Effect of Streptozotocin Induced Diabetes on the Adult Rat Prostate and the Possible Protective Role of Vitamin E

Original Article

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ABSTRACT

Background: Diabetes mellitus (DM), a disorder of metabolism, has adverse effects on all organ systems including reproductive organs due to insulin deficiency. The aim of the present work was to study the impact of Streptozotocin (STZ)-induced diabetes and the potential protective role of vitamin E on the adult rat prostate.

Materials and Methods: Forty adult male albino rats were divided equally into 4 groups (10 rats per group). First group was control negative, while the second group was control positive. Rats in the 3rd group were received streptozotocin dissolved in a citrate buffer by intraperitoneal injection at a dose of 40 mg/kg body weight once daily. 2 weeks after confirmation of diabetes induction rats were sacrificed. Rats in the fourth group after induction of diabetes were fed with vitamin E supplemented diet for 15 days then the rats were sacrificed. The prostatic lobes were dissected out and processed for histological and immuno-histochemical examinations. Hormonal assay was performed and Statistical analysis was done.

Results: No structural differences were found between the two control groups. The diabetic group showed thinning of acinar epithelial lining; sever cellular infiltration and areas of exudate in interstitial tissue. By immunohistochemical staining, apparent decrease of the acinar cells with positive immunostaining androgen receptor reaction was observed. Also decreased serum testosterone level in diabetic group was noticed. Supplementation of vitamin E was found to improve most of the prostatic changes associated with DM.

Conclusion: Supplementation of vitamin E improves the prostatic changes produced by DM.

Key Words: Diabetes mellitus, prostate, streptozotocin.

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INTRODUCTION

Diabetes is a metabolic disease caused by a deficiency in the pancreatic secretion of insulin and/or the inability of tissues to effectively respond to insulin, leading to chronic hyperglycemia that affects all organs. The main types of diabetes are insulin-dependent (or type I), characterized by a total lack of insulin hormone, and insulin independent (or type II)[1,2].

Diabetes mellitus (DM) prevalence is increasingly worldwide at an alarming rate due to population growth, sedentary lifestyle, aging, and obesity. Data from the ‘‘World Health Organization’’ estimated that by the year 2030, 366 million people will have DM[3].

Reproductive organs are highly sensitive to changes in the organism's metabolic status and energy reserves. Adverse metabolic conditions, as observed in DM individuals, are commonly associated with defective reproductive capacity[4,5]. Indeed, uncontrolled diabetes is often associated with sexual and reproductive dysfunction in male humans and experimental animals, and is manifested as erectile dysfunction and infertility due to decreased serum androgen levels[6].

Experimental and clinical studies have reported alterations in different systems including the urogenital system. Both types I and II Diabetes mellitus have adverse effects on male sexual and reproductive functions, including impotence, decreased libido, and sterility[7]. While the adverse effects of diabetes on testicular functions are well established[8] relatively less information on the effect of diabetes on the accessory sex organs is available[9].

Prostate is an androgen-dependent accessory sex organ. It shares in the formation of the major portion of seminal fluid, which is important for sperm viability, motility, and

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fertilizing capacity. The prostate is divided into three pairs of lobes: ventral, dorsal, and lateral, distributed in rodents around the prostatic urethra[10].

The prostatic lobes typically exhibit tubulo-acinar structures, which are lined with simple columnar epithelium and are surrounded by stroma. The prostatic stroma is a complex network of stromal cells, and the extracellular matrix which is associated with growth factors, regulatory molecules, and enzymes that provide biological signals and result in mechanical influence on the epithelial cells[11].

Various studies have reported protective effects of antioxidants such as vitamin E[12] and vitamin C[13] against oxidative damage of diabetes. The levels of vitamins C and E in plasma and renal tissues are significantly reduced in diabetic patients[14].

Previous results showed that vitamin E is important for the prevention or alleviation of complications of diabetes mellitus[15].Therefore, this study was undertaken to observe the effect of streptozotocin-induced diabetes on the histological structure of adult albino rats' prostate, and the potential protective role of vitamin E supplementation.

MATERIALS AND METHODS

Animals

Forty healthy adult male albino rats weighing (200-250g each) were used in this experiment. They were gained from the animal house, Faculty of Medicine, Zagazig University, Egypt. The experiment was performed in accordance with research protocols established by the animal care committee of the National Research Center (IACUC), Zagazig University, Egypt. They were kept in suitable conditions for 1 week for adaptation. They were housed in stainless steel cages and were kept at room temperature. They were permitted water ad libtium and were fed standard diet. At the start of the experiment, blood sugar levels were measured in all animals using a Glucometer to exclude diabetic rats.

Study groups

The rats were randomly divided into four equal groups; 1, 2, 3 and 4. Group 1 (control group) in which rats received no treatment (negative control group). Group 2 (Buffer treated group) in which rats received a single intraperitoneal injection of proportionate amount of citrate buffer just once daily (0.1 ml.0.1 M citrate buffer, pH 4.4) up to the end of experiment (positive control group). Group 3 (diabetic group) in which rats received streptozotocin as a diabetogenic agent (Sigma chemical corporation, Germany), and the vehicle for administration was 0.1 mol/l citrate buffer, pH 4.4. (10 mg dissolved in 0.1 ml of 0.1 mol/l citrate buffer, pH 4.4). The rats were given a single intraperitoneal streptozotocin injection once daily at a dosage of 40 mg/kg body weight[16]. Animals will be sacrificed 2 weeks after confirmation of diabetes induction. Group 4 (vitamin E treated group) rats were injected with streptozotocin (40mg/kg BW) after being dissolved in citrate buffer (0.1 M, pH 4.4) via single intraperitoneal injection once daily. After confirmation of diabetes induction, rats will be fed with vitamin E supplemented diet for 15 days. The vit E supplemented diet contained di- tocopheryl acetate (600 mg) per Kg of feed. VE was obtained in the form of powder, dissolved in distilled water and was added to diet. VE was purchased from El Gomhoria Company for Chemical and Medical Trading, Zagazig, Egypt. Initiation of diabetes was confirmed by estimation of plasma glucose concentration of blood sample collected from animals tail vein and 200 mg/dl is considered to be diabetic[17]. At the end of the experiment, the rats were anesthetized using intraperitoneal injection of thiopental 50 mg/kg (IACUC, 2013). Samples of prostate will be obtained and processed for light and immuno-histochemical examination.

Light microscopic examination:

Prostatic specimens were fixed in 10% neutral buffered formaldehyde solution for 48 h and then after being washed briefly in water the specimens were dehydrated with ascending grades of ethyl alcohol (70, 80, 90, 95, and 100%), followed by clearing the samples and were then embedded into paraffin. Five-micrometer-thick sections were obtained by microtome; then the sections were stained with hematoxylin and eosin for general morphological and structural study and Masson's trichrome stain to demonstrate collagen fibers[18].

Immuno-histochemical staining:

The immuno-histochemical staining of prostate for expression of androgen receptor (AR) was done using rabbit polyclonal anti-androgen receptor primary antibody (Labvision Corporation, Fermont, USA). Then Power Stain TM 1.0 Poly HRP DAB Kit (Genemed Biotechnologies, CA-USA) was used to visualize the antigen-antibody reaction in the tissue. The principle is based on the binding of a primary antibody (dilution of 1:100) to a specific antigen. The formed antibody-antigen complex is incubated with a secondary, enzyme-conjugated antibody. In the presence of substrate and chromogen, the enzyme acts on the substrate to produce colored deposits at the antibody-antigen binding sites which was observed under a binocular microscope. The specificity of an antibody reaction was proven by the lack of staining either in the nuclei or the cytoplasm of the negative control. Antigen retrieval was done on the sections by heating in a citric acid buffer (pH 6.0) at 100ºC for 15 minutes. Bands intensities were quantified using ImageJ software.

Biochemical study:

Blood was collected from the retro-orbital plexus using micro–capillary glass tubes under light ether anesthesia. Serum free testosterone, total testosterone and FSH hormones have been measured by enzyme-linked immunosorbent assay (ELISA)[19].

Image analysis and morphometry:

All sections were analyzed using Leica DM500, (German) photomicroscope and different parameters were assessed using ImageJ (FIJI) software. In Hematoxylin and Eosin stained sections, acinar diameter and epithelial thickness were measured in µm by using a straight line extending from the basement membrane to the top of the tall epithelial lining of the middle area of the ventral lobe of the gland described as a percentage of the control values at ×400 field magnification using 15 random fields from 5 different rats in each group. Moreover, collagen area percentage was calculated in sections stained with Masson Trichrome. In Anti-androgen receptor antibody treated sections, the optical density of the reaction was estimated. All of these parameters were done at Human Anatomy and Embryology Department, Faculty of Medicine, Zagazig University.

Statistical analysis:

Data were expressed as a Mean ±S.D. The values were analyzed using one-way ANOVA followed by the Turkey's post-hoc multiple range test for analysis of morphometric results of the sections stained by Hematoxylin and eosin, As well as, the optical density of androgen receptor (AR) reaction which was assessed in sections treated with AR. Analysis was carried out by Graph Pad Prism 5 software (Graph Pad Software, San Diego, CA, USA). Values were considered statistically significant at $p< 0.05$.

RESULTS

Light microscopic examination

No histological variations were observed between both control groups (negative and positive). So the results of negative control group were chosen to describe both control groups. H&E stained sections of both control groups of ventral lobe prostate showed many normal prostatic acini with variable sizes and shapes filled with prostatic secretions of variable densities. The acini were lined by simple columnar cells with basophilic cytoplasm and basally located rounded vesicular nuclei resting on regular basement membrane. Normal interstitial tissue was seen in between acini in the form of fibro-muscular stroma containing smooth muscle fibers, collagenous and elastic fibers. The acinar lining showed many areas of simple inward branching (epithelial proliferations) (Fig. 1). However, H&E stained sections of diabetic group showed many apparently wide acini with thinning of epithelial lining. The acini showed multiple areas of marked epithelial proliferations and branching; some of them were seen detached from the acinar wall and fallen in the lumens of prostatic acini. In addition, clear loss of interstitial tissue and empty interstitial space with focal areas of interstitial cellular infiltration and large areas of exudate were detected in the interstitial tissue. Severely congested blood vessels were also seen in interstitial tissue (Fig. 2). In group supplemented with vitamin E, H&E stained sections showed some prostatic acini with normal healthy columnar epithelial lining and scanty areas of branching, while others appear with cuboidal lining. Few areas of cellular infiltration were still present in interstitial tissue (Fig. 3).

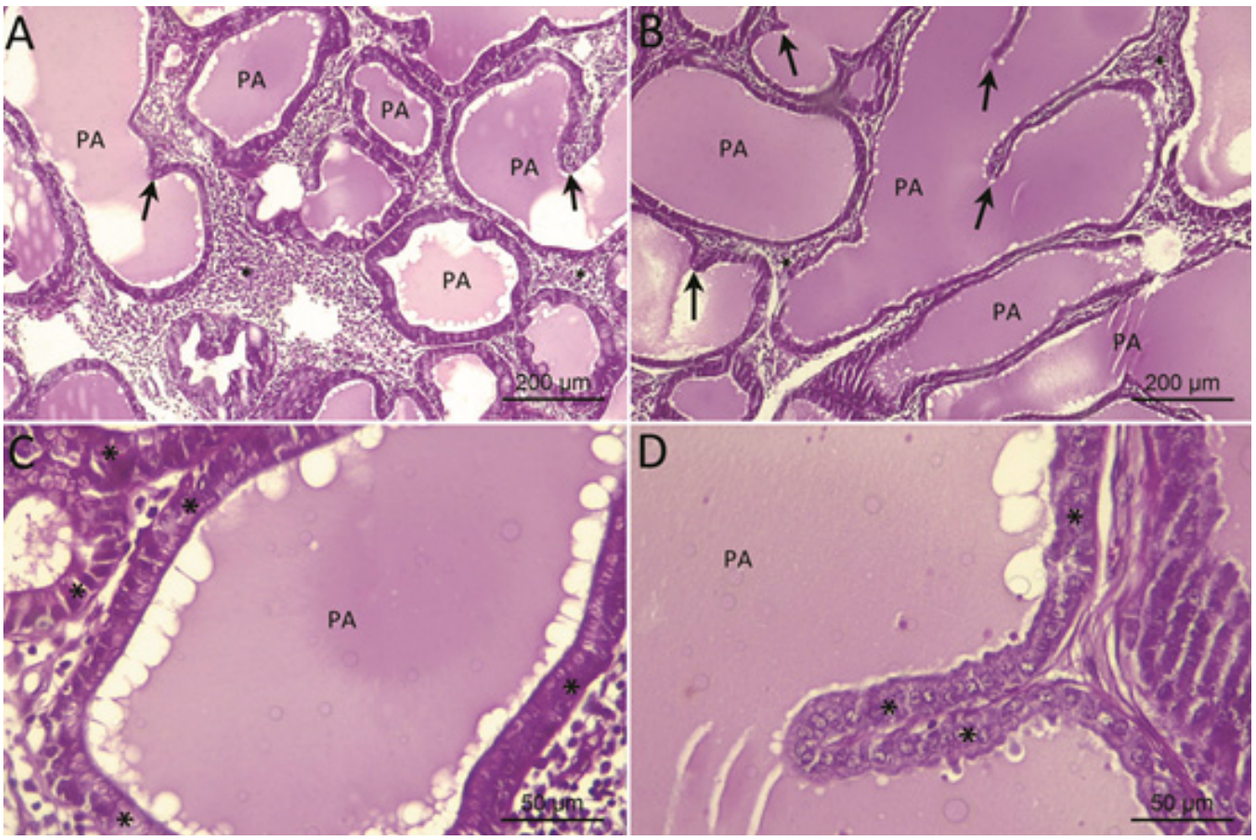


Fig. 1: A photomicrograph of a section of the adult rat prostate in the control group showing (A) many prostatic acini (PA) with variable sizes and shapes, filled with variable density prostatic secretions with normal interstitial tissue distributed in between prostatic acini. (B) Some acini contain areas of branching (epithelial proliferations) (arrow). (A+B) (H&E X100). (C) Showing a part of an acinus epithelial lining. The cells are columnar in shape (*) that rest on regular basement membrane; they have basophilic cytoplasm and basally located rounded vesicular nuclei. The lumen shows slightly dark acidophilic secretions. (D) Higher magnification of a branching epithelial proliferation lined with columnar shaped acinar epithelium (*) (C+D) (H&E X400).

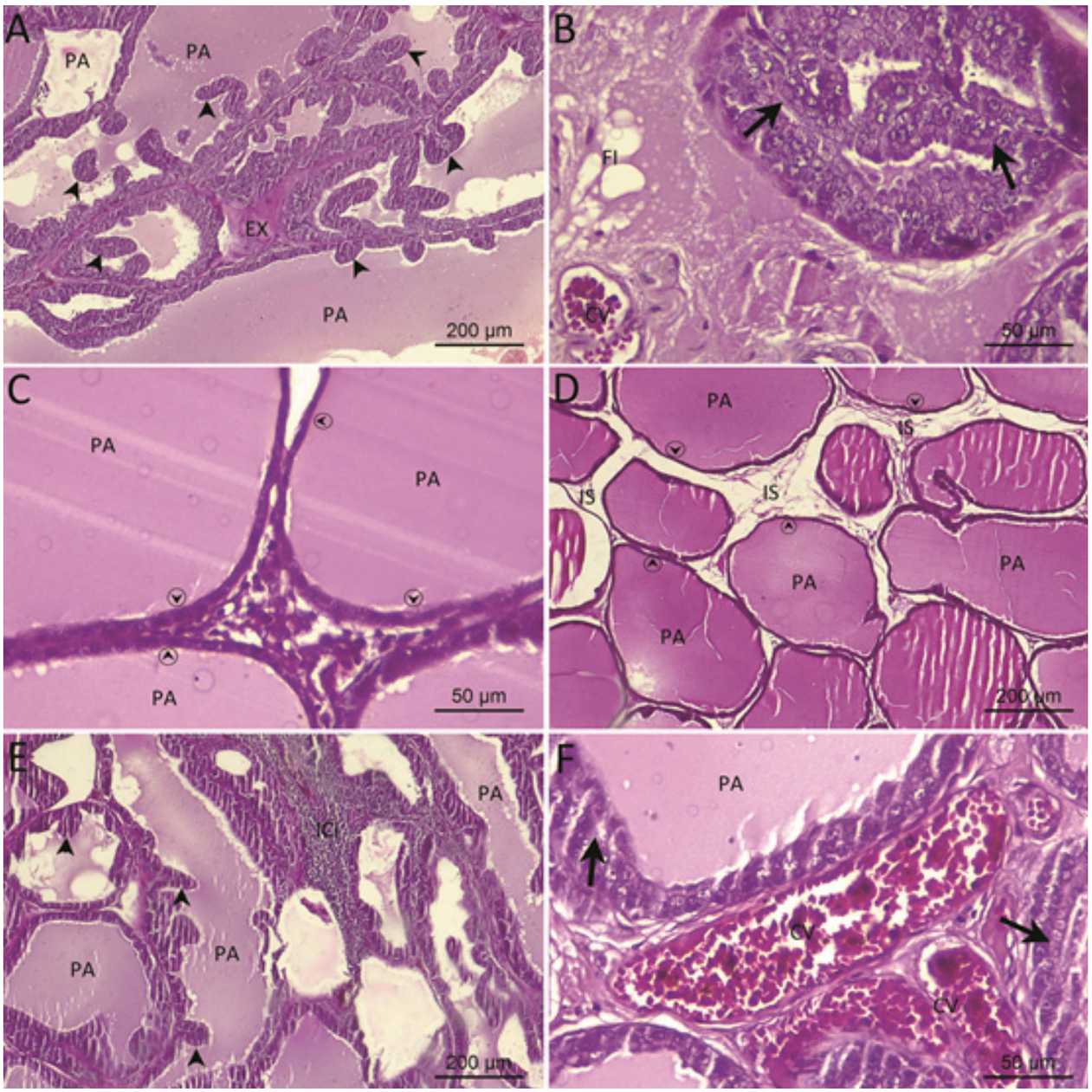


Fig. 2: A photomicrograph of a section of the adult rat prostate in the streptozotocin induced diabetic group showing (A) many prostatic acini (PA) variable in size and shape, filled with prostatic secretions of variable densities. The acini show multiple areas of branching (epithelial proliferations); some of them detach from the acinar wall and fall into the lumens of prostatic acini (Arrow head). A large area of exudate (EX) is present in interstitial tissue (H&E X100). (B) A prostatic acinus with marked epithelial proliferation (Arrow), fatty infiltration (FI) and congested blood vessel (CV) in interstitial tissue. (C) Many prostatic acini (PA) with thin epithelial lining (Arrow head) (B+C) (H&E X400). (D) Loss of interstitial tissue and wide interstitial space (IS) between prostatic acini (PA). (E) Sever interstitial cellular infiltration (ICI) is seen between prostatic acini (PA) (D+E) (H&E X100). (F) Severely congested blood vessels (CV) are present between prostatic acini (PA) (H&E X400).

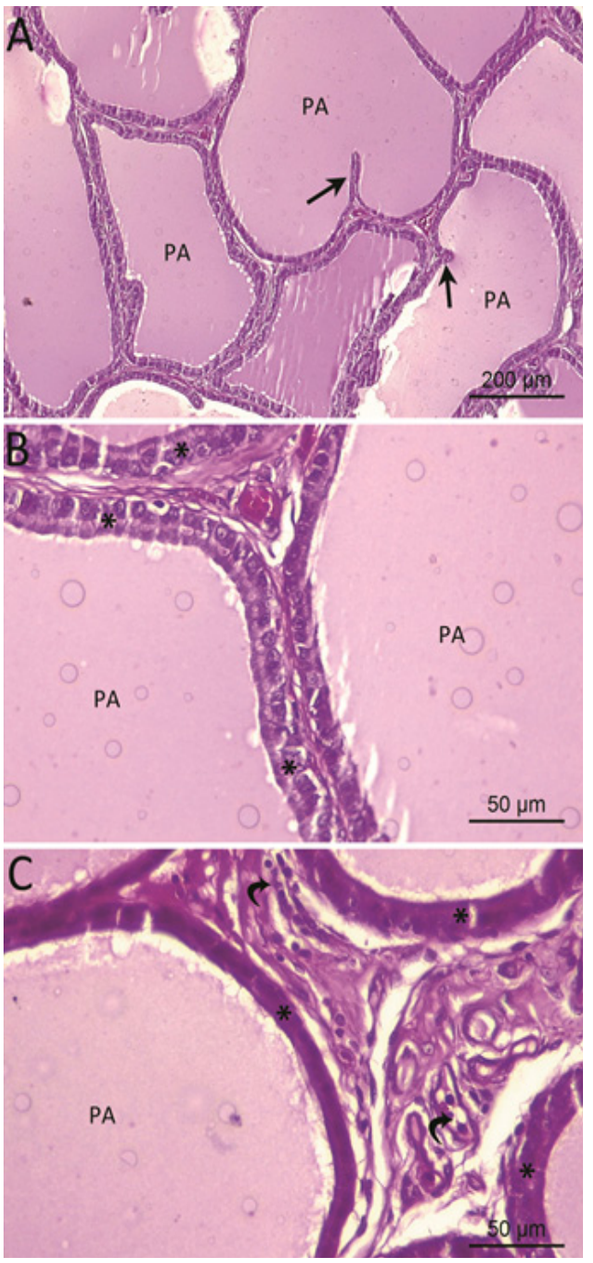


Fig. 3: A photomicrograph of a section of the adult rat prostate in the group supplemented with vitamin (E) showing (A) many prostatic acini (PA) of variable sizes and shapes, filled with prostatic secretions of variable densities and few branching acinar epithelial lining (Arrow) (H&E X100). (B) Prostatic acini (PA) with restoration of acinar simple columnar epithelium (*). (C) Residual interstitial cellular infiltration (curved arrow) in between Prostatic acini (PA) (B+C) (H&E X400).

Masson's trichrome stain:

Masson's trichrome stained sections of control group showed normal distribution of collagen fibers between the prostatic acini and around the blood vessels. While Masson's trichrome stained sections of streptozotocin induced diabetic group exhibited abundant violet stained collagen fibers between prostatic acini. Moreover, Masson's trichrome stained sections of protective group taking vitamin E showed decreased amount of collagen fibers between prostatic acini in comparison with the diabetic group (Fig. 4).

Androgen Receptor immunostaining:

Different expressions of AR were seen in the acinar epithelium. There was strong positive nuclear immunoreaction for AR in the control group. While, the streptozotocin induced diabetic group reported a significant decrease in the number of positive immunoreaction staining of AR. In addition, the vitamin E supplemented group displayed an increased number of positive immunoreaction staining of AR in comparison with the diabetic group (Fig. 5).

Morphometric Study and Statistical Analysis:

No statistically significant difference was found between both control groups. So they were represented as one group. Considering immune morphometry and epithelial height, the results of the present study showed a very highly significant decrease ($P< 0.001$) in the number of prostatic acinar epithelial cells with positive immune reaction for AR and epithelial height in the streptozotocin induced diabetic group relative to other groups. As regards the percentage of acinar diameter and collagen area, the present study showed a very highly significant increase ($P< 0.001$) in the percentage of both acinar diameter and collagen area in the streptozotocin induced diabetic group when compared with other groups as in (Table 1) and (Figure 6).

As regards the use of least significant difference test (LSD) for comparison between groups, it was found that there was a very highly statistically significant decrease in the number of prostatic acinar epithelial cells with +ve immune reaction for AR and epithelial height in streptozotocin induced diabetic group when compared with other groups. Additionally, there was statistically significant difference between control and vitamin E treated groups. However, there was a very highly statistically significant increase in the percentage of both acinar diameter and collagen area in the streptozotocin induced diabetic group when compared with other groups as in (Tables 2).

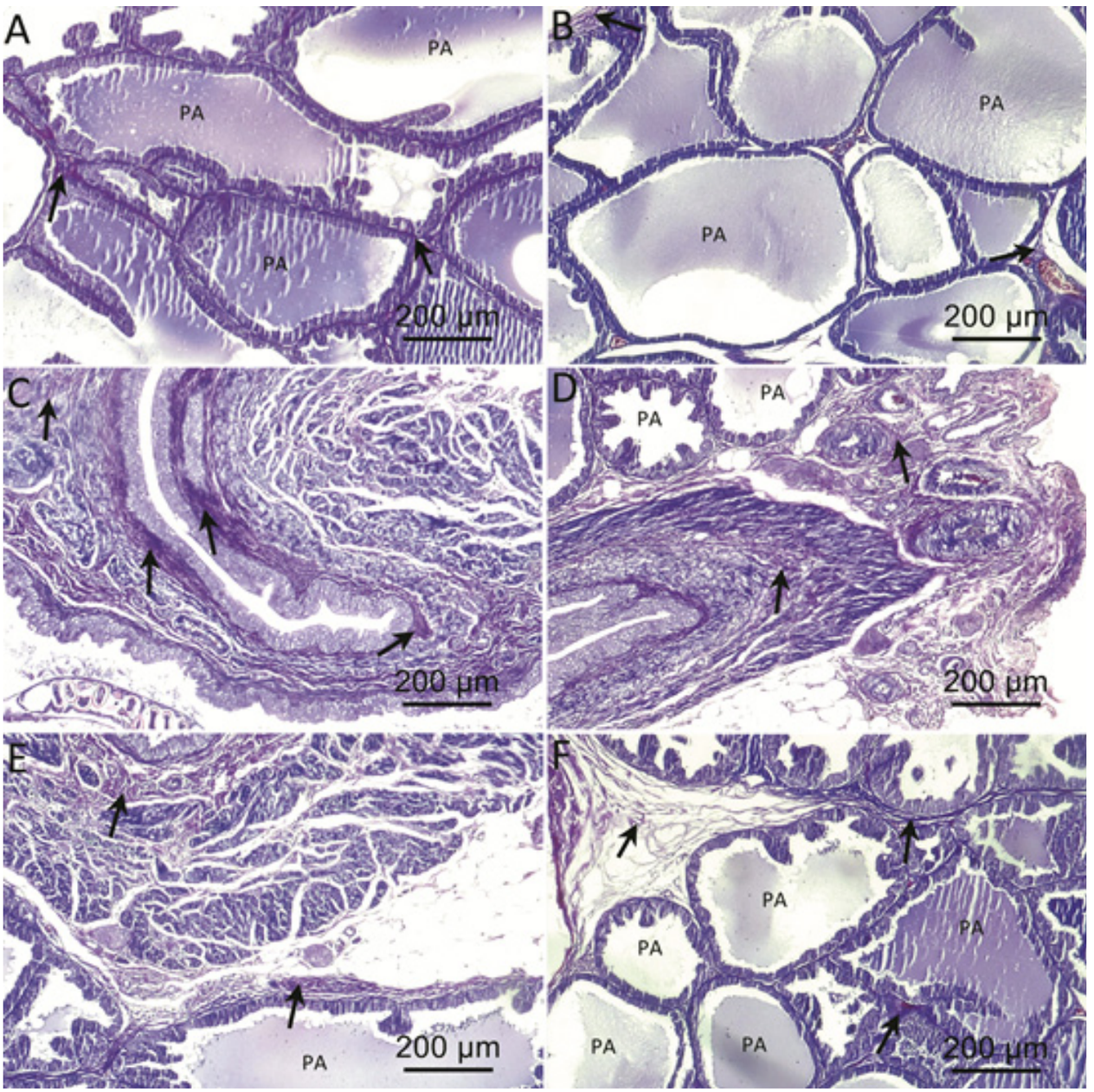


Fig. 4: A photomicrograph of a section of the adult rat prostate in different groups stained by Masson Trichrome. (A+B) A section in the prostate of control adult albino rat showing normal distribution of collagen fibers (arrow) between prostatic acini (PA) and around blood vessels (BV). (C+D) A section in the prostate of streptozotocin induced diabetic group showing abundant violet stained collagen fibers (arrow) around prostatic acini (PA). (E+F) A section in the prostate of protective group taking vitamin E showing decreased collagen fibers (arrow) between prostatic acini (PA) in comparison with the diabetic group. (Masson's trichrome X100).

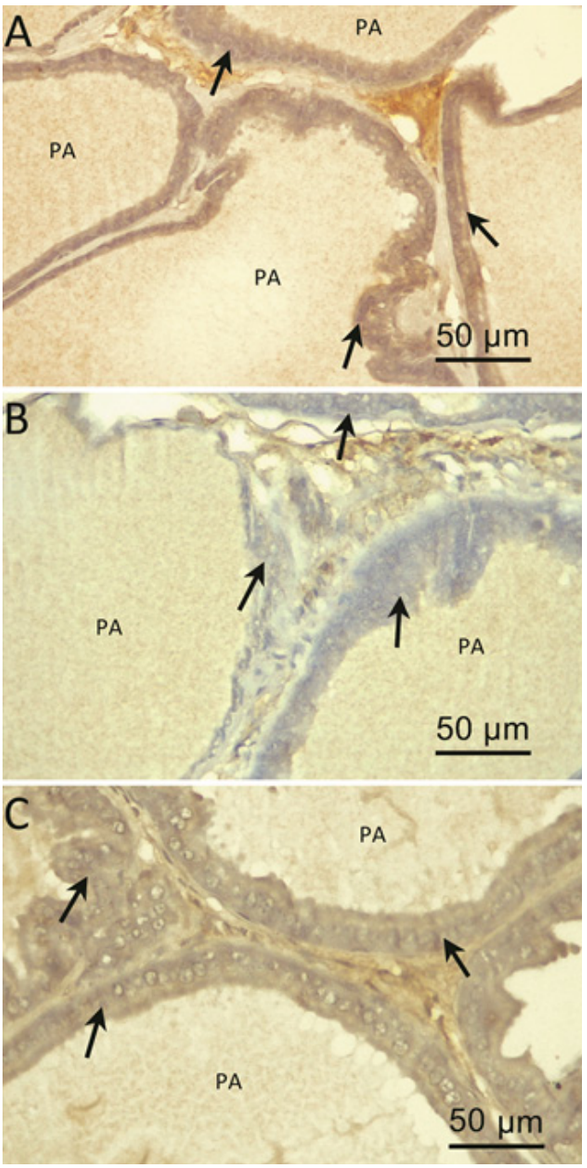
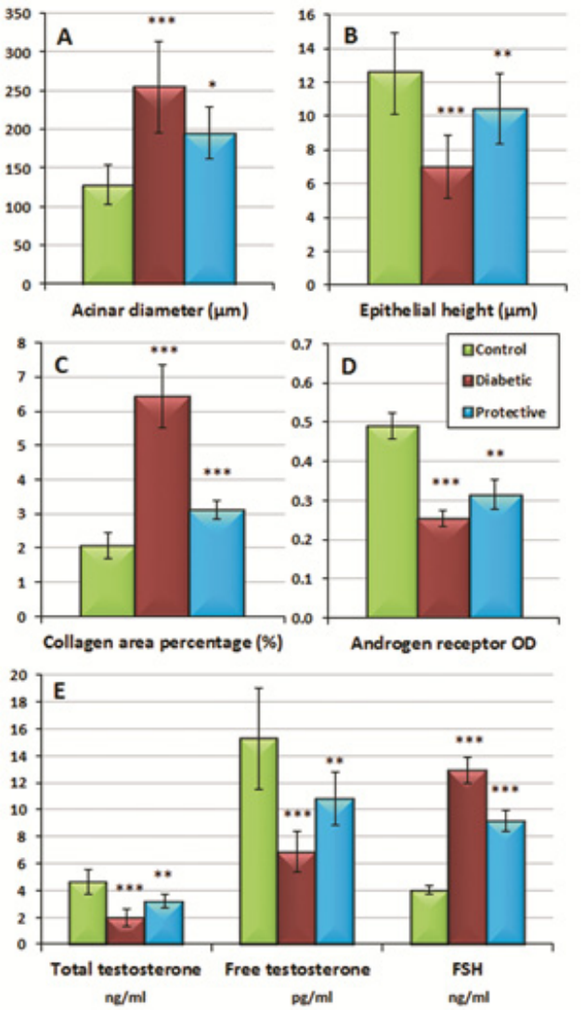


Fig. 5: A photomicrograph of different groups of the adult rat prostate treated with anti-androgen receptor antibody. (A) Control group with strong positive nuclear immunoreaction (arrows) for AR in the acinar epithelial cells and few immunoreactions in the stromal cells. (B) Diabetic group with apparent decrease in number of positive immunoreaction staining of AR (arrows) in the epithelial cells with some positive immunoreaction staining of AR in the stromal cells. (C) Vitamin E supplemented group showed increased number of positive immunoreaction staining of AR (arrows) in epithelial cells in comparison with the diabetic group with some positive immunoreaction in the stromal cells. PA: Prostatic acini. Arrow: Androgen receptor expression in the acinar epithelium. (AR immunostaining ×400).



Figu. 6: A Histogram demonstrating the effects of streptozotocin induced diabetes and vitamin (E) on different morphometrical parameters in the prostate of adult rats (A, B, C and D) and on hormonal analysis (E). Values are presented as means ± SD. *: *P<0.05*, **: *P<0.01* and ***: *P<0.001*.

Table 1: Comparisons between mean values of acinar diameter, epithelial height, collagen area percentage and immune morphometry in the different studied groups using ANOVA (analysis of variance) test.

Parameter \ Groups	Group (1) Control (n=10)	Group (II) streptozotocin induced diabetic group (n=10)	Group (III) protective (vitamin E treated group) (n=10)	*P*
Acinar diameter (µm) Mean± Sd	127.81±25.29	254.37±59.65	195.15±33.78	< 0.001***
Epithelial height (µm) Mean± Sd	12.51±2.38	6.97±1.87	10.43±2.061	< 0.001***
Collagen area percentage (%) Mean± Sd	2.08±0.37	6.44±0.91	3.11±0.27	< 0.001***
AR (OD) Mean± Sd	0.49±0.03	0.25±0.02	0.32±0.04	< 0.001***

*** Very highly significant n= number of rats of each group=10
Sd: Standard deviation OD= Optical density.

Table 2: Least significant difference test (LSD) for comparison of mean values of acinar diameter, epithelial height, collagen area percentage and immune morphometry in between groups:

Variable	Control group	streptozotocin induced diabetic group	vitamin E treated group
Control group (n=10)		***: *P<0.001*	**: *P<0.01*
Diabetic group (n=10)	***: *P<0.001*		*: *P<0.05*
vitamin E treated group	**: *P<0.01*	*: *P<0.05*	

* Significant ** Highly significant *** Very highly significant n= number of rats of each group=10

Hormonal study and Statistical analysis:

No statistically significant difference was found between both control groups. So they were represented as one group. The results of the present study showed a very highly significant decrease in serum levels of Free Testosterone and Total Testosterone ($p < 0.001$) in the streptozotocin induced diabetic group when compared with other groups. While it showed a very highly significant increase in serum level of FSH ($p < 0.001$) in the streptozotocin induced diabetic group when compared with other groups as in (Table 3) and (Figure 6).

By using least significant difference test (LSD) for comparison of mean values of serum levels of Free Testosterone, Total Testosterone and FSH level in between groups. It was found that there was a very highly significant statistical decrease of Free Testosterone and Total Testosterone in the streptozotocin induced diabetic group when compared with other groups. In addition, there was a statistically significant difference in mean values of serum levels of Free Testosterone and Total Testosterone between control group and (vitamin E treated group). Furthermore, it was found that there was a very highly significant statistical increase in serum level of FSH in the streptozotocin induced diabetic group when compared with other groups as shown in (Table 4).

Table 3: Comparison between mean values of Free Testosterone, Total Testosterone and FSH serum levels in the different studied groups using ANOVA (analysis of variance) test.

Parameter \ Groups	Group (1) Control (n=10)	Group (II) (diabetic group) (n=10)	Group (III) (vitamin E treated group) (n=10)	***P***
Free Testosterone (Pg/ml) Mean± Sd	15.25± 3.73	6.84± 1.51	10.79±1.95	< .001***
Total Testosterone (ng/ml) Mean± Sd	4.64± 0.89	1.97± 0.66	3.2± 0.52	< .001***
FSH (ng/ml) Mean± Sd	4.05± 0.30	12.92± 0.97	9.14±0.76	< .001***

*** Very highly significant n= number of rats of each group=10
Sd: Standard deviation

Table 4: Least significant difference test (LSD) for comparison of mean values of Free Testosterone, Total Testosterone and FSH levels in between groups:

Variable	Control group		
Control group (n=10)		*P< 0.001***	*P< 0.001***
Diabetic group (n=10)	*P< 0.001***		*P< 0.05**
(vitamin E treated group) (n=10)	*P< 0.001***	*P< 0.05**	

* Significant ** highly significant
*** Very highly significant n= number of rats of each group=10

DISCUSSION

Streptozotocin selectively destroys the pancreatic B- cells causing inhibition of synthesis and release of insulin hormone leading to onset of DM[20,21]. It is well known that DM-induced hyperglycemia leads to oxidative stress caused by impairment of mitochondrial electron transfer and activation of the polyol pathway resulting in the excessive generation of reactive oxygen species (ROS)[22]. In the current study the ventral prostate of control rats was composed of many acini of variable sizes and shapes. These acini were lined with a columnar epithelium having basophilic cytoplasm and basally located rounded vesicular nuclei. The acini showed many luminal epithelial folds and dark secretions. The cells were resting on a regular basement membrane. In the present study, the prostatic acini of diabetic group showed wide histological variations. Many acini were dilated and lined by a single layer of flat to cuboidal cells with luminal epithelial projections and cytoplasmic vacuolization. Few acini showed cellular detachment and apoptosis and others showed focal areas of epithelial stratification (i.e. lined by stratified epithelium). But still few acini were lined by a single layer of columnar cells having basal nuclei. This was in agreement with[23] who showed decreased glandular epithelial height and epithelium volume in experimental diabetes. Prostatic atrophy in diabetes is similar to the post castration prostatic involution, which is due to loss of the androgen-dependent secretory epithelial cells due to apoptosis and is accompanied by a marked reduction of both the cytoplasmic and nuclear androgen receptor content. These changes can be prevented by the administration of androgens which reflect testosterone's anabolic effect and its role in cell proliferation and stromal growth[24]. In diabetes, insulin deficiency causes reduced testosterone production because insulin has a stimulating effect on androgen production by affecting the hypothalamic–pituitary–testis axis as well as its local effects through insulin receptors[25]. The diabetic rats that received treatment with insulin and testosterone showed a significant increase in androgen receptor expression[26]. Vikran *et al*.,[27] noted that preventing the production of insulin during sexual maturation retards prostate growth. Also these results were in accordance with [28] who mentioned that the acinar cells were resting on an irregular basement membrane that was disrupted in the areas of epithelial stratifications. Some areas of the acinar epithelium showed marked apoptotic changes that were in agreement with the results obtained in previous studies of[29]. Denis *et al*.,[30] confirmed that diabetes stimulates apoptosis in different body organs including the prostate gland. Increased apoptosis in the prostate positively correlates with the present study immunohistochemical staining for AR protein in the prostate of diabetic rats. It has also been reported that complications from DM may alter the mechanism that regulate reactive stroma biology in prostate anatomically, pathologically and/or biochemically[31]. Many authors stated that DM may depress the activity of Leydig cells resulting in lower testosterone levels[32] that may inhibit the development of male sex glands and accessories, including the prostate gland[33]. The imbalance between the oxidation and the antioxidant state was found to play a major role in the mediation of diabetic complications in different body organs[34]. The increased oxidative stress conditions with reduced levels of the antioxidant enzymes in diabetes directly cause apoptosis by damaging the DNA[35]. Popoola *et al*.,[36] assumed that low levels of LH in diabetic rats, changes in the prostatic fluid phosphorus, and zinc accumulation can lead to marked inhibition of cell growth and proliferation and increased prostatic acinar apoptosis. In the current study the interstitial tissue (stroma) of diabetic group shows many collagen fibers, numerous congested blood vessels, cellular infiltrations and area of exudate. These findings were in accordance with[37,38] who said that the first step in the development of prostate cancer was modification of the stroma cells and hypertrophy of the extracellular matrix. Thus, it may be assumed that diabetes causes impairment of the reproductive process and might lead to premalignant lesions. The inflammatory cellular infiltration revealed in this study was also reported by[39] and were against the results reported by[40] who documented significant prostatitis in diabetic rats compared with control rats, and occupied the majority of the prostate gland. The difference between the outcomes can be due to the difference of the method of induction of diabetes. These results also coincided with those of Acosta *et al*.,[41] who found similar changes in the ventral prostate of elderly, including atypical epithelium and atrophy, epithelial and stromal hyperplasia, the presence of amylaceous bodies and infiltration of inflammatory cells. In the present study, the presence of vascular congestion and inflammatory cellular infiltration could be explained by the work of[42,43] who referred that to changes in the integrity of blood vessels causing disruption of the endothelial barrier and increased capillary permeability evoking an inflammatory response by activating oxidative stress-sensitive signaling pathways. In the current study, protective group taking vitamin E as antioxidant showing partial improvement in the form of some prostatic acini appeared with normal healthy columnar epithelium among others which appeared with cuboidal lining. Decreased cellular infiltration in interstitial tissue is also seen. These findings were in accordance with[44] who reported that vitamin E prevented inflammatory cellular infiltration and thickening of the prostatic interstitial spaces. Also, Zidan,[45] Observed that dietary vitamin E supplementation substantially reduced the extent of pulmonary collagen deposition and histological damage. Vitamin E (VE) is widely promoted for its antioxidant properties[46]. It was reported to play a major protective role against oxidative stress and prevents the production of lipid peroxides by scavenging free radicals which are toxic products of many metabolic processes in biological membranes[47]. Moreover, it was also observed to increase testosterone level in aged animals[48]. In addition, it is

essential in maintaining the physiological integrity of testis, epididymis and accessory glands, which has a vital role in spermatogenesis and sperm maturation[49]. There are reports supporting the protective role of VE against damage related to aging in Sprague-Dawley rats through removal of 8-isoprostane and reduction of oxidative damage[50]. In the current study, the prostate of diabetic group, treated with vitamin E showed approximately more or less similar results to those of control. This is in disagreement with Edger *et al*.,[51] who reported that dietary supplementation of antioxidants to normal tissue induced harmful effects due to storage of excess in adipose tissue of the body which might become toxic. This contradiction could be due to the little (therapeutic) doses of antioxidants that are used in this work.

In the present study, examination of streptozotocin induced diabetic group showed increase area percentage of the collagen fibers content compared with the control and diabetic rats treated with vitamin E. This was confirmed by statistical analysis. These results were in accordance with other investigators [52,53,38].

The expression of AR varied in the different cells of rat ventral prostate, the nuclear staining for AR in the epithelial cells was stronger than that of the stromal cells and these variations in the expression of AR in different types of cells of rat ventral prostate indicate that these cells have different AR contents and different responses to androgen[54]. In this study, there was a significant decrease in the androgen receptor expression in the diabetic rats. This finding was in accordance with other studies that mentioned that the intensity of AR reaction was lower one week after diabetes when compared to respective controls and they attributed that to the lower testosterone level in diabetic rats[55]. Also, they documented that three months after alloxan-induced diabetes, there was no changes in the frequency of AR-positive cells in the prostatic acinar epithelium compared with control group and related that to the already low level of testosterone in older rats. It was stated that the expression of AR mRNA decreases in testis, epididymis and prostate of diabetic rats, that weakening the biological effects of AR and it might be one of the causes responsible for the sexual and reproductive dysfunction in the diabetic rats[56]. In the present study, the diabetic rats received treatment with vitamin E showed significant increase in the AR expression; these observations were in accordance with the ability of combined insulin and testosterone to restore the weight of the accessory sex gland with partial structural recovery[26]. In the present study, it was found that serum levels of free and total testosterone were markedly decreased in streptozotocin induced diabetic group while FSH level was markedly increased when compared with other groups. This was in agreement with other researchers[57] who demonstrated that diabetes caused altered gonadotrophic hormones, resulting in reduced testicular hormone secretion with subsequent elevation of FSH level by the feedback mechanism of hypothalamo-hypophyseal gonadal axis. This observation is also consistent with the study of Cai *et al*.,[58] who reported that serum testosterone impairment may be linked with various degrees of testicular and epididymal structural lesions caused by STZ-induced DM.

Therefore, pathophysiological mechanisms which explain changes in metabolic syndrome of DM may include changes in prostatic functions, reduction in reproductive hormones and induction of oxidative stress[59].

CONCLUSION

The present study concludes that Diabetes-induced marked structural changes in the adult rat prostate. And demonstrates the importance of oral consumption of vitamin E supplemented diet on the correction of metabolic disorders of diabetes mellitus.

RECOMMENDATIONS

Further studies should be undertaken on the benefits of vitamin E supplementation as an alternative therapy to improve diabetic complications.

CONFLICT OF INTEREST

There are no conflicts of interest.

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