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Original Article

The Sensitivity of Adult Male Albino Rat Prostate to Low-Dose Biphenyl A: a Histological and Immunohistochemical Study.

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ABSTRACT

Context: While, the prostate is sensitive to endocrine hormone levels; bo estrogen and androgen are critical in its growth. As a well-known endocri disruptor compounds (EDCs), bisphenol A can disturb the normal functic of these hormones and affects the prostate.

Aim of this study: Hence, this study explored the effect of the exposure low dose bisphenol A on the histology of dorsolateral prostatic lobes in adu albino rats. Also, this work aimed to highlight the roles of estrogen ar androgen.

Materials and methods: Adult (12-14 weeks, 180-200 grams) male albino rats (n = 28) obtained from the breeding animal house, Faculty of Medicine, Zagazig University. These rats were randomly equally divided into two main groups: **control group I** and **bisphenol A treated group II.** The rats in group II received 50 mg/kg BPA dissolved in 0.5ml corn oil by oral gavage once daily for 4 weeks. At the time of sacrifice, all rats were anesthetized with ether and blood samples were collected for various biochemical parameters. The prostate glands were dissected out and processed for different histological analysis.

Results: These results showed that BPA at low dose may have deleterious alterations on the prostate and disturbed reproductive hormones.

Conclusion: It would be imperative to phase out BPA from its uses and healthcare goods in favour of safer alternatives. Also, we recommended further studies need to analyze the molecular basis of these alterations.

Keywords: prostate, low dose bisphenol A, rat

INTRODUCTION

The prostate is an androgen dependent organ and has a fundamental role in the reproductive process. Androgen hormones play an essential role in normal and hyperplastic prostate growth. Their actions are mediated via androgen receptors (ARs) **[1].**

The last five decades have witnessed a progressive decline in male reproductive health due to the release of endocrine-disrupting chemicals (EDCs) into the environment. It has been recognized that Bisphenol -A (BPA) as a well-known EDC. BPA is used primarily as a monomer to manufacture polycarbonate plastics and epoxy resins. It is present in water pipes, lining of metal cans, all disposable plastics **[2]**. Previous experimental animal studies, **[3, 4]** have demonstrated adverse effects on male reproductive health due to BPA exposure. Though the male reproductive toxicity of BPA has been studied but the underlying mechanisms have not been well elucidated.

Moreover, few literatures were available to elucidate the alterations in the male accessory genital glands due to BPA. So, the aim of our study was to clarify the possible structural alterations in the dorsolateral prostatic lobe (DLP) of adult albino rats as a result of exposure to a low dose of BPA.

Materials and methods: Chemicals

Bisphenol A (BPA) is odorless white crystalline powder (purity >97%). Its CAS No was 80-05-7. It was purchased from Sigma-Egypt.

Animals: Twenty eight healthy adult male albino rats (12-14 weeks, 180-200 grams) (Wister strain) were utilized in this study. They were obtained from the breeding animal house, Faculty of Medicine, Zagazig University. Throughout the duration of the experiment, the rats were housed in clean cages and kept under the same environmental

conditions regarding light, feeding and temperature. They were allowed ad-libitum access to food and water. All rats received care in compliance with the guidelines of the Medical Research Ethics Committee of Zagazig University, Egypt (The protocol approval number was ZU-IACUC/3/F/55/2019).

Animals: Twenty eight healthy adult male albino rats (12-14 weeks,180-200 grams) were utilized in this study. They were obtained from the breeding animal house, Faculty of Medicine, Zagazig University. Throughout the duration of the experiment, the rats were housed in clean stainless steel cages and kept under the same environmental conditions regarding light, feeding and temperature. They were allowed ad-libitum access to food and water. All rats received human care in compliance with the guidelines of the Medical Research Ethics Committee of Zagazig University, Egypt (The protocol approval number was ZU-IACUC/3/F/55/2019) and was conformed to the National Institutes of Health guide for the care and use of laboratory animals.

All animal experiments comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals.

Experimental design

Control group (I): Included fourteen rats were received no treatment.

BPA treated Group (II): fourteen rats were received 50 mg/kg BPA dissolved in 0.5ml corn oil by oral gavage once daily **[5]** for 4 weeks **[6].**

At the designated time, (after 4 weeks), the rats were anaesthetized by ether inhalation. Venous blood samples were obtained from the retro-orbital plexus as described by **[7].** Intra-cardiac perfusion was carried out through the heart apex with 300 ml of 2.5% gluteraldehyde in 0.1 mol/l cacodylate buffer (pH 7.3) for 5 min for partial fixation of the glands. A midline lower abdominal incision was performed and the prostate glands were taken out. The right DLP were dissected and immediately processed for light microscope and immunohistochemical study.

Biochemical analysis: The samples were collected at a fixed time to minimize the diurnal variation**.** Total serum testosterone hormones in samples were assessed by an enzyme-linked immunosorbent assay (ELISA)**.** Total testosterone fluctuates quite a bit during the day. Testosterone levels are highest in the morning, to get the best result , we took blood samples for testosterone lab tests between 7 a.m. and 10 a.m **[8]**.

Histological study: The right DLP lobes were processed for light microscope examination. Specimens were fixed in 10% neutral formol saline. They were processed to prepare 5-µm-thick paraffin sections for H&E and Mallory trichrome staining **[9]**.

Immunohistochemical study

The paraffin sections were treated to block endogenous peroxidase by incubating in 3% H2 O2-methanol for 15min. After washing twice in phosphate buffer saline (PBS), the slides were incubated with anti-rabbit Androgen Receptor (AR) antibodies (catalogue number: ab133273). After washing in PBS, sections were incubated for 30 min. with a biotinylated swin anti-rabbit immunoglobulin (Dako, Glostrup, Denmark) and then incubated with horseradish peroxidase streptavidin biotin for 20min. (Dako Corp., Carpinteria, California, USA). After two additional washes in PBS, bound antibodies were visualized using diaminobenzidine tetra-hydrochloride (Dako Corp.). Sections were then washed in distilled water and lightly counterstained with hematoxylin **[10].** The positive results were indicated by nuclear brown coloration.

Morphometrical & statistical analysis

Statistical analysis for morphological measurement, image analysis was done for H&E stained sections of the right DLP lobes were used. They were assessed by an ordinary light microscope using Leica 500 image analyzer computer system (England) at the Image Analyzing Unit of the Pathology Department, Faculty of Dentistry, Cairo University. Statistical analysis is used for the number of positive nuclear AR immunoexpression and blood testosterone level.

RESULTS

Biochemical results: Serum testosterone level: Statistical analysis showed a highly statistically significant decrease in group II when compared to group I. **(Table 1).**

Histological results:Group I Stained sections with hematoxylin & eosin showed closely packed secretory acini of almost regular sizes and shapes. These acini showed few luminal epithelial folds and homogenous acidophilic secretions filled their lumina **(Fig. 1A).** These acini were lined by simple cuboidal to columnar epithelium with rounded to oval basal nuclei with prominent nucleoli **(Fig. 1B).** Minimal inter-acinar stroma with blood vessels was observed **(Fig. 1A &1B).** BPA treated group (II) showed disturbance of size and shape in some secretory acini with wide spaces in between them. Some acini with numerous mucosal folds were found **(Fig. 2A).** Also, luminal secretions with variable densities, pale, acidophilic and vacuolated were observed **(Fig. 2A&2B).** These acini were lined by different forms of epithelium. Some of them were lined by cuboidal to columnar epithelium **(Figs. 2B, 2D, 2E, 2F & 2G),** while, others showed flattening

of their epithelial lining **(Fig. 2C).** Numerous acini showed focal areas of epithelial proliferation and stratification **(Figs. 2D, 2E, 2F &2G)**. The abundant stroma in the wide inter acinar spaces showed mast cells and distinct intraepithelial inflammatory cells (**Fig. 2D)**, congested blood vessels and inflammatory cellular infiltration **Fig. (2E, 2F &2G).**

In toluidine blue stained sections from Group I, the prostatic acini were lined by columnar secretory cells with apical pale cytoplasm and basal rounded or oval vesicular nuclei and also flat, elongated or trigonal basal cells with darkly stained nuclei. Inter-acinar stroma showed smooth muscle cells with spindle shaped nuclei and blood capillaries **(Fig. 3A). While, group II** showed secretory acini with different types of epithelium. Nearly all prostatic acini were lined by tall columnar cells with different nuclear patterns; pale or vesicular, dark, irregular and apical foamy or vacuolated cytoplasm. In addition, many basal cells with flat or elongated darkly stained nuclei can be easily demonstrated **(Figs. 3B &3C)**. Also, numerous acini with focal stratification areas of their epithelium can be seen in several sections. Their epithelium showed irregular shaped nuclei with foamy or vacuolated cytoplasm **(Figs. 3C, 3D& 3E)**. Acinar epithelium with invading blood capillaries was observed **(Figs. 3B &3C).** A part of secretory acini with irregular thick basement membrane including smooth muscle fibers with spindle shaped nuclei were clearly clarified **(Figs. 3E).** Also, detached cells with irregular nuclei and cytoplasmic bodies can be seen in several acinar lumina **(Fig. 3E).**

Mallory trichrome stained sections Group I revealed minimal collagen fibers in the interacinar stroma **(Fig. 4A).** While, group II revealed abundant amount of collagen fibers in the interacinar stroma and around congested blood vessels **(Fig.4B)** in comparison to control group **(Fig.4A).**

Immunostaining for detection of ARs showed brown coloration localized in the nuclei of nearly all luminal acinar cells **(Fig. 5A).** While, group II showed nearly all acinar cells in all the examined sections with negative nuclear immunoreaction but, a few cells still with positive reaction **(Fig. 5B).**

Morphometrical and statistical results :

Statistical analysis to the number positive nuclear ARs immunoexpression of groups showed a highly statistically significant decrease in group II when compared to group I (P<0.001) **(Table 2)**

Table (1): Comparison between the Serum testosterone levels of the groups:

erum testosterone level (ng/ml)	Group I	Group II	P Value
Min.-Max.	5.57-7.46	2.75-3.79	<0.001*
Mean± S.D	6.041±0.387	3.087±0.341	

Table (2): Comparison between the number positive nuclear ARs immunoexpression of the groups:

Number of positive nuclear reaction	Group I	Group II	P Value
Min.-Max.	35-50	11-16	<0.001*
Mean± S.D	41.14±5.080	13.57±1.718	

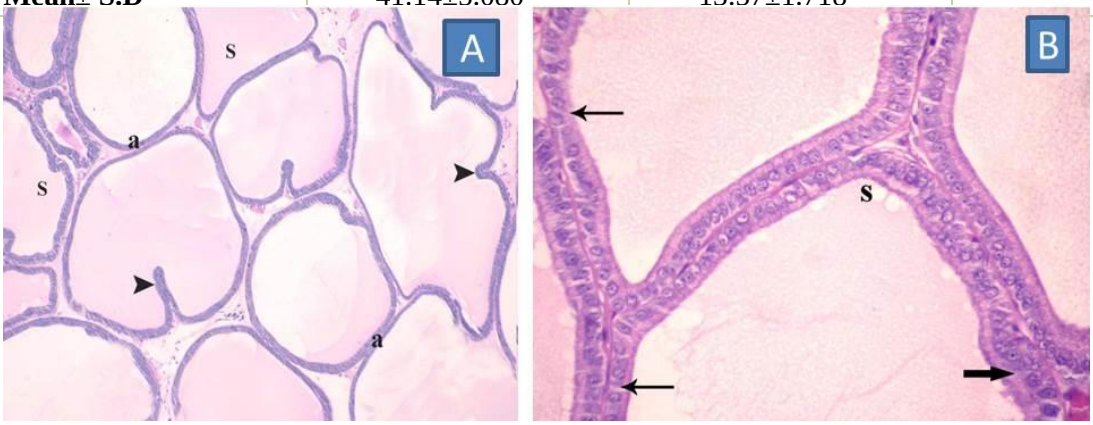

FIG.1

Figure (1): Photomicrographs of sections from right DLP of the studied groups (H &E); (A) & (B) group I (control group)

(A): secretory acini of nearly regular sizes and shap having homogenous acidophilic secretions **(s)** fill their lumina. The acinar epithelial folds are few **(arrowhead).** The interacinar area shows a minimal connective tissue **(a).** (H&E, x100)

(B): showing secretory acini lined by simple cuboidal **(thin arrow)** to columnar **(thick arrow)** epithelium with round to oval basal nuclei. Notice, few, small vacuoles in acinar secretion **(s).** (H&E, x400)

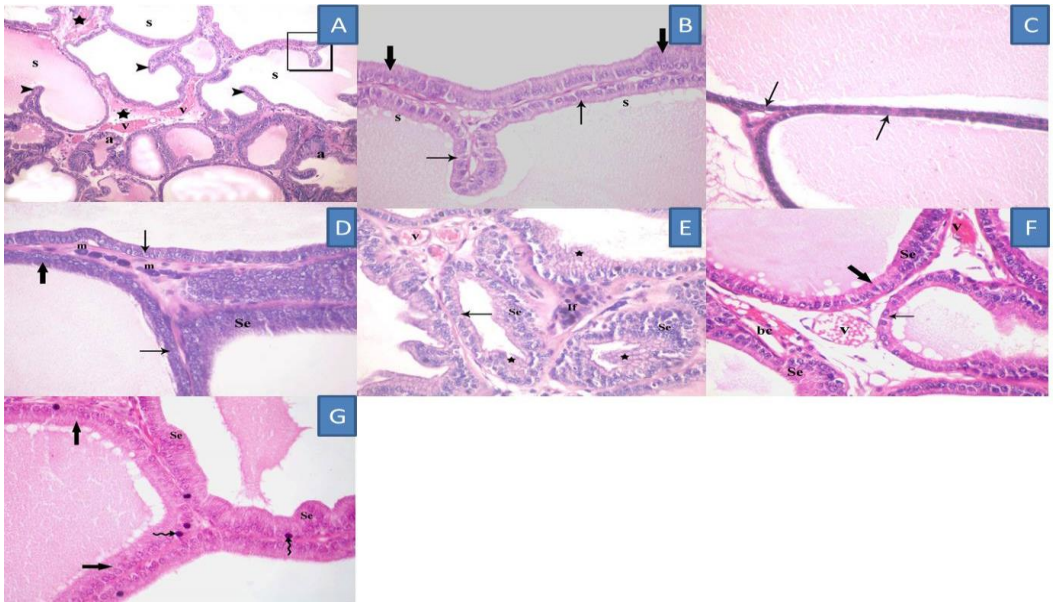

FIG.2

Figure 2: Photomicrographs of sections from right DLP of group II (H &E); (A, B, C, D, E, F, G).

(A): secretory acini of variable size and shape **(a)** having luminal secretions of variable densities **(s)**, mostly pale. The acinar epithelial folds are numerous **(arrowhead).** The interacinar area is wide and interstitial connective tissue **(star)** with numerous congested blood vessels **(v).** (H &E, x100)

(B): A higher magnification of the boxed area in the previous figure showing secretory acini lined by simple cuboidal **(thin arrow)** to tall columnar **(thick arrow)** epithelium with round to oval basal nuclei. Notice, large, numerous vacuoles in luminal secretion **(s).**

(H &E, ×400)

(C): other secretory acini lined by simple squamous **(arrow)** epithelium with darkly stained flat nuclei.

(H &E, ×400)

(D): some secretory acini lined by simple cuboidal **(arrow)** to tall columnar **(thick arrow)** epithelium with round to oval basal nuclei. Areas with stratified epithelium **(Se)** are also noticed. The wide interacinar space shows numerous mast cells **(m).**

(H &E, x400)

(E): several secretory with different lining epithelium. Some acini show stratified epithelium with darkly stained nuclei **(Se)** and vacuolated cytoplasm **(star)**.While, other parts show simple cuboidal epithelium with round nuclei **(arrow).** Numerous blood vessels **(v)** and inflamatory cellular infiltration **(If)** are noticed.

(H &E ×400)

(F): secretory acini lined by simple cuboidal **(arrow)** with round nuclei. Other acini show tall columnar **(thick arrow)** epithelium with oval nuclei. Also, acini with stratified epithelium **(Se)** and invading capillaries **(bc)** are noticed. Congested blood vessels **(v)** in the wide interacinar space are seen.

(H &E, x400)

(G): parts of secretory acini lined by simple columnar **(thick arrow)** with rounded or oval nuclei. These acini show areas of stratification **(Se).** Noticed, numerous intraepithelial inflamatory cells **(tailed arrow).**

(H &E, ×400)

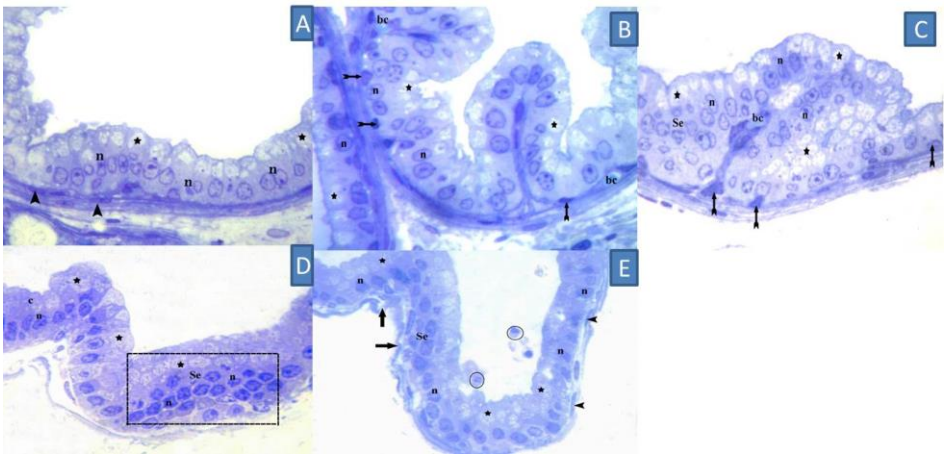

Figure (3): Photomicrographs of semithin sections in right DLP of the studied groups (Toluidine blue); (A) group I, (B, C, D, E) group II

(A): a part of secretory acinus. It shows cuboidal cells with rounded nuclei **(n)** and apical slightly vacuolated cytoplasm **(star).** Smooth muscle fibers with spindle shaped nuclei **(arrow head)** can be noticed. (Toluidine blue, x1000)

(B): parts of secretory acini with mucosal fold. They lined by tall columnar epithelium with rounded to oval nuclei **(n)** and extensive apical vacuolated cytoplasm **(star).** Also, numerous basal cells with darkly stained elongated or flat nuclei **(bifid arrow)** and invasive blood capillaries **(bc)** can be observed. (Toluidine blue, x1000)

(C): other parts of secretory acinus with stratified epithelium **(se)**. This part shows different shaped vesicular nuclei **(n)** and extensive apical vacuolated cytoplasm **(star).** Also, numerous basal cells with darkly stained elongated or flat nuclei **(bifid arrow)** and invasive blood capillaries **(bc)** can be observed. (Toluidine blue, x1000)

(D): area of high columnar epithelium **(c)** and other focal area of stratification **(square)**. It shows this different shaped darkly stained nuclei **(n)** and apical vacuolated cytoplasm **(star**). Other part of same acinus with columnar cells having irregular nuclei **(n)** and also vacuolated cytoplasm **(star)** can be seen. (Toluidine blue, x1000)

(E): a part of secretory with irregular thick basement membrane **(thick arrow)** including smooth muscle fibers with spindle shaped nuclei **(arrow head**). This acinus lined by columnar to stratified epithelium **(Se)** with irregular darkly stained nuclei **(n)** and apical vacuolated cytoplasm **(star)**. Rounded detached cytoplasmic bodies with dark nuclei **(circle)** are observed in this acinar lumen. (Toluidine blue, x1000)

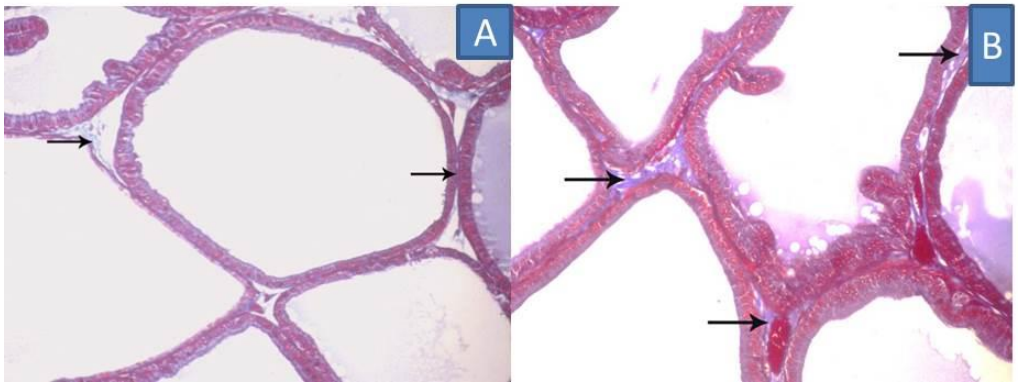

FIG.4

Figure (4): Photomicrographs of sections in right DLP of the studied groups (Mallory trichrome**)**; (A) group I, (B) group II.

(A): a minimal amount of collagen fibers **(arrow)** in the stroma (Mallory Trichrome, x400).

(B): abundant collagen fibers **(arrow)** in the stroma and around blood vessels. (Mallory Trichrome Stain, x400).

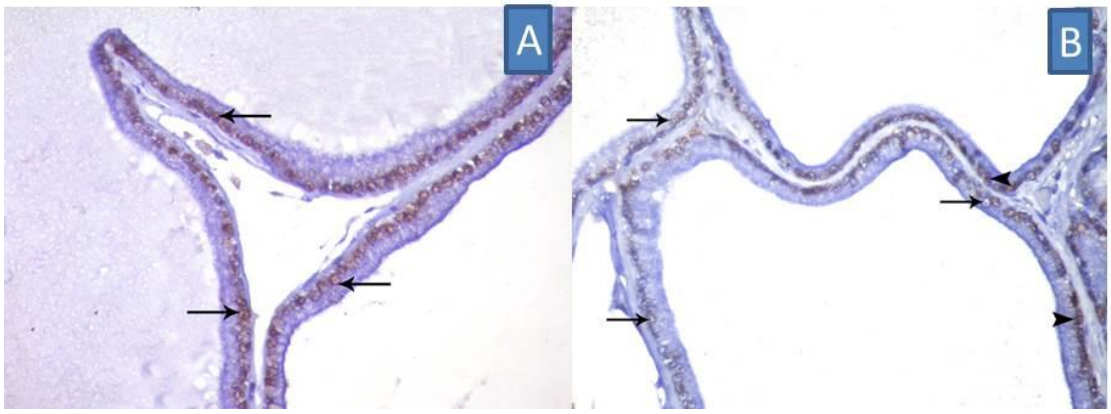

FIG.5

Figure 5: Photomicrographs of a section from right DLP of the studied groups (Immunoperoxidase technique for AR); (A) group I, (B) group II

(A): a strong positive nuclear immunoexpression of ARs **(arrow)** nearly in all luminal acinar epithelial cells. (Immunoperoxidase technique for AR, x400)

(B): negative nuclear immunoexpression of ARs **(arrow)** in numerous luminal acinar epithelial cells. Noticed, few cells with a weak positive reaction **(arrow head).**

(Immunoperoxidase technique for AR, x400)

DISCUSSION

EDCs are exogenous environmental compounds can be grouped according to their origin as follow; industrial, agricultural, residential (e.g. BPA) and pharmaceutical**.** Even heavy metals may be included in the long list of EDCs**.** Also, these chemicals display different routes of exposure; food intake and direct contact represent the most common routs EDCs may interfere with synthesis, secretion, transport and metabolism of hormones by interfering with hormonal receptors and or regulating genomic expression **[12].**

Reproduction is a definitive function of organisms. Among the factors causing male infertility, one of the most debated is the exposure to environmental contaminants. Recently, EDCs as (BPA) have drawn attention from the reproductive science community, due to its ubiquitous presence in day-to-day life. So, reproductive disorders with respect to male infertility are more common nowadays caused by EDCs. Male accessory sex glands are also vulnerable to these disruptors with adverse effects in adulthood. The (DLP) in rodents is histologically identical to the human prostate and more sensitive to low-dose BPA . Also, it might be homologous with the peripheral or transitional zones. For this reason, the morphology of the DLP was evaluated in this study. **[13]**.

In the present work, the used BPA dose was equal to the lowest dose that is commonly used to refer to environmentally relevant doses i.e., doses resulting in serum levels close to those observed in human serum **[14]**. Moreover, this dose of BPA (50mg/kg/day) was chosen as it is the Lowest Observed Effect Level (LOAEL) below which no adverse side effects could be detected **[15].**

There was a highly statistical significant decrease in group II when compared to group I regarding testosterone level. Previous authors **[16]** revealed that BPA could decrease the expression of both steroidogenic enzymes and steroidogenic acute regulatory (StAR) protein thus inhibits testosterone production by Leydig cells. In addition, others **[17]** clarified that BPA reduces testosterone synthesis and secretion by generating alterations in hypothalamic-pituitary-testicular axis.

In the current work, BPA treated group showed a wide structural variations in the DLP. Some of their secretory acini were irregular in shape and separated by abundant stroma. This stroma showed congested blood vessels, extensive mononuclear inflammatory cells with numerous mast cells and also abundant collagen fibers. Similar findings were observed by several researchers in other organs **[18, 19].** These studies declared that BPA induced organ toxicity by lowering the activities of antioxidant enzymes with elevating levels of nitric oxide (NO) and malondialdehyde (MDA). This perception describes the hypothesis that BPA also motivate antioxidants depletion, oxidative stress and release the free radicles**.** These radicals mediated the inflammatory cellular infiltration. Moreover, dilated and congested blood vessels are parts of inflammatory response, bringing more blood to degenerative areas.

In addition, **[20]** found that cyclophilin-A (CyPA) is a chaperone protein which is secreted from vascular smooth muscles as a result of reactive oxygen species (ROS). It plays a crucial role in vascular smooth muscle proliferation/migration and inflammatory cells recruitment. Moreover and recently, **[21]** stated that after BPA administration,

ROS products could also activate nuclear factor-kappa-β (NF-κβ). This pathway control and adjust pro-inflammatory cytokine production and inflammatory cells recruitment, which participate in the inflammatory response.

In the present study, mast cells with blood capillaries heavily invading the basement membrane were reported. Previous studies **[22, 23]** referred that factors as stem cell and vascular endothelial growth factors (VEGF) could produce migration of mast cells to vascularization sites by chemotactic activity. The invading capillaries are a complex phenomenon begins with degradation of the basement membrane by tryptase enzyme "a mast cell product" allowing the endothelial cells to penetrate and then proliferate. In their studies, they have related mast cells degranulation and activation with the production of new blood vessels.

This study showed increase in the collagen area in the stroma and also around blood vessels in BPA group. It has been reported that BPA could induce fibroblast hyperplasia **[24].**

Furthermore, **[25]** found that mast cell is a key player in the process of regulation and stimulation of inflammation as well as fibrous tissue formation through toll-like receptor-4 signaling and increased production of pro-inflammatory cytokine. More recently, **[26]** found that extensive thyroid fibrosis after BPA exposure was due to the increase level of lipid peroxidation and ROS.

In the current work and addition to previous mentioned results, the secretory acini were lined by different forms of epithelium. Some of them were lined by normal simple cuboidal to columnar. Others showed flattening of their lining epithelium. All these findings in different organs were observed and clarified as follow. **[27]** found a similar perceptible reduction in the height of epithelium of the epididymis of adult male rats after exposure to BPA. These results were interpreted by the low testosterone level as a result of BPA effects.

In this study, additionally, numerous basal cells with intraepithelial inflammatory cells, high columnar epithelium, focal areas of stratification and also numerous infoldings of the prostatic epithelium were observed in other acini. **[28]** found that BPA itself is mutagenic as it can cause uncontrolled proliferation which was explained by the expressions of proliferating cell nuclear antigen (PCNA).

. Also, **[29]** reported that T-lymphocytes form about 80% of prostatic inflammatory cells. Infiltrating intraepithelial lymphocytes could enhance and promote the proliferation via alteration signaling pathways.

Consistently, histological analysis of this animal model demonstrated that there were significantly increased mast cells infiltrated into the prostatic hyperplastic tissues **[30],** implicating a potential role of mast cells in enhancing benign prostatic hyperplasia (BPH) development and progression.

In the current study, the one of important degenerating findings were alteration in the nuclear pattern as; darkly stained or apoptotic, irregular or indented. Several studies were observed, confirmed and also explained these alternations**.** Furthermore, **[31, 32]** referred these findings to oxidative damage and lipid peroxidation, as a result of BPA exposure. Lipid peroxidation then stimulates endonuclease enzymes and interacts with DNA, causing DNA damage and break. These activities were expressed by nuclear deformity and irregularity.

In the current work, other degenerating findings were extensive cytoplasmic vacuolations and cellular detachment. These were observed in few prostatic acini of BPA group. Also, **[33]** referred this to the imbalance between osmotic and ionic changes which result in water imbibition. In accordance with this finding, **[34]** found sloughing of these cells that could be linked to changed expression of intercellular adhesion molecule, cadherin-10 which is an important marker for luminal cells in acini. Moreover, **[35]** stated that it could be a cellular defense mechanism against harmful substances. These injurious substances were isolated in vacuoles and blocked away from interacting with cellular metabolism.

In accordance with our findings regarding thickening of acinar basal lamina, **[36]** demonstrated that glomerular basement membrane thickening might be referred to activated glycoprotein deposition.

In the current study, the BPA-treated group showed a statistical significant decrease in AR immunoreactivity nearly in all luminal acinar cells. This result was concomitant with that of other researchers **[37].** They analyzed AR immunoreactivity to verify the effect of low dose of BPA on the rat prostate. They revealed that ARs were expressed in nuclei and cytoplasm of luminal acinar cells, but this expression less than the control group.

Androgen receptor (AR) is expressed in many organs including the hypothalamus, pituitary, prostate and testes. While, the prostate is an androgen-dependent organ so, androgen/AR are known to play a key role in regulating its function, growth and differentiation. The biological functions of androgens are primarily mediated by these receptors signaling. Upon binding to its endogenous androgens (testosterone & dihydrotestosterone), the AR undergoes a conformational change and translocates from the cytoplasm to nucleus to bind androgen response elements (ARE), thus regulating

the transcription of growth factors **[38, 39]**. In fact, this AR is a ligand-activated transcription factor. Data from the study of **[39]** clarified that BPA antagonizes AR activities by competition of androgen binding, reducing the AR movement from cytoplasm into the nucleus and prohibit the formation of functional complexes which are the prerequisite for the process of transcription, leading to disturbance of transcription and androgen-independent cell proliferation. In addition **[37]** mentioned that BPA is commonly considered to have an anti-androgen effect. It competes with androgens to bind ARs as an antagonist.

Previous authors **[40]** stated that compounds with anti-androgenic properties are capable of modulating male reproductive functions by suppressing the binding of androgens to AR hence, down-regulate androgen-induced gene expression. Mostly, these compounds contain at least an aromatic ring with a hydroxyl group. In the case of BPA, this hydroxyl group on BPA-phenyl ring is necessary for the inhibitory effect on the AR. Also, BPA interfere with androgen-dependent signaling pathways through multiple mechanisms, modulation of AR function is a major mechanism.

In conclusion, the results of our study showed that BPA at low dose exposures may have outcomes deleterious effects on the histological structure of the prostate and disturbed reproductive hormones.

So, **we recommend,** the use of BPA should be limited or carried out with cautions. Further studies need to analyze the molecular basis of these alterations.

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