The Effects of Oral 5-alpha Reductase Inhibitors on Penile Intracavernosal Pressures and Penile Morphology in Rat Model

Sahin Kilic[1]*, Engin Kolukcu[2], Fikret Erdemir[3], Ismail Benli[4], Akgul Arici[5]

Purpose: Benign prostatic hyperplasia (BPH), and erectile dysfunction (ED) are urological diseases which affect more than 50 % of men older than 50 years of age. It has been reported that 5-alpha-reductase inhibitors (5-ARIs) used in clinical studies for the treatment of BPH caused ED in 0.8-15.8% of the patients. The aim of this study is evaluation of the effects of oral finasteride and dutasteride on penile intracavernosal pressures and penile morphology in a rat model.

Materials and Methods: Thirty Wistar Albino strain male rats were randomized into control (n = 10), finasteride (n = 10), and dutasteride (n = 10) groups. After 8 weeks of treatment erectile responses were evaluated in all rats measuring intracavernosal pressure (ICP) changes during erectile responses to cavernosal nerve electrical stimulation. Serum hormone levels were studied and all rats underwent prostatectomy and penectomy. All tissue samples were examined histomorphologically and a semiquantitative scoring system was used for cavernosal tissue collagen density grading.

Results: Approximately 50% decrease was seen in mean ICPs in the finasteride and dutasteride groups compared to the control group for all voltages (2.5 V, 5 V. 7.5 V). Mean ICPs for 7.5 V were 62.17 ± 30.89 mmHg in control group, 35.27 ± 31.94 in the finasteride, and 36.01 ± 19.20 mmHg in the dutasteride group. But regarding ICPs there was no statistically significant difference between the groups ($P > .05$). The serum testosterone (T) concentrations were higher in treatment groups ($P < .001$). Serum dihydrotestosterone (DHT), luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations were not significantly different between the groups. As a result of histomorphological studies, a statistically significant increase in cavernosal tissue collagen density, and marked atrophic changes in prostatic epithelial tissues were observed in the treatment groups.

Conclusion: Although 5-ARIs cause marked atrophic changes in prostatic epithelial tissues, and prominent collagen deposition in penile cavernosal tissues, no significant effect on penile ICPs was seen in this study. The failure to show a statistically significant difference was attributed to higher standard deviations of ICP values. The penile morphology evaluation results point to a negative effect of 5-ARIs on erectile function.

Keywords: dutasteride; erectile dysfunction; finasteride; intracavernosal pressure; penile morphology; prostate.

INTRODUCTION

BPH, accepted as a disease of advanced age, which impairs quality of life of the patients, is seen in approximately 50% of men between 51-60 years and approximately 90% over the age of 81 years[1]. In the etiology of BPH, androgens, estrogens, stromal-epithelial interactions, growth factors, and neurotransmitters can play a role alone or in combination[2]. Medical treatment methods of BPH include use of 5-ARIs, which target decrease in the prostatic volume. 5-ARIs ensure decrease in the size of prostate (nearly 30%) by preventing the production of dihydrotestosterone (DHT). Testosterone enters into prostatic epithelial cells and is converted into DHT through the action of 5-alpha reductase enzyme. DHT promotes the prostate enlargement by stimulating DNA synthesis in nuclei, and cellular growth[3]. In animal models, androgen deprivation has been demonstrated to cause deterioration of dorsal nerve structure, and endothelial morphology, decrease in trabecular smooth muscle, increase in extracellular matrix, and penile tissue atrophy. Furthermore, androgen deprivation leads to venous leak, and increase in the number of adipocytes in the subtunical region in the corpus cavernosum[4]. Androgen deprivation inhibits the production of protein, and enzymatic activities of endothelial nitric oxide synthase (eNOS), and neuronal nitric oxide synthase (nNOS) (5). Still, as is understood from available data, androgen deprivation leads to a de-

[1]Fethiye State Hospital, Department of Urology, Fethiye, Mugla.
[2]Tokat State Hospital, Department of Urology, Tokat.
[3]Gaziosmanpasa University, Faculty of Medicine, Department of Urology, Tokat.
[4]Gaziosmanpasa University, Faculty of Medicine, Department of Biochemistry, Tokat.
[5]Gaziosmanpasa University, Faculty of Medicine, Department of Pathology, Tokat.
*Correspondence: Fethiye State Hospital, Department of Urology, Fethiye, Mu□la 48300, Turkey.
Telephone: +90 507 240 71 86, Fax: +90 252 614 10 02, E-Mail: sahinkilic84@hotmail.com
Received September 2017 & Accepted June 2018

crease in the smooth muscles of the corpus cavernosum, and the elastic fibres of the tunica albuginea, and an increase in collagen fibres[6].

ED is defined as the persistent inability of a male to achieve and/or maintain a penile erection sufficient to permit satisfactory sexual performance[7]. Its prevalence ranges between 30-52% in men aged 40-70 years, while it climbs to 80%, among men older than 70 years of age[8]. Psychogenic, hormonal, neurogenic, and arterial pathologies, iatrogenic causes, systemic, and chronic diseases, and drugs play a role in the etiology of ED[9]. As indicated in various studies, the use of 5-ARIs may cause loss of libido, ejaculatory disorders and erectile dysfunction[10]. However, most of the studies investigating the correlation between 5-ARIs and ED have consisted of clinical research, and an extremely limited number of experimental animal studies investigated cavernosal tissues. As far as we know in English medical literature, finasteride, and dutasteride have not been evaluated in combination in any animal studies. Accordingly, our study appears to be the first trial which evaluated the effects of 5-ARIs on rat cavernosal tissue, prostate morphology, and penile cavernosal response to electrical stimulation in rats. To this end in our study we aimed to evaluate the effects of 5-ARIs on penile cavernosal pressures, serum androgen levels, and penile tissue.

MATERIALS AND METHODS

A total of 30 10-week-old male Wistar Albino strain rats weighing 250-300 g (median, 270 g) were used. All procedures were realized in accordance with the stipulations of the 1986 Strasbourg Universal Declaration of Animal Rights in Gaziosmanpa□a University Experimental Medicine Application Centre after the approval, and with the support of the Gaziosmanpa□a University Animal Studies Ethics Committee (2012 HADYEK 036). The rats were housed in standard rat cages at 20-23 °C, and under 12-hour dark, and 12-hour light cycles. The rats were fed with special rat pellet, and water ad libitum.

The rats were randomized into 3 groups, each containing 10 rats with simple randomization. Group 1 was the control group which did not receive any drug therapy. Group 2 rats received daily doses of 4.5 mg/kg finasteride via oral gavage for 8 weeks. In Group 3 each rat received daily doses of 0.5 mg dutasteride for 8 weeks via oral gavage.

Measurement of Penile Cavernosal Pressure

At the end of 8 weeks rats were anesthesized with intraperitoneal 50 mg/kg ketamine, and 10 mg/kg xylazine. The rats were laid on an operating table warmed at a stable temperature of 36 °C (AOT 0811 Animal Operating Table), and through midline scrotal incision of the skin, and prostate and penile roots of the rats were approached. A 25 gauge penile cavernosal pressure needle irrigated with heparin mounted to a pressure transducer (Biopac-MP 45 System, USA) integrated to a data gathering system was inserted into the left corpus cavernosum for continuous measurement of intracavernosal pressure (ICP). The left major pelvic ganglion, and cavernosal nerve were identified, and bipolar, a stainless steel hook electrode was advanced through the left posterolateral prostate, and placed around the cavernosal nerve. While continuously measuring ICP, the cavernosal nerve was stimulated with an electrical nerve stimulator (STN 0211 Nerve Stimulator) for 30 seconds with 50 Hz, 2.5 V, 5 V, and 7.5 V at square wave times of 2 msec to achieve erection. ICP, measured before 2.5 V electrical stimulation, was considered as baseline, and maximum changes in ICP with reference to baseline ICP up to termination of 7.5 V stimulation were recorded for each voltage (2.5 V, 5 V, and 7.5 V, respectively).

Then intracardiac blood samples of 3cc were drawn from each rat to determine testosterone, DHT, FSH and LH levels. Subsequently the rats underwent prostatectomy, and penectomy through the previously made midline scrotal incision. At the end of the study all rats were sacrificed by cervical dislocation.

Biochemical Measurements

Blood samples drawn were centrifuged, and sera were kept at -80 oC pending biochemical analysis. Testosterone, DHT, FSH, and LH levels of samples were measured using the ELISA method (Organon Teknika Reader 230S, Austria). For the measurement of serum testosterone, FSH, and LH levels, Cayman (Cayman Chemical Company, MI, USA) brand, and for DHT levels General (WUHAN EIAAB Science CO., LTD, Wuhan, China) brand kits were used.

Histopathological Evaluation

Prostatectomy, and penectomy samples were fixated in a 10% buffered formaldehyde solution, then routinely embedded in paraffin blocks. Rat penises were cut in 5 μ sections, and stained with Masson trichrome dye so as to evaluate the collagen content in the tissue. Smooth muscle collagen ratios in penile cavernosal tissues were histopathologically evaluated. Rat prostates were cut in 5 μ sections, and stained with hematoxylin/eosine dye, and examined under a light microscope (Nikon ECLIPSE E600) at 100x magnification for the evaluation of muscular, and glandular structures. Microscopic images were obtained from a total of 4 serial sections, with 2 sections per slide of each rat. Then 16-20 areas were analyzed for each rat in total, with at least 4-5 areas on each section. Grading of tissue collagen density was performed based on scoring used by Erdemir et al[11]. The percentage of collagen concentration in each cut section, and field of examination was determined semiquantitatively and expressed in comparison with blue-stained collagen positive areas. Masson trichrome stained areas were graded on a scale between 1 and 4, based on percentages of penile cavernosal collagen content. Collagen percentages of < 30%, 30-50%, 51-70%, and > 71% were graded as 1, 2, 3, and 4, respectively.

Statistical Analysis

Descriptive analyses were performed so as to get information about the general characteristics of the groups. After assessing of the normality, one-way analysis of variance was used for intergroup comparisons of variables. Repeated measures analysis of variance was used for comparisons based on changes in variables over time. For two group comparisons Tukey HSD test was used as post hoc test of one way analysis of variance. Data concerning continuous variables were expressed as mean ± standard deviation. $P < .05$ was accepted as the level of statistical significance. For statistical calculations commercially available software programs were utilized (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Table 1. Mean values for maximum changes in intracavernosal pressures induced by electrical stimulation of cavernosal nerve at each voltage

	Control Group (mmHg) (n=10)	Finasteride Group (mmHg) (n=10)	Dutasteride Group (mmHg) (n=10)	*p**
Measurement 2.5V	8.05 ± 14.58	2.86 ± 3.97	2.06 ± 2.85	0.278
Measurement 5V	25.70 ± 30.30	15.07 ± 15.08b	15.15 ± 13.21d	0.438
Measurement 7.5V	62.17 ± 30.89 a	35.27 ± 31.94 c	36.01 ± 19.20 e	0.062
*p***	< 0.001	0.001	< 0.001	

** One-way repeated measures analysis of variance

a A significant correlation was detected between measurements performed at 2.5 V and.5 V

b A significant correlation was detected between measurement at 2.5 V

c A significant correlation was detected between measurements performed at 2.5 V and.5 V

d A significant correlation was detected between measurement performed at 2.5 V

e A significant correlation was detected between measurements performed at 2.5 V and.5 V

Data are given as mean ± SD

RESULTS

Penile cavernosal pressures

Mean ICP values for electrical stimulation of cavernosal nerve with 2.5 V were calculated as 8.05 ± 14.58 mmHg in Group 1, 2.86 ± 3.97 mmHg in Group 2, and 2.06 ± 2.85 mmHg in Group 3. Intergroup differences were not statistically significant ($P = .278$). Mean ICPs for 5 V were estimated as 25.70 ± 30.30 mmHg in Group 1, 15.07 ± 15.08 in Group 2, and 15.15 ± 13.21 mmHg in Group 3 without any statistically significant intergroup difference ($P = .438$). Mean ICPs for 7.5 V were 62.17 ± 30.89 mmHg in Group 1, 35.27 ± 31.94 in Group 2, and 36.01 ± 19.20 mmHg in Group 3. But intergroup differences were not statistically significant ($P = .062$). An approximately 50% decrease was seen in mean ICPs in the finasteride and dutasteride groups compared to the control group for all voltages in qualitative evaluation performed during the procedure. But in statistical analysis, no significant intergroups differences were seen.

In one-way repeated measures of variance analysis in intragroup comparisons of mean ICP values for all voltages (2.5 V, 5 V. 7.5 V), a statistically significant difference was detected in all groups ($P < .001$, **Table 1**). Generally, in all groups as the voltage of electrical stimulation of the cavernosal nerve increased, increases in mean ICP values were seen (**Figure** 1).

Serum Hormone Levels

The mean serum testosterone level in Group 2 was significantly higher relative to Group 1 ($P < .001$). The mean serum testosterone level in Group 3 was significantly higher relative to Group 1 ($P < .001$). However no significant intergroup difference was detected for other serum hormone levels (**Table 2**).

Penile morphology

When compared with Group 1, prominently increased collagen density was observed in Groups 2 and 3 (**Figure 2**). In Group 1 Grade 3, and 4 collagen densities were not seen, while Groups 2 and 3 had no Grade 1 collagen density. In Group 1, Grade 1, and Grade 2 collagen densities were observed in 80% and 20% of the specimens, respectively. In Group 2, Grade 2, Grade 3, and Grade 4 collagen densities were detected in 50%, 30%, and 20% of the specimens, respectively. In Group 3, Grade 2, Grade 3, and Grade 4 collagen densities were observed in 30%, 40%, and 30% of the specimens, respectively. As a result of histomorphological studies, a statistically significant increase in cavernosal tissue collagen density was observed in the treatment groups. (**Table 3**).

Prostate Morphology

In Group 1 high columnar epithelium, and papillary folds were markedly observed in prostatic glandular tis-

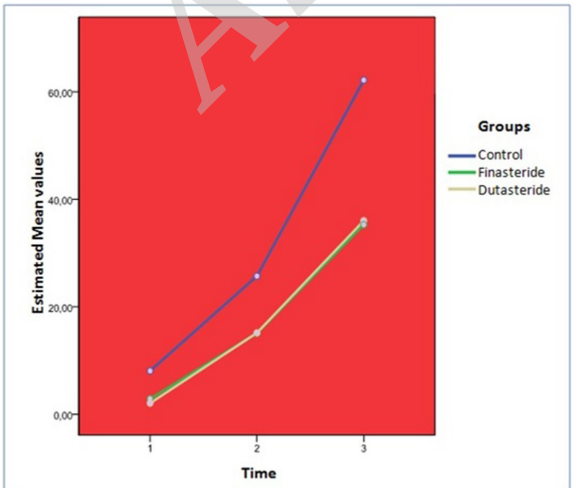
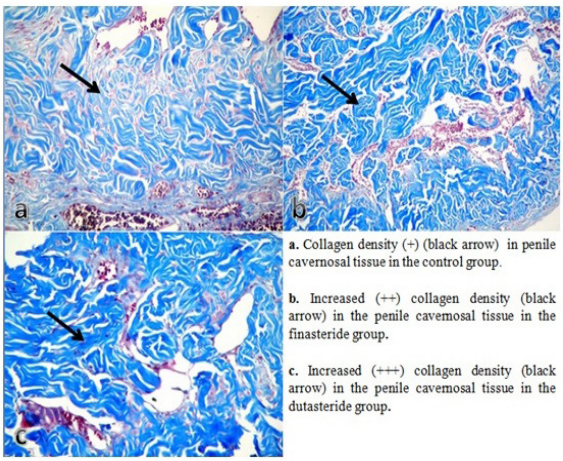


Figure 1. Time- dependent changes in mean ICP values of groups.



a. Collagen density (+) (black arrow) in penile cavernosal tissue in the control group.

b. Increased (++) collagen density (black arrow) in the penile cavernosal tissue in the finasteride group.

c. Increased (+++) collagen density (black arrow) in the penile cavernosal tissue in the dutasteride group.

Figure 2. Collagen density (blue-stained areas) in penile cavernosal tissues in all groups (MT x 400).

Table 2. Mean hormonal values of all groups

	Control Group(n=10)	Finasteride Group (n=10)	Dutasteride Group (n=10)	*P**
FSH (mIU/mL)	1.29 ± 0.59	2.04 ± 1.43	1.68 ± 0.70	0.248
LH (mIU/mL)	6.80 ± 0.39	6.80 ± 0.35	6.99 ± 0.31	0.377
Testosterone (pg/mL)	308.97 ± 146.29	628.40 ± 153.97a	613.64 ± 179.24[b]	< 0.001
Dihydrotestosterone (pg/mL)	2.57 ± 1.07	2.90 ± 1.23	2.43 ± 0.96	0.621

* One-way analysis of variance

a A significant correlation was found versus control group.

b A significant correlation was found versus finasteride group

Data are presented as mean ± SD

sue (**Figure 3**). However, predominant atrophic changes were seen in prostatic epithelial tissues in Groups 2, and 3, being more marked in Group 3 (**Figure 3**).

DISCUSSION

Effects of androgens on erectile function, libido, and sexual behaviour are very well known[4-6,9]. Androgens exert their effects in erectile physiology by directly binding to their receptors or via conversion to their more active form of 5-alpha dihydrotestosterone which is mediated by the 5-alpha reductase enzyme. In experimental animal models androgen deprivation has led to morphologic deterioration in the dorsal nerve, and endothelium; decrease in the content of trabecular smooth muscle; increase in connective tissue components, together with atrophy of the penile tissue [4,12]. Androgen deprivation causes apoptosis of spongious, and cavernosal cells which can be prevented by androgen administration[13]. It has been detected that DHT prevents disruption of erectile function in castrated rats, and this effect has been correlated partially with an increase in the levels of nitric oxide synthase (NOS)[14]. In the light of these data the effects of androgens on erectile physiology are apparently very important.

5-ARIs used in the medical treatment of BPH inhibit the conversion of testosterone to more potent androgen DHT. As a result of their effects, prostate volume decreases by 20%-30%, and within 6-12 months a nearly 50% decrease in prostate specific antigen (PSA) levels is induced[3,15]. A decrease in the volume of prostatic glandular tissue caused by 5-ARIs effects the static component of BPH, with a resultant increase in urine flow, and a decrease in BPH-related LUTS, acute urinary retention, and risk of surgery[3,10]. Also 5-ARIs decreases the serum levels of DHT, which is the major androgen involved in erectile physiology, by 70-90 percent[16-17].

Many clinical, and experimental studies have revealed the correlation between 5-ARIs, and erectile dysfunction. The most frequently reported unwanted adverse sexual effect of 5-ARIs is ED, followed by ejaculatory disorder, and decrease in libido (18). Finasteride at a dose of 1 mg is frequently used in dermatology practice, and finasteride-related ED is reported in 0.8-3.8% of these patients, while ED is detected in 3.4-15.8% of the patients who used daily doses of 5 mg finasteride in the treatment of BPH[18-21]. Findings in studies on dutasteride rates of ED are similar to those indicated above. In a double-blind, placebo-controlled study by Andriole et al. statistically significantly higher incidence rates of ED have been detected in the dutasteride group (4.7%) when compared with the placebo group (1.7%)[22].

The effects of 5-ARIs on erectile function are clearly seen not only in clinical, but also in experimental studies. Within the last four decades, animal experiments have provided evidence demonstrating the key role of DHT in erectile physiology[23,24]. Besides, an animal study has demonstrated that castration induces a 50% decrease in erectile response, and testosterone treatment reverses this effect. However this study has showed that in castrated rats when finasteride is given in combination with testosterone, the erectile response is not improve. When finasteride is administered with DHT, improvements in nNOS expression, and activity, and erectile response to electrical stimulation are detected[14]. This finding underlines the important hormonal role of DHT in erectile physiology. In a different study the effects of finasteride (4.5 mg/kg/day for one month), and castration on serum hormone levels, cavernosal, and prostatic morphology, and intracavernosal pressure response to cavernosal nerve stimulation were evaluated[25]. In the control, and finasteride group similar testosterone levels were observed, while significantly reduced DHT levels were detected in the finasteride, and castration groups. In the castration group the relative proportion of cavernosal smooth muscle markedly decreased, while the mass of connective tissue (collagen) increased prominently, and no change in the smooth muscle/collagen ratio was observed. In the castration group a decreased intracavernosal pressure response to cavernosal nerve stimulation was detected, while no difference was detected between control, and finasteride groups as for the intracavernosal pressure response [25]. In another study the effects of long-term (16 weeks) use of finasteride on cavernosal tissues, and erectile response was evaluated

Table 3. Grading of collagen density in penile cavernosal tissues

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Group 1 (n)	8	2	0	0	10
Group 2 (n)	0	5	3	2	10
Group 3 (n)	0	3	4	3	10
Total (n)	8	10	7	5	30

Since more than %20 of 'n' values in each cell of the table is smaller than '5' "'p' value was not calculated.

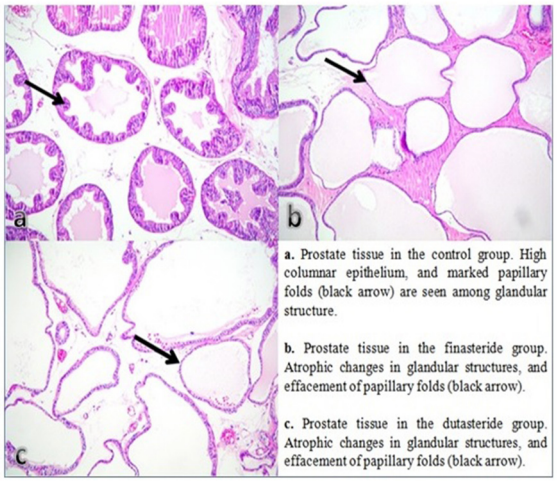


Figure 3. Prostate tissues in all groups (HE x 100).

in old (16 months) rats. Decreases in cavernosal smooth muscle cells, and cavernosal smooth muscle/collagen ratio were detected. During in vivo evaluation a significant decrease in erectile response was observed[26]. In our study, mean ICP values in the finasteride, and dutasteride groups are similar and decreased by nearly 50% when compared with the control group, without reaching any level of statistical significance. Generally, in all groups as the voltage of electrical stimulation of the cavernosal nerve increased, increases in ICP values are seen ($P < .001$). This indicates that the ICP measurements are done correctly. The failure to show a statistically significant difference was attributed to higher standard deviations of ICP values. This is in some rats maximum change in ICP values were reached after electrical stimulation with 2.5 V, while in some maximum change in ICP values were reached after electrical stimulation with 5 V or 7.5 V. We conclude that increasing the sample size and the duration of the treatment can give statistically significant results. When compared with the control group, increase in serum testosterone levels are detected in the finasteride group. However no significant intergroup difference was detected in serum DHT levels. In the semiquantitative histopathological evaluation, significant atrophic changes are detected in the prostate tissues, and significantly increased collagen deposition is observed in the cavernosal tissues in the finasteride group versus the control group.

Effects of 5-ARIs on penile cavernosal tissue, and prostate have been investigated in many experimental studies. Pinsky et al. evaluated the effects of dutasteride on cavernosal tissues, and erectile response in an animal study[27]. They observed 86.5% suppression of mean serum DHT levels, increased collagen accumulation in cavernosal tissues, a decrease in nNOS activity, and in in vivo assessments significant reduction in erectile response in the treatment group. Öztekin et al. evaluated the effects of long term dutasteride treatment and treatment withdrawal on cavernosal tissues and erectile responses. They observed that 8 weeks of dutasteride treatment significantly decreased erectile response in in vivo assessments, when compared with the control group, and the group where the dutasteride treatment had been discontinued for 2 weeks after 6 weeks treatment. However erectile responses in the withdrawal group were not so strong as those seen in the control group. The researchers concluded that decreased erectile response caused by dutasteride could persist after its withdrawal[28].

In our study, the impact of dutasteride on mean ICP values is similar when compared with the finasteride group. Furthermore similar to the finasteride group, the serum DHT levels decreased relative to the control group without reaching any level of statistical significance. However, in our study, if the prostatic tissue hormone levels were measured instead of the serum hormone levels, it is possible that statistically significant results for DHT levels would be obtained[29]. On the semiquantitative visual score, collagen accumulation in cavernosal tissues is more markedly observed in the dutasteride group, relative to the control, and finasteride groups. In the evaluation of prostatic tissues, atrophic changes in the dutasteride group are more prominent versus the control, and finasteride groups. These findings demonstrate that even though in clinical studies dutasteride decreases serum DHT levels, in the long term when compared with finasteride, in animal tissue studies they indicate that dutasteride can induce prostatic atrophy to a greater extent, and greater amount of collagen deposition in the cavernosal tissues. It should be noted that in clinical studies, similar incidence rates of sexual side effects related to finasteride or dutasteride treatment have been observed.

Although 5-ARIs treatment results in marked atrophic changes in epithelial tissues, and prominent collagen accumulation in penile cavernosal tissue, a significant impact on penile cavernosal pressures is not detected. Even though 5-ARIs demonstrate similar efficacy, and side effect profiles, acording to our study dutasteride induces more severe atrophic changes in the prostatic tissue, and more diffuse collegen accumulation in the cavernosal tissue compared with.

CONCLUSIONS

Androgens are critical for cavernosal smooth muscle integrity. Treatment with 5-ARIs decreases serum DHT levels up to 95%. Although 5-ARIs cause marked atrophic changes in prostatic epithelial tissues, and prominent collagen deposition in penile cavernosal tissues, they were not seen to produce a significant effect on penile ICPs in this study. Inability to demostrate a statistically significant difference was attributed to the higher standard deviations of ICP values. This condition is a shortcoming of the study. Serum testosterone levels were observed to be statistically significantly higher in the treatment groups than in the control group. But there was no significant intergroup difference for serum DHT levels. Although dutasteride and finasteride have similar efficacy and side-effect profile in clinical studies, in our study dutasteride caused more atrophy in prostatic tissues and caused more intense collagen deposition in cavernosal tissues than finasteride. The penile morphology evaluation results are pointing to a negative effect of 5-ARIs on erectile function.

ACKNOWLEDGEMENTS

This study was funded by Gaziosmanpaşa University Unit of Scientific Research Projects (project no: BAP 2013-34).

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132:474-9.
2. Nicholson TM, Ricke WA. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. Differentiation. 2011;82:184-99.
3. Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin Endocrinol Metab 2004;89:2179-84.
4. Traish A, Kim N. The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function. J Sex Med. 2005;2:759-70.
5. Traish AM, Goldstein I, Kim N. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol. 2007;52:54-70.
6. Shabsigh R. The effects of testosterone on the cavernous tissue and erectile function. World J Urol. 1997;15:21-6.
7. Hatzimouratidis K, Giuliano F, Moncada I et al. European Association of Urology; Male Sexual Dysfunction. Publishing Guidelines Uroweb. 2016. http://uroweb.org/guideline/male-sexual-dysfunction/#3. Accessed 15 March 2017
8. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151:54-61.
9. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction Nat Rev Dis Primers. 2016;2:16003
10. O'Leary M.P, Roehrborn C.G, Andriole G et al. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5α-reductase inhibitor. BJU Int. 2003;92:262-6.
11. Erdemir F, Firat F, Markoc F et al. The effect of pentoxifylline on penile cavernosal tissues in ischemic priapism-induced rat model. Int Urol Nephrol. 2014;46:1961-7.
12. Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. J Androl. 2003;24:381-7.
13. Podlasek CA, Meroz CL, Korolis H, Tang Y, McKenna KE, McVary KT. Sonic hedgehog, the penis and erectile dysfunction: a review of sonic hedgehog signaling in the penis. Curr Pharm Des. 2005;11:4011-27.
14. Lugg JA, Rajfer J, González-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. Endocrinology. 1995; 136:1495-501.
15. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5α-reductase inhibitors for the enlarged prostate. Clin Ther. 2007;29:17-25.
16. Sudduth SL, Koronkowski MJ. Finasteride: the first 5 alpha-reductase inhibitor. Pharmacotherapy. 1993;13:309-325.
17. Shigehara K, Miyagi T, Nakashima T, et al. Effects of dutasteride on lower urinary tract symptoms: a prospective analysis based on changes in testosterone/dihydrotestosterone levels and total prostatic volume reduction. Aging Male. 2016;19:128-133.
18. Erdemir F, Harbin A, Hellstrom W. 5-Alpha Reductase Inhibitors and Erectile Dysfunction: The Connection. J Sex Med. 2008;5:2917-24.
19. Nickel JC, Fradet Y, Boake RC, et al. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). Proscar Safety Plus Efficacy Canadian Two year Study. CMAJ. 1996;155:1251-9.
20. Lowe FC, McConnell JD, Hudson PB, et al. Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. Urology. 2003;61:791-6.
21. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med. 1998; 338: 557-63.
22. Andriole GL, Kirby R. Safety and tolerability of the dual 5alphareductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. Eur Urol. 2003;44:82-8.
23. Gray GD, Smith ER, Davidson JM. Hormonal regulation of penile erection in castrated male rats. Physiol Behav. 1980;24:463-8.
24. Bradshaw WG, Baum MJ, Awh CC. Attenuation by a 5 alpha-reductase inhibitor of the activational effect of testosterone propionate on penile erections in castrated male rats. Endocrinology. 1981;109:1047-51.
25. Zhang MG, Wu W, Zhang CM, et al. Effects of oral finasteride on erectile function in a rat model. J Sex Med. 2012;9:1328-36.
26. Zhang MG, Wang XJ, Shen ZJ, Gao PJ. Long-term oral administration of 5α-reductase inhibitor attenuates erectile function by inhibiting autophagy and promoting apoptosis of smooth muscle cells in corpus cavernosum of aged rats. Urology. 2013;82:9-15.
27. Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom JG. The Effects of Chronic 5-Alpha-

Reductase Inhibitor (dutasteride) Treatment on Rat Erectile Function. J Sex Med. 2011;8: 3066-74.

28. Oztekin CV, Gur S, Abdulkadir NA, Hellstrom JG. Incomplete recovery of erectile function in rat after discontinuation of dual 5-alpha reductase inhibitor therapy. J Sex Med. 2012;9:1773-81.

29. Cook MB, Stanczyk FZ, Wood SN, et al. Relationships between Circulating and Intraprostatic Sex Steroid Hormone Concentrations. Cancer Epidemiol Biomarkers Prev. 2017;26:1660-6.