Slov Vet Res 2016; 53 (3): 151-60
UDC 616.379-008.64:611.66+611.671:616-008.9-092.18:66.094.3.098:599.323.452

Original Research Article

CHANGES IN THE UTERUS AND VAGINA OF RATS WITH EXPERIMENTALLY INDUCED DIABETES AND THE EFFECT OF LYCOPENE ON THE CHANGES

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Summary: The aims of this study were to identify the changes that occurred in the uterus and vagina of rats with experimental diabetes, and the effects of orally administered lycopene on these changes. For this research, 42 four-month-old female Wistar Albino rats were used. Experimental diabetes was induced using a single dose of 50 mg/kg streptozotocin (STZ). The control and diabetic rats were randomly separated into four groups as follows: control+corn oil, control+lycopene, diabetes+corn oil, and diabetes+lycopene. Crossman's triple staining and the Periodic Acid Schiff (PAS) methods were applied to the uterine and vaginal slides. Additionally, the uterus was stained with Alcian Blue (AB) pH: 2.5. While the number of glands, the thickness of the endometrium, and the PAS-positive reaction in the glandular epithelium were lower, the AB positive reaction in the glandular epithelium was higher in the diabetes+corn oil group in comparison with the control+corn oil group in the uterus. In contrast, while the height of the lamina epithelialis and the thickness of the tunica muscularis were smaller in the diabetes+corn oil group, in comparison with the control+corn oil group, the thickness of the tunica muscularis was larger in the diabetes+lycopene group, in comparison with the vagina of the diabetes+corn oil group. The changes caused by diabetes in the uterus and vagina, as well as the existence of the protective qualities of lycopene were revealed for the first time, to the best of our knowledge.

Key words: experimental diabetes; lycopene; rat; uterus; vagina

Introduction

Diabetes mellitus is an endocrine disease with serious complications (1). In the uterus, the thicknesses of the endometrium (2), myometrium (3), and the height of the epithelium decrease with the effects of diabetes. The endometrial stroma is also disrupted (4). Furthermore, the immune and vascular defects can occur in gestational endometrium (5). In addition, it was stated that the rate of luminal epithelial cell division was depressed in the uterus with the effect of diabetes (6). In contrast, the mRNA expressions of insulin-like growth factors and their receptors change during the preimplantation periods in the uterus of diabetic animals and thus, may result in diabetic embryopathy (7). In the vagina, the thickness of the epithelial layer decreases (2), and the amount of collagen and apoptosis rate increase with diabetes (8). A narrowing in the muscularis area and truncation in the elastic fibres are observed (9) while the submucosal vasculature decreases and the risk of fibrosis increases (10). Moreover, it was emphasized that the oestrogen, progesterone, and androgen receptor expressions significantly

Received: 2 August 2015
Accepted for publication: 5 July 2016

were reduced with the effect of diabetes in the vagina and thus, the vaginal functions may be affected negatively (11). Conversely, increased free radicals play a major role in the pathogenesis of the complications of diabetes (12). While the glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels decrease, the malondialdehyde (MDA) level increases with the effects of diabetes in the uterus (13). However, diabetes increases the reactive oxygen species but reduces the SOD levels in the vagina (8).

Lycopene is a member of the carotenoid family and has antioxidant properties (14). It causes a decrease in the glucose, hydrogen peroxide (H_2O_2), and thiobarbituric acid reactive substance (TBARS) levels, and it increases the catalase (CAT), SOD, GPx antioxidant enzyme activity, and insulin concentration (15). In addition, it attenuates diabetic neuropathic pain (16) as well as endothelial (17) and erectile dysfunction by reducing oxidative stress (18). Moreover, it was stated that it had a cardioprotective effect (19) and may be useful in the prevention of atherosclerosis (20). However, it was indicated that lycopene inhibited tumour growth (21) and decreased the metastatic capacity (22).

The aim of the present study was to examine the histological, histometrical, and histochemical changes that occur in the uterus and vagina of rats induced with diabetes, and the effects of orally administered lycopene on these changes.

Materials and methods

Animals

In this study, 42 adult female Wistar Albino rats (average body weight 160 g, 4 months old) were used. The rats were obtained from the Department of Laboratory Animals, Ege University in Izmir, Turkey. The rats were housed in a room with a temperature of 24±1°C. The animals were kept under conventional conditions, with a 12-h light/dark cycle, while they were provided with food and water ad libitum. All procedures were approved by the Ethics Committee of Adnan Menderes University, Turkey.

Induction and assessment of diabetes

Experimental diabetes was induced in 30 rats using a single dose of 50 mg/kg of streptozotocin (BioShop STR 201.1), in a 0.01 M citrate buffer (pH 4.5), administered intraperitoneally. After three days, the fasting blood glucose levels were measured, using a glucometer (Contour TS Bayer), in the blood samples taken from the tails of the rats (15). The rats with fasting blood glucose levels of 250 mg/dl or more were included in this study (16). An equal amount of 0.01 M citrate buffer (pH 4.5) was applied to the rats in the control groups, intraperitoneally. Experimental diabetes did not develop in five animals. Therefore, they were removed from the study. Seven animals died in the experiment term in diabetes groups. Therefore, the study was carried out with 30 animals.

Experimental design

Three weeks after diabetes was induced, the control and diabetic rats were randomly separated into four groups as follows: control+corn oil (n=6), control+lycopene (n=6), diabetes+corn oil (n=8), and diabetes+lycopene (n=10). The control+lycopene and diabetes+lycopene groups of rats were fed 4 mg/kg of lycopene (10% FS; Redivivo TM; Code 7803; DSM Inc., Istanbul, Turkey) dissolved in 4 ml/kg of corn oil via gavage for four weeks. The control+corn oil and diabetes+corn oil rats were fed 4 ml/kg of corn oil every day.

Sample collection and preparation

At the end of the experiment term, all animals in all groups were checked for oestrous cycles using the vaginal smear method. When the animals were in the diestrus period, they were sacrificed by cervical dislocation under ether anaesthesia. Samples were taken from the right horn of the uterus and the vagina; then, the tissues were fixed for 24 hours, at +4°C in 4% paraformaldehyde in phosphate-buffered saline (PBS) (pH: 7.4). After routine histological processing, the tissues were embedded in Paraplast, and 5 µm-thick cross-sections were taken.

Histological, histometrical and histochemical analyses

All histological and histometrical evaluations of the tissue sections were performed using Crossman's triple-staining method. In addition, the Periodic Acid Schiff (PAS) staining method was

used in the uterus and vagina, as was Alcian Blue (AB) (pH: 2.5) staining method was applied to the uterus for histochemical examinations. PAS and AB pH 2.5 histochemical staining techniques were employed in order to demonstrate the neutral and acidic mucosubstances, respectively. Changes in the amount of carbohydrate components in the uterus and vagina of the animals in the different groups were determined, and the effect of lycopene with these dyes was identified.

The changes that occurred (in comparison with the normal histological appearance of the tissues), numerical values, and histometrical measurements were determined in the two sections that belonged to each animal. The thickness of the endometrium and the height of the surface epithelium were identified by the measurements taken from five different areas. The height of the glandular epithelium and gland area were measured from five different randomly selected glands in the endometrium, and the glands of the uterus were counted in the sections of each animal. The height of the lamina epithelialis and the thickness of the tunica muscularis were determined using the measurements taken from five different areas in the vagina. The relative PAS and AB pH: 2.5 positive reaction intensities in the surface and glandular epithelial cells of the uterus, as well as the PAS-positive reaction intensity in the lamina epithelialis of the vagina, were evaluated by one person subjectively, and given a score as follows: 0: no reaction (-); 1: weak reaction (+); 2: moderate reaction (++); and 3: strong reaction (+++) (23). PAS-positive cell counts were obtained from five different 28224 μm^2 unit areas. Finally, a light microscope (Leica DMLB) equipped with an image analysing system (Leica Q Win Standard) was used for measuring, counting and scoring the procedures; photographs were also taken.

Statistical analysis

The SPSS statistical package (version 17.00) software was used for all analyses, and the data were analysed using the one-way analysis of variance (ANOVA). If there was a difference in the ANOVA, Duncan's test was used as a post hoc test. The values are presented as the means ± standard errors, and values of $P<0.05$ (*), $P<0.01$ (**), and $P<0.001$ (***) were considered to be statistically significant.

Results

Histological and histometrical evaluations

The heights of the surface and glandular epithelia, gland area, number of glands, and thickness of the endometrium were examined in the uterus. The number of glands in the endometrium and the thickness of the endometrium were lower in the diabetes+corn oil group, in comparison to the control+corn oil group. Similarly, it was observed that the gland area was smaller in the diabetes+lycopene group, in comparison to the control+lycopene group ($P<0.01$, $P<0.001$) (Figures 1, 2 and 7).

The height of the lamina epithelialis and thickness of the tunica muscularis were measured in the vagina, where they were smaller in the diabetes+corn oil group, in comparison to the control+corn oil group. However, they were larger in the control+lycopene group, in comparison to the control+corn oil group. Similarly, the thickness of the tunica muscularis was larger in the diabetes+lycopene group, in comparison to the diabetes+corn oil group ($P<0.001$) (Figures 3 and 8). Furthermore, vacuoles were observed in the lamina epithelialis of the vagina in the diabetes groups (Figure 9).

Histochemical evaluations

A positive PAS reaction was seen in the apical parts of the surface and glandular epithelia in the uterus. PAS-positive cells were also observed in the endometrial connective tissue. The intensity of the PAS-positive reaction in the glandular epithelium was lower in the diabetes+corn oil group, in comparison to the control+corn oil group ($P<0.001$) (Figure 10). However, a positive PAS reaction was observed in the superficial cell layers of the lamina epithelialis in the vagina. It was seen that the intensity of the PAS-positive reaction was higher in the diabetes+lycopene, in comparison to the control+lycopene group ($P<0.05$) (Figure 11).

A positive AB pH: 2.5 reaction was observed in the apical parts of the surface and glandular epithelia in the uterus. It was determined that the intensity of the AB pH: 2.5 positive reaction was higher in the glandular epithelium in the diabetes+corn oil group, in comparison to the control+corn oil group ($P<0.001$) (Figure 12). Figures 4–6: include units in the figures.

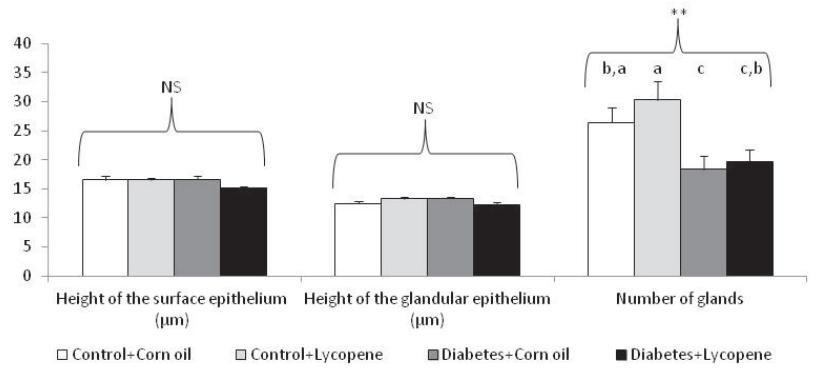

Figure 1: Heights of the surface and the glandular epithelium, and the number of glands in the uterus of the control and diabetes groups a,b,c: Different superscripts in the bars indicate a significant difference. NS: Non-significant. **: P<0.01

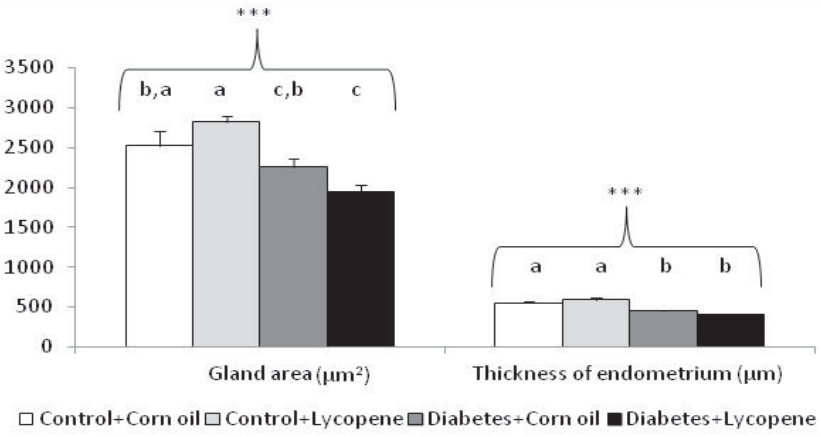

Figure 2: Values of gland area and thickness of endometrium in the uterus of the control and diabetes groups. a,b,c: Different superscripts in the bars indicate a significant difference. ***: P<0.001

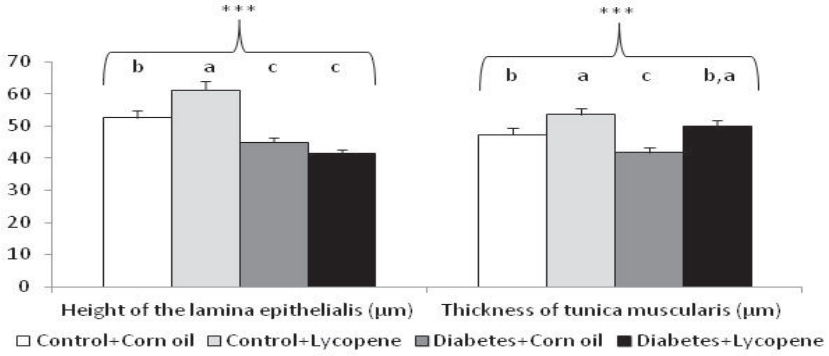

Figure 3: Histometrical measurement values in the vagina of the control and diabetes groups. a,b,c: Different superscripts in the bars indicate a significant difference. ***: P<0.001

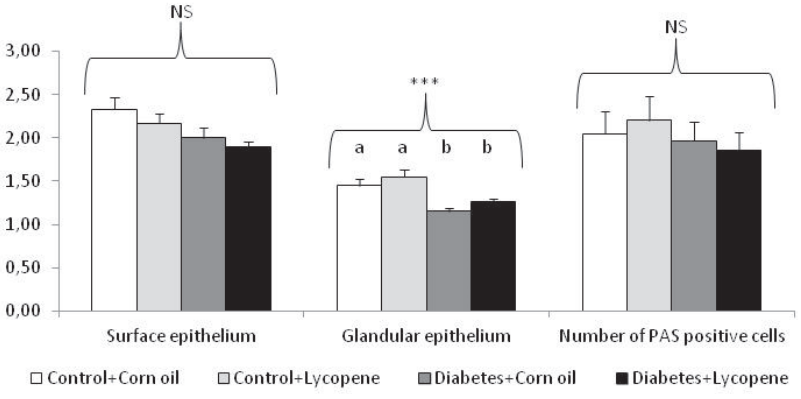

Figure 4: The intensity values of the PAS-positive reactions in the surface and glandular epithelia of the uterus, and the number of PAS-positive cells in the unit area in the endometrial connective tissue of the control and diabetes groups. a,b: Different superscripts in the bars indicate a significant difference. NS: Non-significant, ***: P<0,001

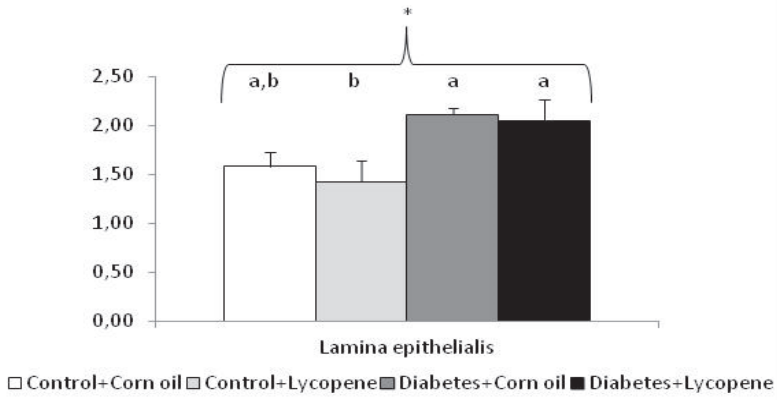

Figure 5: The intensity values of the PAS-positive reaction in the lamina epithelialis of the vagina in the control and diabetes groups. a,b: Different superscripts in the bars indicate a significant difference. *: P<0,05

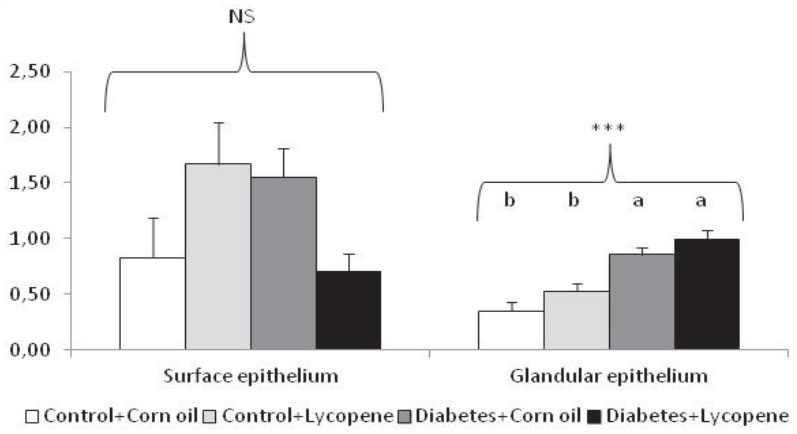

Figure 6: The intensity values of the AB pH: 2.5 positive reactions in the uterus of the control and diabetes groups. a,b: Different superscripts in the bars indicate a significant difference. NS: Non-significant, ***: P<0,001

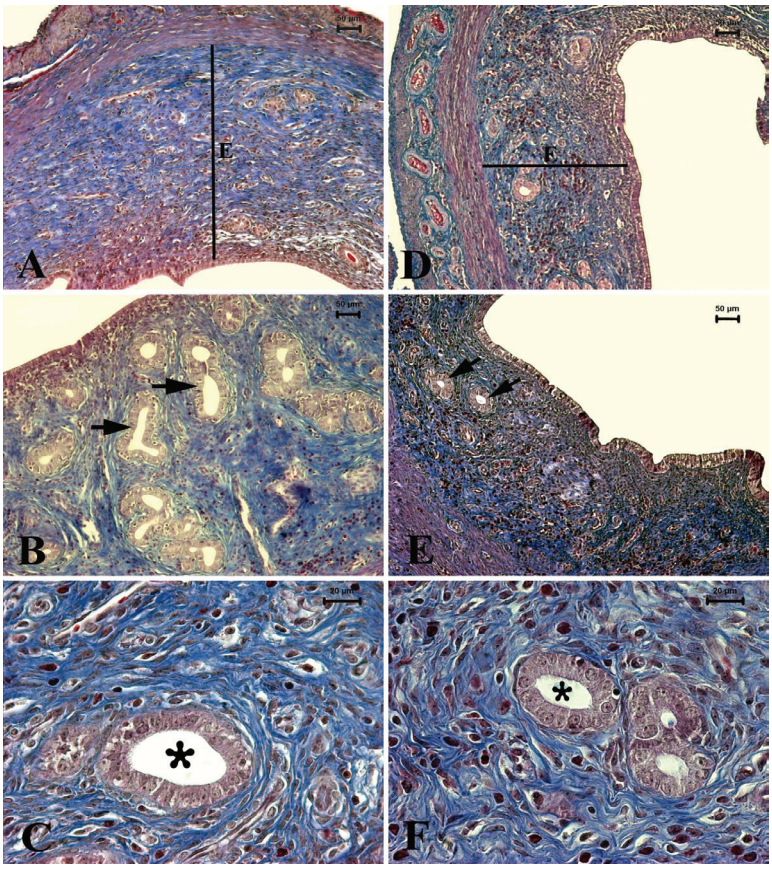

Figure 7: Uterine sections in the control and diabetes groups. It can be seen that the thickness of the endometrium (A, D) (black lines, E) and the number of glands (B, E) (arrows) were lower in the diabetes+corn oil group (D, E), in comparison to the control+corn oil group (A, B). It was also determined that the gland area (asterisks) was smaller in the diabetes+lycopene group (F), in comparison with the control+lycopene group (C). Triple staining method. Bar: 50 µm (A, B, D, E); 20 µm (C, F)

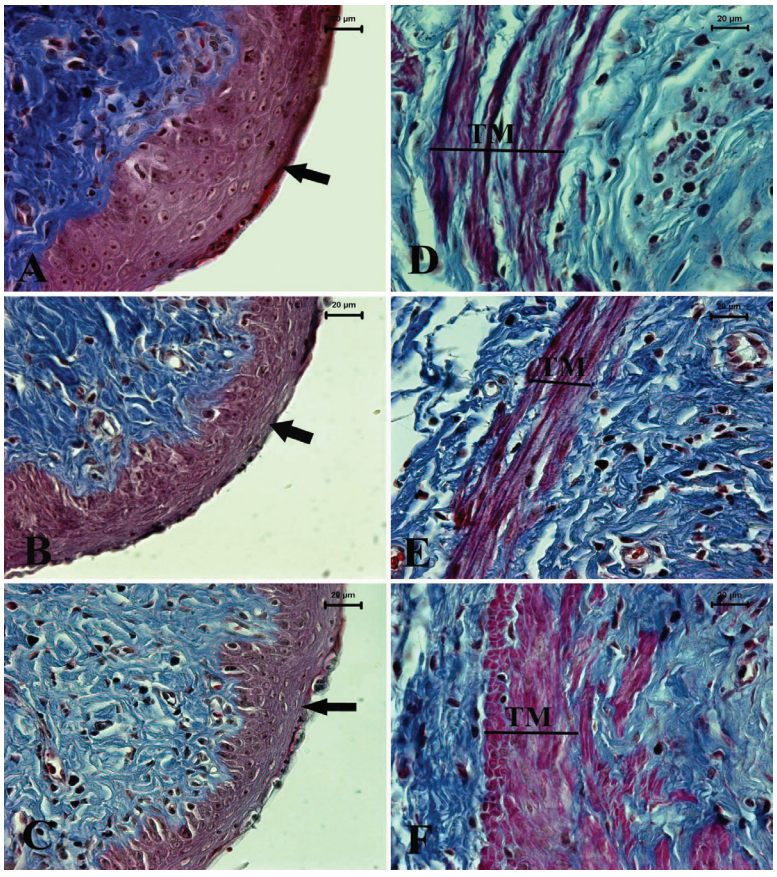

Figure 8: Vaginal sections in the control and diabetes groups. It can be seen that the height of the lamina epithelialis (A-C, arrows) was smaller in the diabetes+corn oil (B) and diabetes+lycopene (C) groups, in comparison to the control+corn oil group (A). Similarly, it was determined that the thickness of the tunica muscularis (D-F) (black lines, TM) was smaller in the diabetes+corn oil group (E), in comparison to the control+corn oil (D). However, it was larger in the diabetes+lycopene group (F), in comparison to the diabetes+corn oil group (E). Triple staining method. Bar: 20 µm

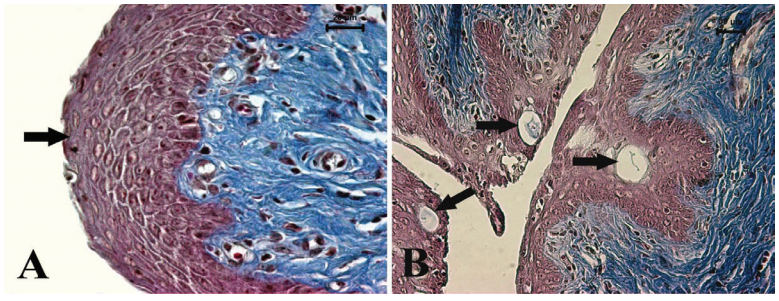

Figure 9: Lamina epithelialis of the vagina in the control+corn oil group (A) (arrow). Vacuoles in the lamina epithelialis of the vagina in the diabetes+corn oil group (arrows). Triple staining method. Bar: 30 µm

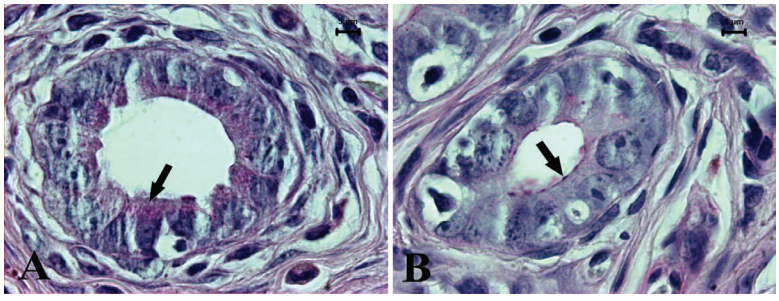

Figure 10: PAS-positive reaction in the glandular epithelium of the uterus in the control+corn oil (A) and diabetes+corn oil (B) groups. It can be seen that the intensity of the PAS-positive reaction was lower in the glandular epithelium of the uterus in the diabetes+corn oil group, in comparison to the control+corn oil group (arrows). PAS method. Bar: 5 µm

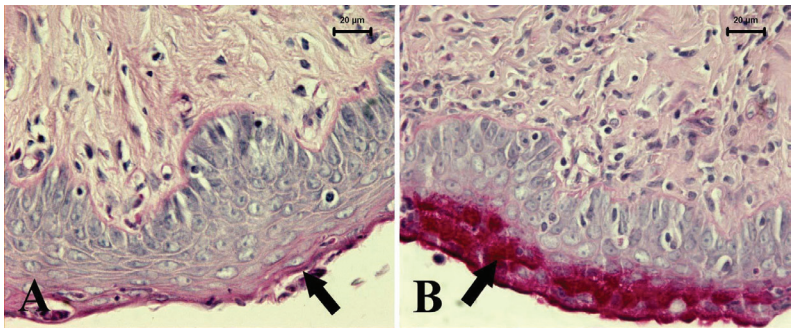

Figure 11: Vaginal sections in the control+lycopene (A) and diabetes+lycopene (B) groups. It can be seen that the intensity of the PAS-positive reaction was higher in the lamina epithelialis of the vagina in the diabetes+lycopene group, in comparison to the control+lycopene group (arrows). PAS method. Bar: 20 µm

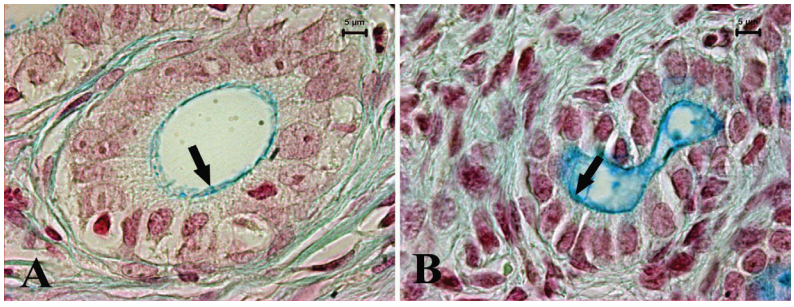

Figure 12: AB pH: 2.5 positive reaction in the glandular epithelium of the uterus in the control+corn oil (A) and diabetes+corn oil (B) groups. It can be seen that the intensity of the AB positive reaction was higher in the glandular epithelium of the uterus in the diabetes+corn oil group, in comparison to the control+corn oil group (arrows). AB pH: 2.5 staining method. Bar: 5 µm

Discussion

Diabetes mellitus causes various complications in the uterus and vagina. Garris and Smith (4) determined that the endometrial stroma and secretory activity of the epithelium of the uterus were disrupted by the effects of diabetes. In addition, Tatewaki *et al.* (24) showed that the lipid deposits increased in the uterine epithelium of diabetic animals. In our study, it was seen that the number of glands in the endometrium was lower in the diabetes+corn oil group, in comparison to the control+corn oil group. Based on these results, it can be seen that the secretory activity might change in the uterus with the effects of diabetes. It has been reported that the submucosal vasculature (10) and α-smooth muscle actin decreased in the vagina, but the amount of collagen and the apoptosis rate increased with the effects of diabetes (8). In this study, vacuoles were observed in the lamina epithelialis of the vagina in the diabetes groups; therefore, it was confirmed that diabetes mellitus led to structural disruptions in the vagina.

The effects of diabetes on the histometrical measurements of the uterus and vagina have been reported in various studies. In the uterus, it has been reported that diabetes decreased the height of the uterine epithelium (4) and the thickness of the myometrium (24). Similarly, Kim *et al.* (25) and Cushman *et al.* (9) determined that diabetes resulted in the thinning of the epithelium and a decrease in the muscularis area in the vagina. Park *et al.* (10) showed that the fibrosis risk increased in the vagina, with diabetes. In this study, it was observed that the thickness of the endometrium in the uterus, the height of the lamina epithelialis and thickness of the tunica muscularis in the vagina were smaller in the diabetes+corn oil group, in comparison to the control+corn oil group. Therefore, the secretory activity may decrease in the uterus, and structural atrophy may occur, with the effects of diabetes in the uterus and vagina. Moreover, the gland area in the uterus was smaller in the diabetes+lycopene group, in comparison to the control+lycopene group in the study. Based on these results, it may be expressed that this result is produced in diabetic animals only. However, the height of the lamina epithelialis and thickness of the tunica muscularis were larger in the control+lycopene group, in comparison to the control+corn oil group in the study. Therefore, it may be considered that lycopene might be beneficial in healthy individuals.

Lycopene is a powerful antioxidant with some protective effects. Zhou *et al.* (26) indicated that lycopene partially alleviated pulmonary fibrosis. In addition, Atessahin *et al.* (27) stated that lycopene ameliorated pathological changes, including tubular necrosis and degeneration. It was also found that lycopene reduced myocyte (28) and myocardial

damage (29), as well as having pharmacological potential in protecting against cardiomyocyte apoptosis (30). In our study, it was determined that the thickness of the tunica muscularis was larger in the diabetes+lycopene group, in comparison to the diabetes+corn oil group in the vagina. It may be suggested that lycopene might decrease the rates of fibrosis, apoptosis, and degeneration; therefore, it might prevent atrophy in the vagina.

A positive PAS reaction has been identified in the uterus and vagina. For example, Larsen (31) reported that PAS was observed in the uterine epithelium, staining the luminal cytoplasm of the non-ciliated cells. In addition, Pluta *et al.* (32) determined that the neutral mucin content was affected by the epithelial location and that it was greater in the basal than in the apical areas of the cervix. Noci *et al.* (33) found that an accumulation of glycogen was present at the cell base of the glandular epithelium in the endometrium; however, PAS-reactive cytoplasmic granules were seen in the natural killer (NK) cells in the uterus (34, 35). In addition, Wick and Kress (36) stated that macrophages showed PAS-positive reactions in the endometrial stroma in most cases. In this study, the PAS-positive reactions were seen in the apical parts of the surface and glandular epithelia in the uterus. Furthermore, the intensity of the PAS-positive reaction in the glandular epithelium was lower in the diabetes+corn oil group, in comparison to the control+corn oil group. For this reason, it can be indicated that the neutral mucin synthesis changed with the effects of diabetes in the uterine glandular epithelium. PAS-positive cells were observed in the endometrial connective tissue; based on the literature, these could be NK cells or macrophages (34–36).

Flamini *et al.* (37) reported that the epithelium in the vagina had two to three cellular layers with PAS-positive superficial cells, which is consistent with our results. Additionally, Groot *et al.* (38) determined that the PAS-positive granules showed an increase in the superficial layer of the vaginal epithelium due to androgenic influences. In our study, a PAS-positive reaction was observed in the superficial cell layers of the lamina epithelia in the vagina, and the intensity of the PAS-positive reaction was higher in the diabetes+lycopene group, in comparison to the control+lycopene group. This shows that the neutral mucins may be higher with the effect of diabetes in the vagina, and this result is only produced in diabetic animals.

It has been reported that the non-ciliated cells of the luminal epithelium in the uterus along the apical membrane stained (positive) with AB (36). In this study, an AB pH: 2.5 positive reaction was observed in the apical parts of the surface and glandular epithelia in the uterus. In addition, it has been found that the intensity of the AB pH: 2.5 positive reaction was higher in the glandular epithelium in the diabetes+corn oil group in comparison to the control+corn oil group. Therefore, it could be said that the acid mucosubstance may be higher with the effect of diabetes in the glandular epithelium of the uterus.

In conclusion, the changes in the uterus and vagina caused by diabetes, as well as the existence of the protective qualities of lycopene (in some parameters) have been revealed for the first time. We believe that further studies increasing the lycopene dosage and the implementation duration for diabetic animals will show that lycopene has a pronounced antioxidant effect on the uterus and vagina.

Acknowledgements

This paper has been summarized from a part of the first author's doctoral thesis. This study was supported by the Adnan Menderes University research fund. Project no: VHF-12018. Furthermore, the study was presented as an oral presentation at the 12th National Congress of Histology and Embryology, May 27-30 2014, Ankara, Turkey.

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SPREMEMBE V STENI MATERNICE IN NOŽNICE PODGAN Z EKSPERIMENTALNO POVZROČENO SLADKORNO BOLEZNIJO IN VPLIV LIKOPENA NA TE SPREMEMBE

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Povzetek: Namen raziskave je bil ugotoviti spremembe, ki so se zgodile v steni maternice in nožnice podgan z eksperimentalno povzročeno sladkorno boleznijo ter učinke peroralno apliciranega likopena na povzročene spremembe. Raziskava je zajela 42 štirimesečnih podganjih samic seva Wistar. Eksperimentalni diabetes je bil povzročen z enojnim odmerkom 50 mg/kg streptozotocina (STZ). Podgane iz kontrolne skupine in skupine s sladkorno boleznijo so bile naključno razdeljene v štiri skupine: kontrolna skupina podgan + koruzno olje, kontrolna skupina podgan + likopen, podgane s sladkorno boleznijo + koruzno olje in podgane s sladkorno boleznijo + likopen. Trojno barvanje po Crossmanu in metoda barvanja PAS (iz angl. Periodic Acid Schiff) sta bili uporabljeni pri histoloških rezinah maternice in nožnice. Dodatno so bile rezine maternic obarvane z barvilom alcian modro (AB). Število žlez, debelina endometrija in PAS-pozitivna reakcija žleznega epitelija v maternici so bili nižji pri podganah s sladkorno boleznijo, pozitivna reakcija AB v žleznem epiteliju pa je bila višja pri skupini podgan s sladkorno boleznijo v primerjavi s kontrolno skupino. Višina epitelija ter debelina mišične plasti stene maternice sta bili nižji pri podganah s sladkorno boleznijo, zanimivo pa je, da je likopen pozitivno vplival na debelino mišične plasti, saj je bila ta pri podganah s sladkorno boleznijo, ki so dobivale likopen, višja kot pri podganah, ki likopena niso dobivale.

Ključne besede: eksperimentalna sladkorna bolezen; likopen; podgana; maternica; nožnica