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Histological Study of The Effect of Administration of Exogenous Glucocorticoids on the Testis of Albino Rats

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ABSTRACT

Glucocorticoids are prescribed by many physicians to treat inflammatory conditions that affect the different body organs as lungs, skin, joints, digestive tract and eyes. Common diseases that frequently require treatment with glucocorticoids include bronchial asthma, inflammatory bowel syndrome and some types of arthritis. Cortisol is the principal circulating glucocorticoids in human and is secreted under the control of the hypothalmo-pituitary-adrenal axis. Dexamethazone is a synthetic pregnane corticosteroid and derivative of cortisol (hydrocortisone). It was first made in 1957 and is used in the treatment of many conditions, including rheumatic problems, a number of skin diseases, severe allergies, bronchial asthma, chronic obstructive lung disease, croup in children, brain and spinal cord surgery. Also cortisol has frequently been indicated as a major factor mediating the suppressive effect of stress on reproductive system problems because the stress interferes with the function of the brain-pituitary-gonad (BPG) axis so prolonged elevated cortisol levels, implicated in stress adaptation, inhibit pubertal development in the male gonads.

The aim of the work is to study the histological changes that may occur in the albino rat testis after administration of dexamethasone and to investigate the possibility of recovery of testis after drug stoppage.

Thirty prepubertal male albino rats were used in this study and divided into three equal groups. Group I (control), group II (dexamethasone-treated for 2 weeks) and Group III (recovery group) it manage as group II, then left untreated for further 2 weeks for studying the possibility of testicular recovery. At the time of animal sacrifice, the testes of all groups were dissected out, processed and stained with H&E. and toluidine blue stains then examined by light microscope.

Histological examination of the sections of the testes of the dexamethasone treated group showed that the seminiferous tubules attained different shapes and had lost the normal distribution of their epithelial lining with the appearance of several layers of dark type spermatogonia that were ensheathed by the irregular basement membrane. The lumina of the affected tubules contained exfoliated germ cells. Also some germ cells showed apoptosis with small peripheral nuclei. Leydig cells appeared with peripherally located nuclei. Histological examination of the sections of the testes of the dexamethasone recovery group had manifested still distorted seminiferous tubules with no absolute return to its normal histological structure. So in clinical practice, therapeutic doses and periods of administration of dexamethasone must be carefully adjusted especially in younger ages.

INTRODUCTION

Glucocorticoids are prescribed by many physicians to treat inflammatory conditions that affect the different body organs as lungs, skin, joints, digestive tract and eyes. Common diseases that frequently require treatment with glucocorticoids include asthma, inflammatory bowel disease and some types of arthritis. Cortisol is the principal circulating glucocorticoids in human and is secreted under the control of the hypothalmo-pituitary-adrenal axis (WeiL et al., 2004).

The human male reproductive system includes the testis, the ductus deferentes, the seminal vesicles, the ejaculatory ducts, and the penis, together with the prostate and the bulbourethral glands (Guyton and Hall, 2015).

The major reproductive organs of the male rats are the testes which are located in the scrotal sac. The epididymis is a coiled tube located on the surface of the testis, which collects and stores sperm cells. The tubular vas deferens transmits sperm from the epididymis to the urethra, which carries sperm through the penis and out the body (John, 2009).

The brown glands located to the left and right of the urinary bladder are the seminal vesicles. The gland below the bladder is the prostate gland and it is partially wrapped around the penis. The seminal vesicles and the prostate gland secrete materials that form the seminal fluid (semen) (Robert, 1989).

Glucocorticoids bring about their multiple effects by activating the intracellular glucocorticoids receptor that binds to specific glucocorticoids-responsive elements in the vicinity of regulated genes and subsequently affects their expression. It is estimated that glucocorticoid receptors can interact as transcription factors for about 30% of genes, so it is not surprising that glucocorticoids induce a wide range of responses (Walker BR., 2007).

Stress interferes with reproduction and the functioning of the brain-pituitary-gonad (BPG) axis and cortisol has frequently been indicated as a major factor mediating the suppressive effect of stress on reproduction. Prolonged elevated cortisol levels, implicated in stress adaptation, inhibit pubertal development in male (Consten D et al., 2002).

The effects of glucocorticoids on different organs were widely studied, but studies concerning the influence of glucocorticoids on the testes before puberty were scarce. So, the present study aims to investigate the histological changes that may occur in the prepubertal albino rat testis after administration of glucocorticoids and to study the possibility of recovery of testis after drug stoppage.

MATERIALS AND METHODS

This study was carried out on 30 prepubertal male albino rats aged from 3 to 7 weeks. The animals were supplied by the laboratory Animal Unit, Al-Azhar University. They were housed at room temperature, fed standardized diet and tap water. These animals were divided into three equal groups (ten rats each):

•Group I (Control Group):

They were further subdivided into two equal subgroups:

Subgroup IA (rats aged 3-4 weeks) that was used as a control group for the dexamethasone-treated group.

Subgroup IB (rats aged 7 weeks) that was used as a control group for the dexamethasone-recovery group.

Rats were injected with saline intra-peritoneally, in the same doses and periods corresponding to the experimental groups.

•Group II (Dexamethasone-Treated Group):

Rats of this group (3-4 weeks age) were injected daily intraperitoneally with dexamethasone (7 mg/kg body weight) for 2 weeks, then were sacrificed
(Yazawa H *et al.,* 2000).

•Group III (Dexamethasone-Recovery Group):

Rats of this group (3-4 weeks age) were injected daily intraperitoneally with the same dose of dexamethasone for 2 weeks as group II , then left untreated for further 2 weeks for studying the possibility of recovery. At the time of sacrifice, the experimental animals and corresponding control were anaesthetized by ether inhalation. The testes were dissected out carefully from each animal without damage to tunica albuginea and were fixed in Bouin's fixative for 24 hours, processed for light microscopy to get (5µm) paraffin section and stained with hematoxylin and eosin (H & E) stain (Bancroft JD and Gamble M, 2002).

Specimens were dehydrated, embedded in epoxy resin. Sections were obtained and stained with toluidine blue and examined by the light microscope at the research's unit of Anatomy Department, Faculty of Medicine, Al-Azhar University.

RESULTS

•Group I (Control Group): All control subgroups (I-A and I-B) showed nearly the same histological finding. Light microscopic examination of the sections of the testes revealed that the parenchyma of testis was formed of rounded seminiferous tubules. Most of them attained narrow lumina and lined by stratified germinal epithelium (Figs.1and 2).

The epithelium was formed of several types of spermatogenic cells: spermatogonia, primary spermatocytes, spermatids, spermatozoa and Sertoli cells. Spermatogonia appeared as small rounded cells, resting on a thin basement membrane and had rounded nuclei. Primary spermatocytes were larger in size than the spermatogonia with large rounded nuclei. Early spermatids appeared as small rounded cells with paler nuclei. Sertoli cells appeared as column cells in-between spermatogonia. The tubules were separated by the interstitium that contained groups of interstitial Leydig cells with acidophilic cytoplasm. The epididymal tissue showed partially filled average tubules lined by normally vacuolated epithelial cells (Fig. 3).

Examination of toluidine blue stained sections from the testis of the same group showed that the stratified epithelium of seminiferous tubules had the same features as in H & E. Sertoli cells with pale oval nuclei were seen lying on the basement membrane in-between the germ cells. The seminiferous tubules were ensheathed by flattened myoid cells with flattened nuclei. The interstitial tissue showed groups of interstitial leydig cells with small vacuoles and blood capillaries (Fig.4).

•Group II (Dexamethasone-Treated Group):

Examination of H & E stained testis sections of dexamethasone injected albino rats showed the seminiferous tubules that attained different shape (Figs.5 and 6).

The seminiferous tubules had lost the normal distribution of their epithelial lining with the appearance of several layers of dark type spermatogonia not one layer as in

control. The lumina of the affected tubules contained sloughed germ cells.The basement membrane of the seminiferous tubules was irregular and disrupted. It was ensheathed by myoid cells . The interstitial tissue exhibited groups of Leydig cells with irregularly shaped nuclei,some collagen fibers and congested blood capillaries (Fig.7).

Some germinal epithelial cells appeared apoptotic. Apoptotic germinal epithelial cells appeared with bright acidophilic cytoplasm and small eccentric nuclei (Fig.8).

The cytoplasm of Sertoli cells contained multiple vacuoles.

Examination of the toluidine blue stained sections of testes of the same group revealed seminiferous tubules that ensheathed by irregular basement membrane. The seminiferous tubules were lined by vacuolated germinal epithelium (Fig. 9).

•Group III (Dexamethasone-Recovery Group):

Light microscopic examination of the sections in the recovery group revealed distorted seminiferous tubules with loss of the normal distribution of their epithelial lining and presence of several layers of dark type spermatogonia. Sloughed germ cells were also seen in their lumina. The cells of the stratified germinal epithelium were still containing multiple vacuoles in their cytoplasm. The basement membrane of the seminiferous tubules was disrupted. (Figs. 10 and 11)

Apoptotic germ cells were still present in some areas. However, other areas showed mild recovery in the form of seminiferous tubules with average epithelial lining, average basement membrane and average interstitium that showed leydig cells. (Fig. 12)

Examinatoin of toluidine blue-stained sections of the testes of the same group showed seminiferous tubules with thin germinal lining and less prominent interstitium. However, other areas showed intact basement membrane, average interstitium and average germinal lining (Figs. 13 and 14).

DISCUSSION

Corticosteroids are potent medications that have been extensively used to treat many inflammatory and autoimmune conditions. They have two groups: glucocorticoids and mineralocorticoids. Glucocorticoids play a vital role in the maintenance and regulation of immune and circulatory functions (Wilson JD *et al.,* 1989). Also, it was reported that synthesis of cortisol can increase 5 to 10 fold under conditions of severe stress, to a maximal level of approximately 100 mg/m2/day (Deshmukh CT *et al.*, 2007.

In the present study, examination of the sections of the testes of the dexamethasone treated group showed that the seminiferous tubules attained different shapes and had lost the normal distribution of their epithelial lining with the appearance of several layers of dark type spermatogonia. The lumina of the affected tubules contained exfoliated germ cells. These results were in agreement with the finding of some of researchers who attributed the exfoliations of these cells to retraction of the cytoplasmic processes of the Sertoli cells, which extend between the different layers of germ cells and support them. So the cells became loosely arranged and were easily sloughed out (Rai J *et al.*, 2003).

Also, some germ cells showed apoptosis with small peripheral nuclei while spermatids were not seen in this group. Leydig cells appeared with irregularly shaped nuclei. These findings were in agreement with previous investigators who observed that chronically elevated

glucocorticoids have adverse effects on the reproductive system. They found that glucocorticoids affect both steroidogenesis, spermatogenesis and cause spermatogenic arrest at a certain level of germ cells. Also, they reported that glucocorticoid receptor has been found on Leydig cells, early pachytene and zygotene primary spermatocytes, peritubular myoid cells, fibroblasts and basal cells of the epididymis (Page KC *et al.,* 2001; Nair N *et al.,* 2002).

The regulation of spermatogenesis depends primarily on an interaction between Follicle-Stimulating Hormone (FSH) and testosterone. FSH plays a key role in the development of immature testis by stimulating Sertoli cell proliferation and later progression of A- to B-spermatogonia. Testosterone alone can maintain complete spermatogenesis, but the synergistic action of FSH is necessary to normalize quantitative aspects pf spermatogenesis. This effect is explained by FSH-dependent formation of Androgen-Binding Protein (ABP) by the Sertoli cells which accumulate androgens in the tubules (Walker WH *et al.,* 2005; Ortega Pacheco A *et al*., 2006).

Some investigators added that there are no receptors for FSH or testosterone on germ cells and hence there are intermediate steps in this action, the nature of which are unknown. However, as the Sertoli cell contains receptors for both FSH and testosterone, it is likely that these hormones exert their influence on germ cells by modulating Sertoli cell function (Sofikitis N *et al.,* 2008).

It was reported that the onset and regulation of puberty are determined by the functional development of the Brain-Pituitary-Gonad (BPG) axis. Chronically elevated cortisol levels affected all parts of the (BPG)- axis. Moreover, it is suggested that cortisol acts directly on Sertoli cells and/or on germ cells and induces retardation of testicular development (Goos HJ and Consten D., 2002).

It was also mentioned that glucocorticoids are important for spermatogenesis in pigs and are regulated via 11β-hydroxysteroid dehydrogenase (11β-HSD) as an inactivator of cortisol (the active form of cortisone). The amount of 11β-HSD in germ cells was greatest at birth, then decreased after and was absent after age of 3 weeks (Wagner A and Claus R., 2008).

Other authors added that glucocorticoids act on Leydig cells directly, through the classic Glucocrticoid Receptor (GR) and that access to the GR is controlled by a metabolizing pathway mediated by 11β-HSD. This enzyme is bidirectional (with both oxidase and reductase activities) and in the rat testis is exclusively localized in Leydig cells where it is abundantly expressed and may catalyze the oxidative inactivation of glucocorticoids (Hu GX *et al.,* 2008).

On the other hand, it was reported that high levels of corticosteroids have inhibitory effects on testosterone production from Leydig cell steroidogenesis which appeared to be mediated through inhibition of LH signal transduction (Sankar BR *et al.,* 2000). However, some authors mentioned that cortisol has a direct inhibitory effect on the testicular androgen secretion independent of the LH secretion (Consten D *et al.,* 2002).

In confirmation with the previous data, some researchers stated that glucocorticoids decrease testosterone production in mouse Leydig cell cultures. Also, corticosteroids induced Leydig cell apoptosis (Tomlinson JW *et al.,* 2004; Chai WR *et al.,* 2007).

The apoptosis induced by glucocorticoids was explained by previous researchers. They reported that glucocorticoid hormone binds to the glucocorticoid receptor in the cytoplasm of target cells and the formation of a complex between the ligand and the receptor regulates gene expression of the glucocorticoid response elements that affect the expression of regulated genes (Yazawa H *et al.*, 2000).

In the present study, there was the apparent increase in the populations of Sertoli cells. Some Sertoli cells appeared with multiple vacuoles. These results were consistent with research report of other workers who stated that Sertoli cells extend their proliferation as a result of a delay in their differentiation leading to an increase in Sertoli cell number. The vacuoles of Sertoli cells might be accumulated lipid droplets resulting from phagocytosis of degenerating cells by the Sertoli cells (Wang H *et al.*, 2006).

In confirmation with the above results, it was mentioned that at all stages of differentiation, the spermatogenic cells are in close contact with Sertoli cells which are thought to provide structural and metabolic support to the developing sperm cells (Ross MH and Pawlina W., 2005).

In the present work, the animals of the recovery group had manifested still distorted seminiferous tubules with no absolute return to the normal distribution of epithelial lining with the presence of several layers of dark type spermatogonia. Sloughed germ cells were also seen in the lumen. The basement membrane of the seminiferous tubules was irregular and disrupted in some areas. The cells of stratified germinal epithelium were still containing multiple vacuoles in their cytoplasm. These observations were in accordance with previous studies that mentioned that the pubertal period is critical to the influence of cortisol regarding testicular androgen secretion, because mitosis occurred in both germ cells and Sertoli cells in this age (Francavilla S *et al.*, 2000).

It was mentioned that the specific activities of testicular lipogenic enzymes decreased after dexamethasone injection in prepubertal and adult rats. These changes in the specific activities of enzymes reverted back to normal after dexamethasone withdrawal in adult animals. However, dexamethasone injected intact prepubertal animals did not revert back to normal after the hormone withdrawal (Consten D *et al*., 2002; Dong Q *et al.*, 2004).

Some authors found that the concentration of the glucocorticoid receptors in rat seminiferous tubules revealed an age-dependent decrease, coinciding with the increase in the number of germ cells. Glucocorticoid receptor levels were higher in Sertoli cells from immature rats than in cells from adult rats (Larry J *et al*., 2008).

Some investigators mentioned that Sertoli cell is the only somatic cell type in seminiferous tubule epithelium that plays a critical role to endocytose and degrade residual bodies and apoptotic spermatogenic cells (Pineau C *et al.*, 1991; Miething A., 1992).

CONCLUSION

The present work showed that dexamethasone injection for 2 weeks produced changes in the histological structure of albino rat testes. Also, this work showed incomplete recovery of these changes after drug withdrawal. So, in clinical practice dexamethasone adverse effects must be taken into consideration for fear of infertility. The therapeutic doses of dexamethasone and periods of administration must be carefully adjusted especially in younger ages.

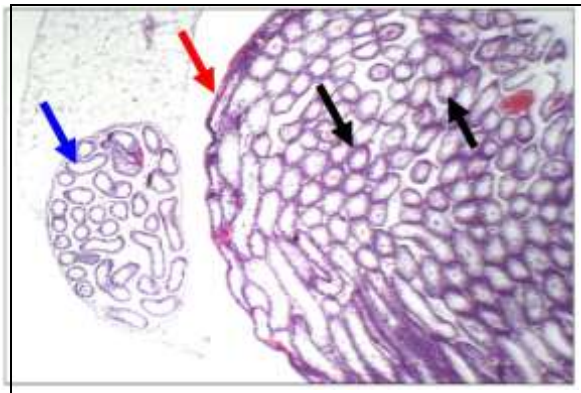

Fig. (1): A photomicrograph of a transverse section in the testis of control albino rat showing closely-packed well formed semineferous tubules with relatively thick lining (black arrows), normal tunica albuginea (red arrow) and small-sized empty epididymal tubules (blue arrow). (H&E stain X 100)

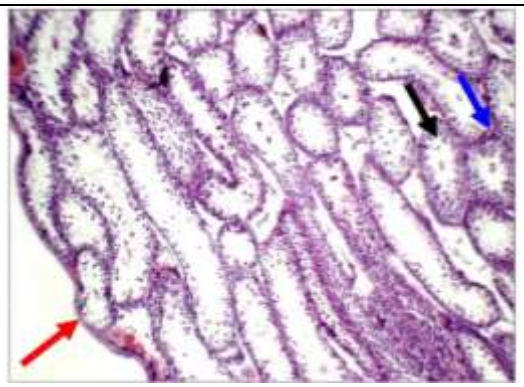

Fig. (2): A photomicrograph of a transverse section in the testis of control albino rat showing closely-packed well formed semineferous tubules with relatively thick lining (black arrow), normal tunica albuginea (red arrow) and less prominent interstitium (blue arrow). (H&E stain X 200)

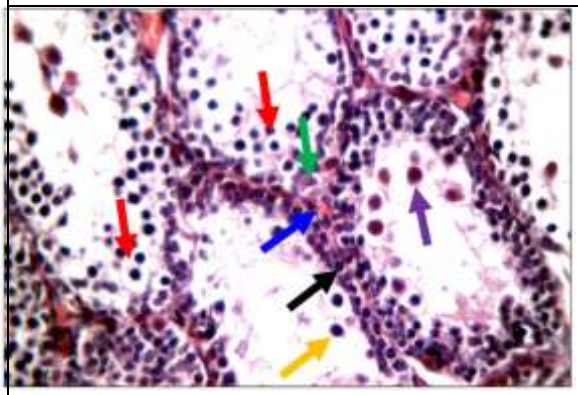

Fig. (3): A photomicrograph of a transverse section in the testis of control albino rat showing semineferous tubules lined by multiple layers of germinal epithelium; spermatogonia (black arrow), primary spermatocytes containing vacuoles (red arrows), Sertoli cells (green arrow), few scattered rounded spermatids (yellow arrow), desquamated epithelial cells (violet arrow) and less prominent interstitium showing few leydig cells (blue arrow). (H&E stain X 400)

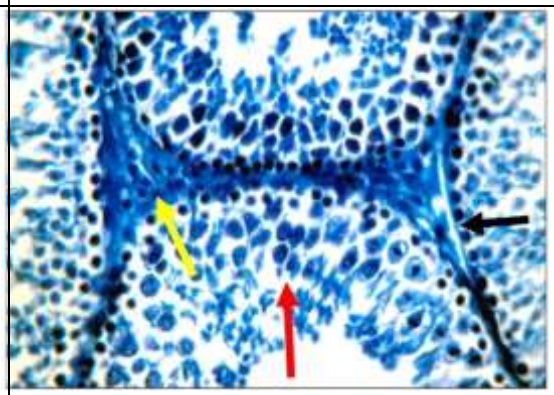

Fig. (4): A photomicrograph of a transverse section in the testis of control albino rat showing semineferous tubules with normal germinal lining (red arrow), normal interstitium (yellow arrow), and intact basement membrane (black arrow) . (Toluidine blue stain X 400)

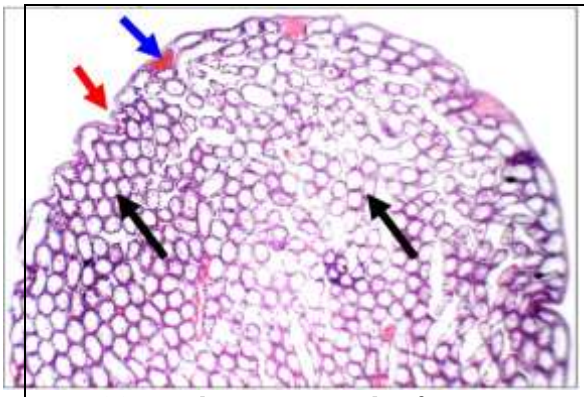

Fig. (5) :A photomicrograph of a transverse section in the testis of treated rats group II showing closely-packed well-formed small sized tubules with relatively thin lining (black arrows), irregular tunica albuginea (red arrow) showing dilated congested blood vessels (blue arrow). (H&E stain X 100)

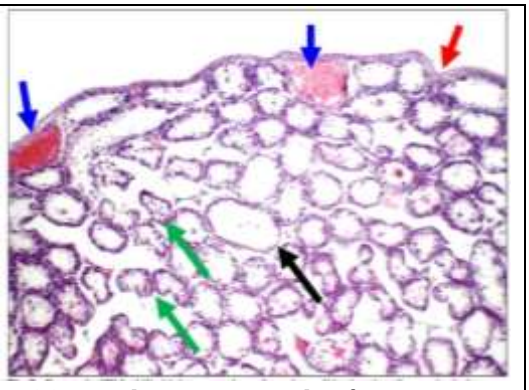

Fig. (6): A photomicrograph of a transverse section in the testis of treated rats group II showing distorted tubules (green arrows) with relatively thin lining (black arrow), irregular thick tunica albuginea (red arrow) showing dilated congested blood vessels (blue arrows) (H&E stain X 200)

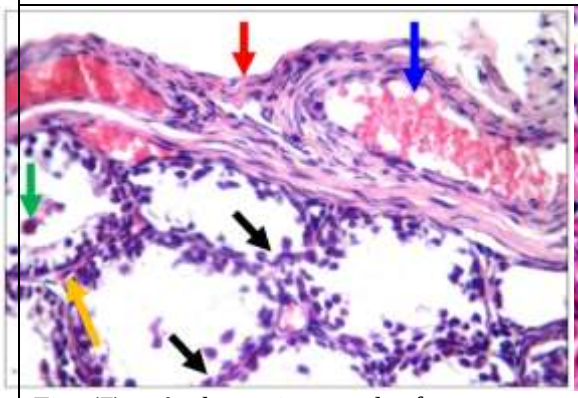

Fig. (7): : A photomicrograph of a transverse section in the testis of treated rats group II showing irregular markedly thickened tunica albuginea (red arrow) showing dilated congested blood vessels (blue arrow) with underlying tubules showing thin germinal lining (black arrows), desquamated epithelial cells (green arrow), and apparent Leydig cells (yellow arrow). (H&E stain X 400)

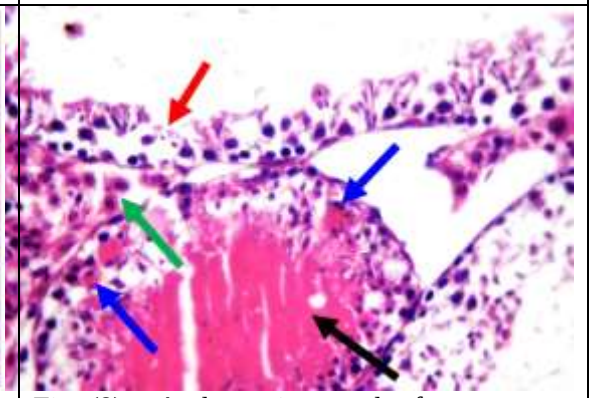

Fig. (8): : A photomicrograph of a transverse section in the testis of treated rats group II showing seminiferous tubules with thin germinal lining (red arrows), lumen filled by eosinophilic hyaline material (black arrow), apoptotic germinal epithelial cells (blue arrow), edematous interstitium showing Leydig cells (green arrow). (H&E stain X 400).

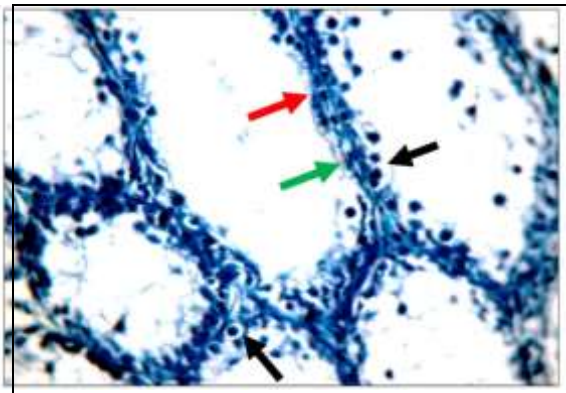

Fig. (9): A photomicrograph of a transverse section in the testis of treated rats group II showing semineferous tubules with thin germinal lining composed mainly of spermatogonia (red arrow) containing vacuoles (black arrows), and another area with no lining (green arrow) (Toluidine blue stain X 400)

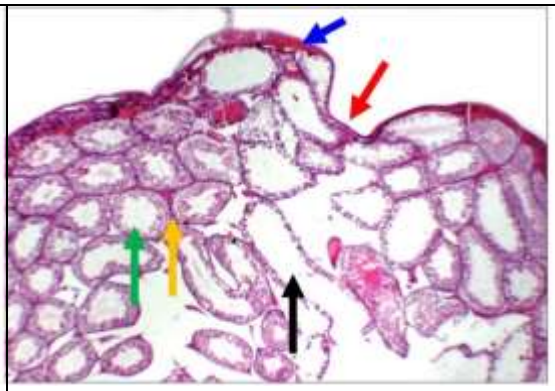

Fig. (10): A photomicrograph of a transverse section in the testis of recovery rats group III showing widely-spaced well formed semineferous tubules with relatively thin lining (black arrows), and another area showing closely-packed tubules with normal lining (green arrow) and normal interstitium (yellow arrow), irregular tunica albuginea (red arrow) showing dilated congested blood vessels (blue arrow). (H&E stain X 100)

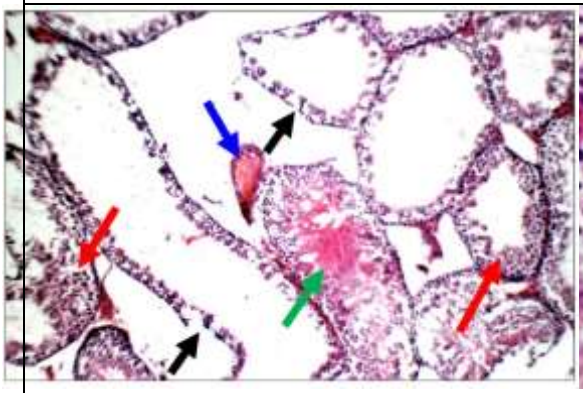

Fig. (11): A photomicrograph of a transverse section in the testis of recovery rats group III showing widely-spaced tubules with thin lining and disrupted basement membrane in area (black arrows), and other tubules with normal lining (red arrows), and another tubule showing eosinophilic hyaline material (green arrow), with interstitial congested blood vessels (blue arrow). (H&E stain X 200)

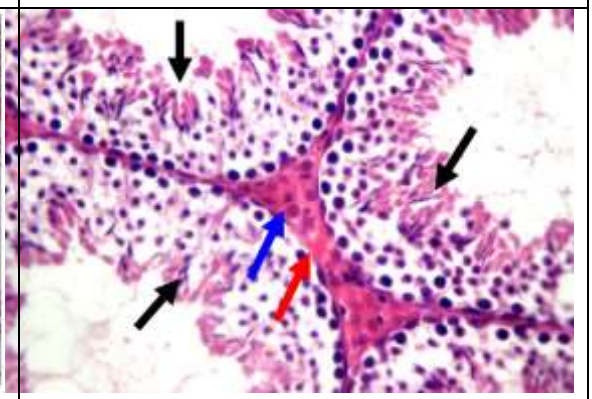

Fig. (12): A photomicrograph of a transverse section in the testis of recovery rats group III showing tubules with normal germinal lining with maturation up to sperm formation (black arrows), intact basement membrane (red arrow) and normal interstitium showing Leydig cells (blue arrow) . (H&E stain X 400)

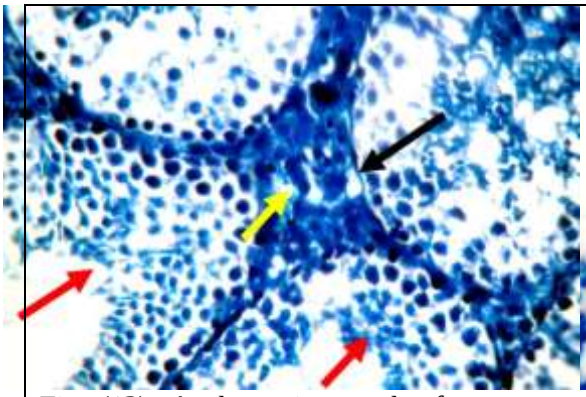

Fig. (13): A photomicrograph of a transverse section in the testis of recovery rats group III showing semineferous tubules with normal germinal lining (red arrows), normal interstitium (yellow arrow), and intact basement membrane (black arrow) . (Toluidine blue stain X 400)

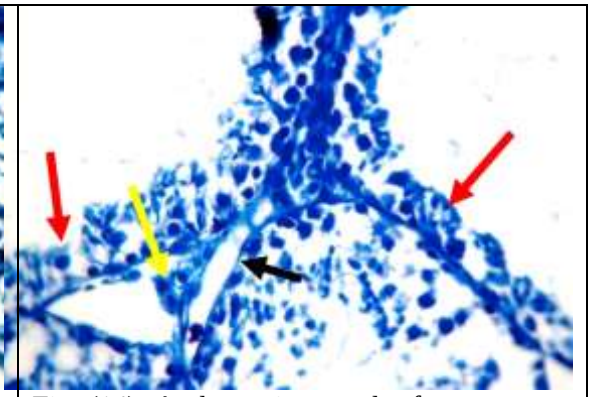

Fig. (14): A photomicrograph of a transverse section in the testis of recovery rats group III showing semineferous tubules with thin germinal lining (red arrows), less prominent interstitium (yellow arrow), and intact basement membrane (black arrow).(Toluidine blue stain X 400)

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ARABIC SUMMERY

دراسه هستولوجيه علي تأثير إعطاء الجلوكوكورتيكويد الخارجي علي خصية الجرذان البيضاء

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يعتبر عقار الكورتيكوستروييد من العقارات الفعاله التي تستخدم بطريقة واسعة في معالجة كثير من الالتهابات والحالات المناعية بالرغم من وجود أثار جانبية له، ولذلك اجري هذا البحث لدراسة التغيرات الهستولوجية التي قد تحدث في نسيج خصي الجرذان البيضاء بعد اعطائها عقار الديكساميثازون (أحد مشتقات الكورتيزون) مع دراسة امكانية عودة الخلايا والانسجة الى طبيعتها الاولي بعد وقف اعطائه.

وقد استخدم في هذه الدراسة ثلاثون من ذكور الجرذان البيضاء، تم تقسيم الحيوانات الى ثلاث مجموعات متساوية: المجموعة الاولى ضابطة والمجموعة الثانية تم حقنها عبر الغشاء البريتوني بجرعه يومية بلغت ٧ مجم /كجم لمدة اسبوعين بينما المجموعه الثالثة أعطيت الديكساميثازون مثل المجموعه الثانية ثم تم ايقاف اعطاؤه لمدة اسبوعين اخرين. وعند نهاية التجربة تم تشريح الخصي من جميع الحيوانات بعد تخديرها وتم تحضيرها للفحص بالمجهرالضوئي.

وقد اظهر الفحص الهستولوجي لخصي حيوانات المجموعة الثانية (المعالجة بالديكساميثازون) وجود تغيرات في النسيج الطلائي المبطن لمعظم الانيبيبات المنوية مع وجود خلايا جرثومية ومنوية ذات انوية داكنة بينما احتوت خلايا سرتولي على فجوات عديدة. كما أظهرت النتائج أن هذه التغيرات لم تتحسن تحسنا ملحوظا بعد وقف اعطاء الديكساميثازون. .

من نتائج هذه الدراسة نستنتج أن عقار الديكساميثازون أحدث تغيرات ضارة في التركيب الهستولوجي لخصي الجرذان البيضاء وأن هذه التغيرات لم تتحسن تحسنا ملحوظا بعد توقف اعطاؤه ولذلك يجب أخذ هذا التأثير في الاعتبار أثناء الاستخدام الاكلينيكي له وخصوصا في الاعمار الصغيرة مع مراعاة ضبط الجرعات المأخوذة وفترات اعطاؤه.