ml) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	3.11±0.08[a]	3.04±0.064[a]	3.01±0.043[a]
7	2.98±0.04[a]	2.41±0.051[b]	2.17±0.081[b]
14	3.08±0.07[a]	1.98±0.035[b]	1.78±0.063[b]
28	3.41±0.095[a]	1.78±0.025[b]	1.22±0.026[c]
56	3.08±0.11[a]	1.49±0.034[b]	1.01±0.015[c]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

Table 9. Impact of dexamethasone on serum calcium concentration (µg/ml) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group I	Group II
1	12.4±1.04[a]	11.45±1.13[a]	10.98±1.08[a]
7	11.39±1.01[a]	10.33±1.08[ac]	8.11±0.89[c]
14	11.58±1.1[a]	8.81±0.88[b]	7.05±0.61[c]
28	12.85±1.24[a]	8.05±0.68[b]	6.11±0.45[c]
56	11.88±1.31[a]	6.18±0.48[b]	4.55±0.34[c]

Significant differences ($P \leq 0.05$).
(Small letters refer to significant differences horizontally).

Table 10. Impact of dexamethasone on serum iron concentration (µg/ml) of adult male rabbits during the experimental period

Days	Experimental Groups		
	Control	Group II	Group III
1	12.33±1.15[a]	11.14±1.08[a]	11.97±1.21[a]
7	11.45±1.04[a]	9.75±1.11[b]	9.44±0.92[b]
14	12.41±1.17[a]	8.65±1.04[b]	8.15±0.79[b]
28	11.44±1.09[a]	8.03±0.98[b]	7.43±0.98[b]
56	12.60±1.33[a]	7.97±0.95[b]	6.51±0.63[b]

Significant differences ($P \leq 0.05$).
Small letters refer to significant differences horizontally.

3.4. Histological Study

The histological examination of the kidney in the control group showed the normal size and shape of the renal glomeruli and the renal tubule (Figure 1). After 56 days post dosing with oral DEX in the GII (0.25 mg/kg body weight/day), the main histological changes in the kidney of rabbits included a hyper pigment and degeneration of tubular cells, cell necrosis, hypertrophied cells, and lumen diminished in proximal tubules (Figures 2 and 3). Moreover, the results showed the absence of lumen in proximal tubules, hemorrhage, and infiltration of lymphocytes (Figures 4 and 5). On the other hand, the dosing with oral DEX in G III (0.5 mg/kg body weight /day) revealed the shrinkage and absence of the glomerulus and expansion of space inside the Bowman's capsule; in addition, degeneration in cells, necrosis, and absence of lumen were observed in proximal tubules (Figures 6-8). The dosing with oral DEX in GIII (0.5 mg/kg body weight/day) showed separation, adhesion part of glomerular with Bowman's capsule, as well as epithelial and pyknotic of glomerular cells with dense aggregations of inflammatory cells (Figures 9 and 10). The histological examination of the liver for the control group shows the normal size and shape of the central vein, hepatic plate of the hepatocytes, and hepatic sinusoids (Figure 11). Figures 12 and 13 represent 56 days after dosing with oral DEX in the GII (0.25 mg/kg/day), and the main histological changes in the liver of rabbits included a mild aggregation of inflammatory cells. Hypertrophy, degeneration, and

necrosis of hepatocytes, as well as congestion of central vein and cytoplasmic vacuolation of hepatocytes, were also noticed. The dosing with oral DEX in the GIII (0.5 mg/kg body weight/day) showed the congestion of central vein, aggregation of inflammatory cells, and fibrosis states; moreover, necrosis and degeneration of hepatocytes, expansion of the hepatic sinusoids, as well as pyknotic of hepatic nuclear and hypertrophy of hepatocytes were observed (Figures 14-16). At the end of the study, the differences in impact intensity on the kidney tissue structure were evident between GII and GIII. However, the control group showed no changes in the kidney tissue during the experiment. Martins, Monteiro (24) reported that glucocorticoids could intervene in the development of several tissues, presenting a higher influence in organs, such as the liver, lungs, and kidneys.

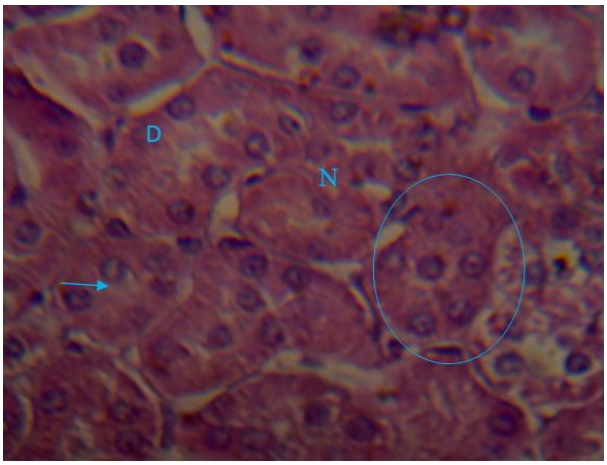

Figure 3. Section of the kidney in the GII (0.25 mg/kg/day); Dexamethasone administration for 56 days showing hypertrophied of cells (circle), degeneration tubular cells (D), necrosis tubular cells (N), absence lumen in proximal tubules (arrow) (H&E 400×)

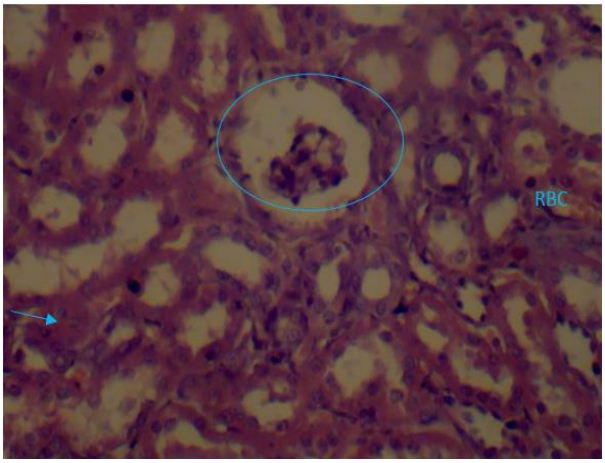

Figure 4. Section of the kidney of GI group (0.25mg/kg/day) dexamethasone of 56 day showing Shrinkage of glomerulus (circle) hemorrhage (RBC) and absence lumen in proximal tubules (arrow) (H and E X400)

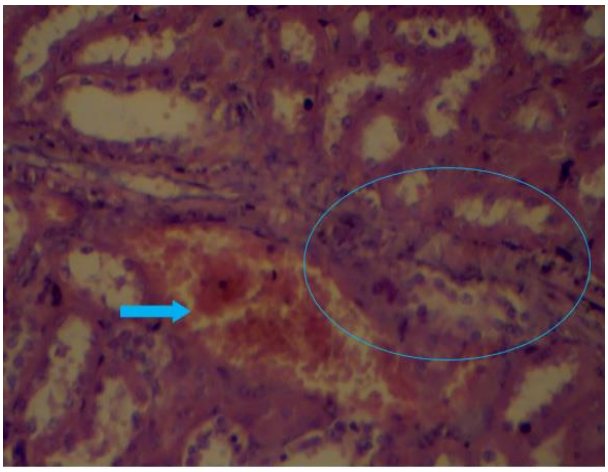

Figure 5. Section of the kidney of GI group (0.25mg/kg/day) dexamethasone of 56 day showing hemorrhage (arrow) and inflammation infiltration (circle) (H and E X400)

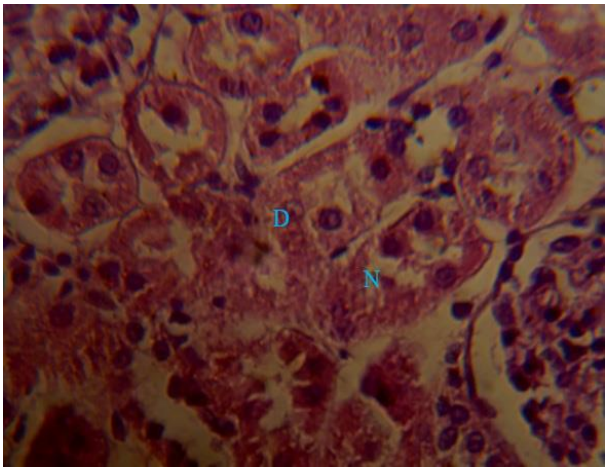

Figure 6. Section of the kidney in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing a degeneration in tubular cells (D) and necrosis in tubular cells (N) (H&E 400×)

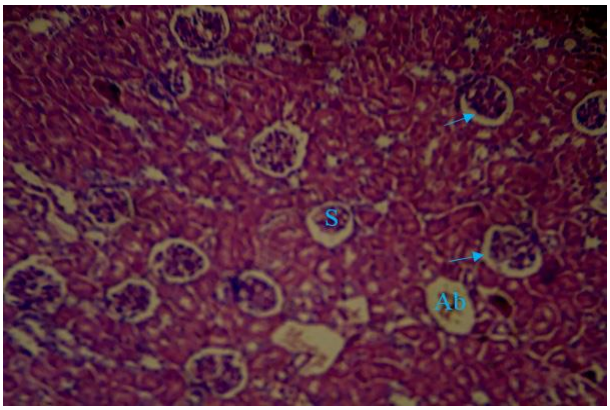

Figure 7. Section of the kidney in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing shrinkage (S), absence of glomerulus (Ab), and expansion of space inside the Bowman's capsule (arrow) (H&E 400×)

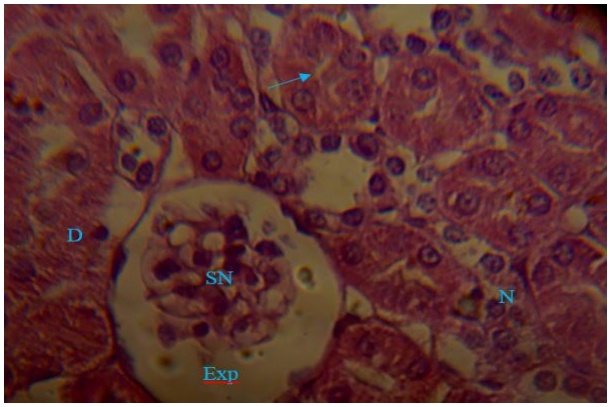

Figure 8. Section of the kidney in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing shrinkage and necrosis of glomerulus's (SN), expansion of space inside the Bowman's capsule (Exp), degeneration in tubules cells (D) necrosis in tubules cells (N), vacuolation of tubules cells (V), and absence of lumen in proximal tubules (arrow) (H&E 400×)

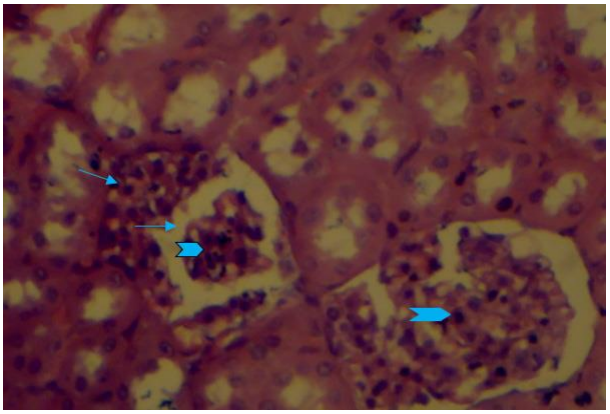

Figure 9. Section of the kidney of GII group (0.5mg/kg/day) dexamethasone of 56 day showing separation and adhesion part of glomerular with bowman's capsule epithelial (arrow) and pyknotic of glomerular cells (head arrow). (H and E X400).

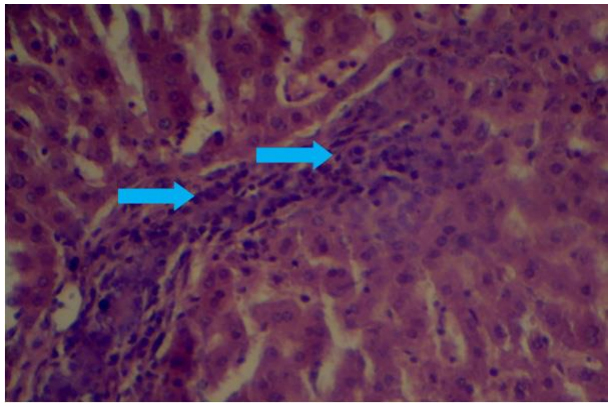

Figure 10. Section of the kidney of GII group (0.5mg/kg/day) dexamethasone of 56 day showing Dense aggregations of inflammatory cells (arrow) (H and E X400).

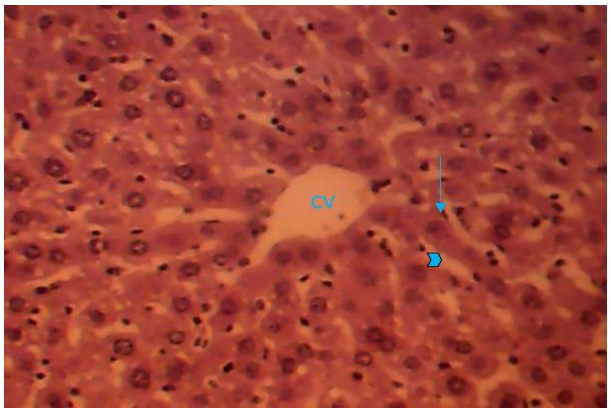

Figure 11. Section of the liver in the control group showing normal central vein (CV), normal hepatocyte (arrow), and sinusoid (arrow head) (H&E 100×)

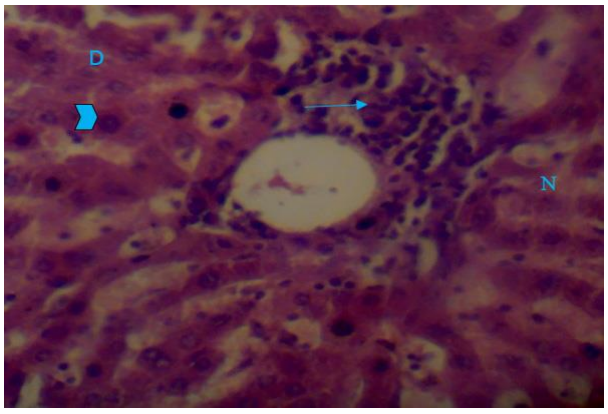

Figure 12. Section of the liver of GI group (0.25mg/kg/day) dexamethasone of 56 day showing mild aggregations of inflammatory cells (arrow), degeneration (D) and necrosis (N) of hepatocytes, hypertrophy of hepatocytes (arrow head). (H and E X400).

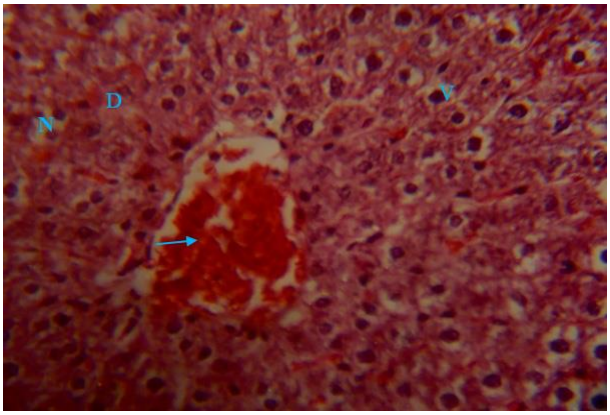

Figure 13. Section of the liver in the GII (0.25 mg/kg/day); Dexamethasone administration for 56 days showing congestion (arrow), degeneration (D), cytoplasmic vacuolation (V), and necrosis (N) of hepatocytes (H&E 400×)

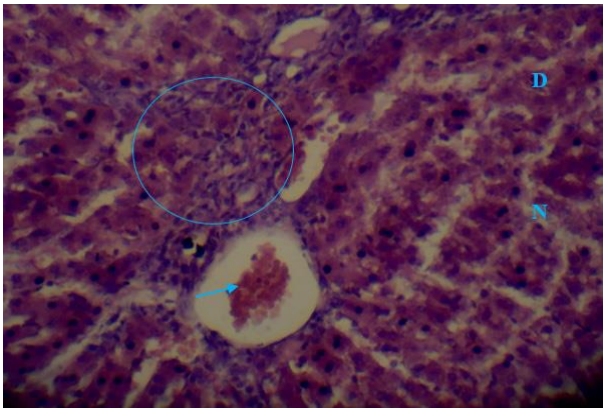

Figure 14. Section of the liver in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing the congestion of central vein (arrow), inflammation and fibrosis (circle), necrosis (N), and degeneration (D) of hepatocytes (H&E 400×)

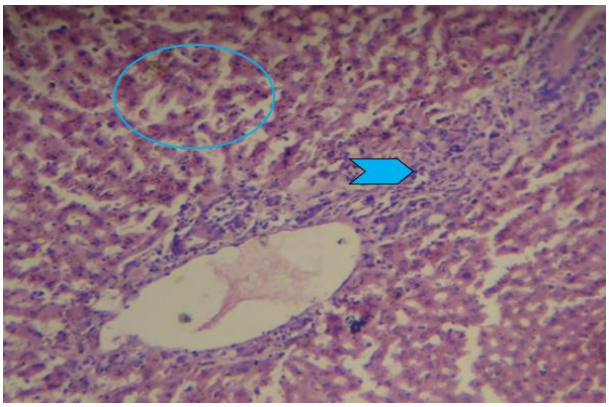

Figure 15. Section of the liver in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing inflammation in cells and fibrosis (arrow head), expansion of the hepatic sinusoids (Circle) (H&E 100×)

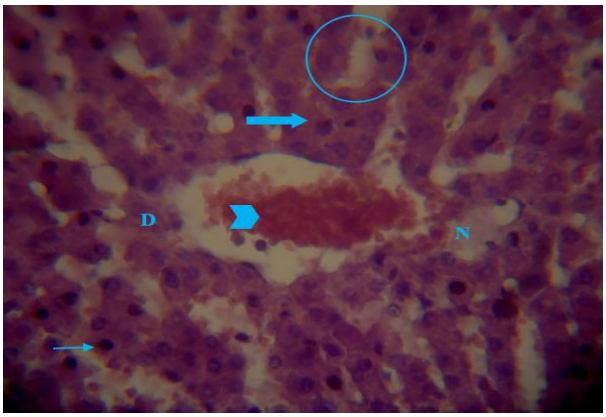

Figure 16. Section of the liver in the GIII (0.5 mg/kg/day); Dexamethasone administration for 56 days showing the congestion of central vein (arrow head), pyknotic of hepatic nuclear (arrow), necrosis (N), degeneration (D) of hepatocytes, expansion of the hepatic sinusoids (circle), and hypertrophy of hepatocytes (thick arrow) (H&E 400×)

Over the tissue of these organs, the DEX may lead to a modification in the patterns of insulin activity in the plasmatic and tissue lipid profile and changes in the patterns of proliferation and cellular deaths. Júnior, Teixeira (25) reported that the treatment with DEX during 5 days of pregnancy did not lead to weight gain and resulted in no changes in the development of the liver and kidneys of the neonate rats. Giannopoulos, Hassan (26) demonstrated the sites of specific cytoplasmic binding for DEX in the thymus, liver, lung, kidney, skin, muscle, heart, small intestine, and brain of the rabbit fetuses, as well as the spleen, kidney, small intestine, liver, thymus, and lung of the adult rabbits. Fetuses of the rabbits appeared at 28-30 days of gestation, and the concentration of the specific binding sites for DEX was higher (1.62 to 1.83 pmoles/mg of DNA) in the placenta and kidney, respectively, somewhat lower (0.69 to 1.25 pmoles/mg of DNA) in the skin and muscle respectively, and much lower (0.35 to 0.49 pmole/mg of DNA) in the liver and thymus, respectively. However, the analysis of the sucrose density gradient of tissue extracts showed the presence of one or two DEX-macromolecular complexes sedimenting at 7 to 8S and 4S. Moreover, 7 to 8S complex was present in all tissues; however, the 4S complex was revealed only in the small intestine, liver,

kidney, and spleen (27). The results explain the presence of DEX-binding components (receptors) in an assortment of fetal and adult rabbit tissues. Generally, it is believed that an early step in the sequence of events that mediate the impacts of steroid hormones on their target tissues is the interaction of the hormones with specific cytoplasmic receptors. However, glucocorticoids are known to affect an assortment of tissues, and the presence of proteins that bind glucocorticoids and have been specifically noticed in each of the hepatoma tissue culture cells, fibroblasts, lymph sarcoma, liver, thymus, brain, and kidney. It suggested that in addition to the kidney and liver, which are usually regarded as the target tissues for glucocorticoids, several of the other rabbit tissues may also be targeted for these hormones (28).

Authors' Contribution

Study concept and design: M. F. A. and N. H. J.
Acquisition of data: N. H. J.
Analysis and interpretation of data: N. H. J.
Drafting of the manuscript: D. A. K.
Critical revision of the manuscript for important intellectual content: M. F. A.
Statistical analysis: B. A. M. A. A.
Administrative, technical, and material support: M. F. A.

Ethics

All the procedures were approved by the ethics committee of the , University of Basrah, Basrah, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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