Received: 20 March 2018 | Revised: 31 May 2018 | Accepted: 19 June 2018

DOI: 10.1111/and.13110

ORIGINAL ARTICLE

WILEY ANDROLOGIA

The effect of dutasteride on microscopic and macroscopic changes of testosterone replacement treatment on prostate tissue

Mehmet Akif Diri[1] | Banu Diri[2] | Levent Yildiz[3] | Recep Büyükalpelli[4]

[1]Department of Urology, Aksaray University School of Medicine, Aksaray, Turkey

[2]Department of Nephrology, Aksaray University School of Medicine, Aksaray, Turkey

[3]Department of Pathology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey

[4]Department of Urology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Correspondence
Mehmet Akif Diri, Department of Urology, Aksaray University School of Medicine, Aksaray 68100, Turkey.
Email: akifdiri55@gmail.com

Abstract

Testosterone replacement therapy has a growing interest in daily practice; however, debates on its safety for prostate cancer still continue. Dutasteride—a 5α-reductase inhibitor—was shown to be effective in preventing prostate cancer. We therefore aimed to evaluate the effect of testosterone replacement therapy and dutasteride treatment on prostate tissue in castrated rats. Rats were randomised in four groups after bilateral orchidectomy as follows: Group I received testosterone + dutasteride, Group II received only testosterone, Group III had no medical treatment, and Group IV was the control group. After 3 months, rats were sacrificed and laboratory and histopathological examinations were performed. In Groups I and II, prostate volume, T and DHT levels were significantly higher compared to Group III and controls. Groups I and II had also significantly greater preneoplastic histopathological signs; however, in intergroup analyses, Group I showed less premalignant changes compared to Group II. We concluded that dutasteride was effective when combined with testosterone therapy in preventing premalignant histopathological changes in prostate tissue. Further evidence is needed to confirm our findings.

KEYWORDS

dihydrotestosterone, dutasteride, prostate cancer, testosterone

1 | INTRODUCTION

Exogenous testosterone therapy has long been used as standard therapy for hypogonadism (Loeb et al., 2017). However, in recent years, testosterone testing and use has increased dramatically and it has been observed that a considerable number of patients have started treatment of testosterone without a definite indication (Layton et al., 2014).

Given the increased use of testosterone, the concern of the risk of developing prostate cancer has arisen, since the discovery of androgen dependence of prostate cancer (Huggins, & Hodges, 2002). Although recent meta-analyses found no absolute correlation between testosterone replacement therapy (TRT) and increased risk of prostate cancer, many studies in those meta-analyses had significant limitations including lack of long-term data and relatively small sample sizes (Cui, Zong, Yan, & Zhang, 2014). On the other hand, in a recent meta-analysis a higher percentage of prostate events have been shown in middle-aged and older men receiving TRT (Calof et al., 2005). Besides, current guidelines also indicate prostate cancer as a contraindication for TRT (Dohle et al., 2016).

The 5α-reductase inhibitors (5-ARIs) are a class of drugs blocking the action of 5α-reductase, which has a key role for the enzyme transforming from testosterone (T) to the metabolically active derivative, dihydrotestosterone (DHT), resulting in a decreased level of DHT and increased level of T. There are three isoenzymes of 5α-reductase identified in humans (Uemura et al., 2008). Today, finasteride and dutasteride are used especially for benign prostatic hyperplasia (BPH) treatment in urology clinics (Clark et al., 2004).

5-ARIs have also been studied for prostate cancer chemoprevention trials, and both trials demonstrated significant reductions in overall prostate cancer incidence (Andriole, et al., 2010; Thompson et al., 2003). However, the effect of combined use of dutasteride and T on prostate tissue is insufficient.

In this study, we therefore aimed to evaluate macroscopic and microscopic changes of dutasteride—a dual inhibitor—and supraphysiological testosterone replacement therapy in castrated prostate tissue of rats.

2 | MATERIALS AND METHODS

This study was approved by the Experimental Animal Ethics Committee of Ondokuz Mayıs University School of Medicine. Sixty sexually active male Sprague-Dawley rats at 12 months of age were randomly grouped into experimental and control groups with 15 rats in each (Groups I, II, III and IV). The rats were fed standard rat food and water, and a 12-hr light/dark cycle per day was maintained during the study.

Bilateral scrotal orchiectomy was performed at the beginning of the study in Groups I, II and III. Group IV was identified as the control group. Surgical antibiotic prophylaxis was performed by administering cefazolin sodium 20 mg/kg dose intramuscularly to all subjects before all surgical procedures. In addition, all surgical procedures were performed under anaesthesia with intraperitoneal (IP) ketamine (Ketalar®) at a dose of 80 mg/kg.

Group I received daily dutasteride 0.5 mg/rat per day p.o. for 90 days and 1 mg/kg testosterone propionate (Eifelfango®) IP every 15 days. For Group II, only testosterone propionate was administered at the same dose and duration. In Group III, no medical treatment was given. On Day 90, total cardiac 4 cc blood samples were taken from all groups and total prostatectomy was performed. Blood samples were centrifuged at 3,000 ppm/min for 10 min and stored at −80°C until analysis. T was measured by the RIA method (Biosource®; Testo-RIA-CT KIP1709) and DHT by the ELISA method (Biosource®; DHT-ELISA KAPD2330).

Samples containing bladder and genital organs were fixed in 10% neutral formalin solution buffered for 24 hr. Following, the prostates were dissected and weighed with a precision scale (Shimadzu; BW420-H). All prostate tissues were sampled by removing a slice to cover the widest axis of the organ. The specimens were fixed in 10% formalin and embedded in paraffin in preparation for tissue sectioning. Four- to six-micrometre-thick sections were taken from paraffin blocks and stained with H&E (Norwood, MA, USA) for histopathological observation. The stained sections were evaluated by the following parameters using a light microscope (BX50; Olympus Hamburg, Germany) by a pathologist who was not informed about the procedures applied to the groups. The observed parameters were as follows: structural atypia in the glands, stromal hyperplasia, glandular epithelial nuclear pleomorphism, cellular stratification, atypical small acinar proliferation (ASAP), glandular epithelial nuclear hyperchromasia, nuclear entity, nucleolus increase, gland dysplasia, glandular atrophy and lipid metamorphosis.

Criteria such as glandular structural atypia, gland epithelial nuclear pleomorphism, cellular stratification, ASAP, nuclear hyperchromasia in the gland epithelium, nucleolus presence and number increase were chosen as the parameters used in the detection of preneoplastic conditions in the prostatic epithelium (Bostwick, Qian, & Schlesinger, 2003; Prehn, 1999). On the other hand, lipid metamorphosis, alteration of prostate tissue with mature fat tissue, erosion of gland epithelium and glandular atrophy were used as markers of regression or involution in prostate tissue. The existence and prevalence of each criterion were examined separately and evaluated according to the following scales:

Focal: The defined feature is scattered and focal.
+1: 0%–25% in defined feature sections.
+2: 26%–50% in defined feature sections.
+3: 51%–75% in defined feature sections.
+4: >75% criteria were used in the defined feature sections.

2.1 | Statistical analysis

Statistical analysis for each criterion was made by chi-square test. The expected value of <5 was confirmed by Fisher's exact test.

Statistical analysis of prostate volume, serum testosterone and DHT levels was performed using the Shapiro–Wilk normality test. The groups had normal distribution for DHT and volume values. DHT and volume were assessed by one-way ANOVA, and testosterone was evaluated by the Kruskal–Wallis variance analysis. One-way ANOVA was used to compare groups in terms of volume and DHT. The difference between the groups was assessed by the post hoc Tukey HSD test. The Kruskal–Wallis variance analysis and Bonferroni correction Mann–Whitney *U* test were used for statistical evaluation of serum testosterone levels among the groups.

3 | RESULTS

During the trial, three, six and four rats died from Groups I, II and III respectively. Table 1 shows the prostate volume, T and DHT levels of the study population. All parameters were found to be statistically significant ($p < 0.001$). In the intergroup analyses, statistically significant differences were also found except between Groups I and IV for prostate volume ($p = 0.291$) and between Groups I and II for T ($p = 0.0183$).

3.1 | Histopathological evaluation of prostate specimens

A microscopic view of a specimen from the control group is shown in Figure 1. Stromal hyperplasia, structural atypia in glands and ASAP

TABLE 1 Baseline characteristics of the study groups

	Orchidectomy + T + dutasteride (Group I), *n* = 12	Orchidectomy + T (Group II), *n* = 9	Only orchidectomy (Group III), *n* = 11	Control (Group IV), *n* = 15	*p*
Prostate volume (cc)	1.13 ± 0.61	1.83 ± 0.42	0.27 ± 0.13	0.75 ± 0.17	<0.001[a]
Serum T levels (ng/ml)	102.7 ± 41.56	192 ± 100	0.012 ± 0.004	0.34 ± 0.30	<0.001[b]
Serum DHT levels (pg/ml)	1560.1 ± 526.3	3,078.6 ± 170.8	33.9 ± 16.9	282.1 ± 183.7	<0.001[c]

[a]*p* value between Groups II and III, II and IV, and III and IV.
[b]*p* value between Groups I and III, I and IV, II and III, II and IV, and III and IV.
[c]*p* value between Groups I and II, I and III, I and IV, II and III, II and IV, and III and IV.

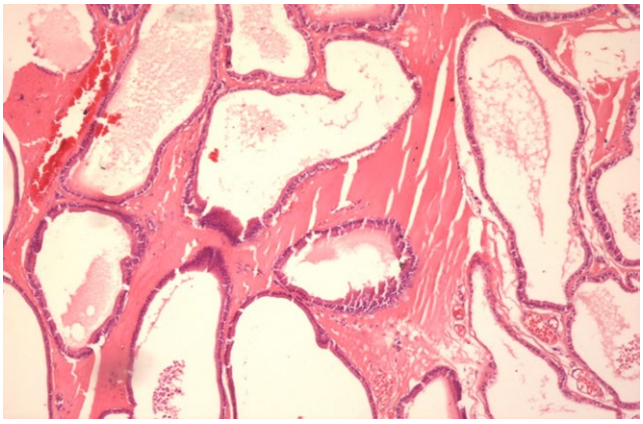

FIGURE 1 A microscopic view of the control group (normal prostate tissue, HE, ×100)

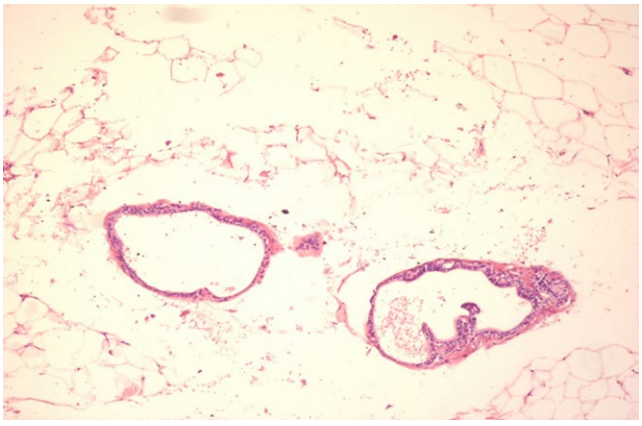

FIGURE 2 Glandular atrophy and fat metamorphosis (HE, ×100)

were not observed in any subjects. Glandular atrophy and fat metamorphosis were only seen in Group III (Figure 2). In Group I, only one subject was noted for inflammatory cell infiltration in gland epithelium and stroma. Table 2 lists the histopathological characteristics of the study groups.

Glandular epithelial nuclear pleomorphism was noted only in subjects in Groups I and II (Figure 3), and a statistically significant difference was found between Groups I and II, $p = 0.007$ ($p < 0.05$). Cellular stratification was not seen in Group III. In the binary comparison of other groups, there was a significant difference between Groups I and II, $p = 0.019$ ($p < 0.05$), whereas no significant difference was not seen between Groups I and IV, $p = 1.000$ ($p > 0.05$). Glandular epithelial nuclear hyperchromasia was only seen in Groups I and II, and there was also a significant difference between Groups I and II, $p = 0.024$ ($p < 0.05$). No finding was observed in Group III regarding the presence of nucleoli (Figure 3); on the other hand, there was a significant difference between Groups I and II, I and IV, and II and IV ($p < 0.05$), when focal findings compared with +1. Besides, when we evaluated the increase in number of nucleoli, only focal findings were observed in Groups I and II and statistically significant differences were observed between those groups, $p = 0.016$ ($p < 0.05$). No finding was observed in Group II when groups were evaluated in terms of glandular dysplasia. Statistical evaluation was performed among the groups by classifying them as "no findings" and "findings observed." In the binary comparison of groups, there was a significant difference between Groups III and IV ($p < 0.05$), whereas there was no significant difference between Groups I and III ($p > 0.05$) and I and IV ($p > 0.05$)

4 | DISCUSSION

Increased use of testosterone preparations in recent years due to the age-related decrease in serum testosterone levels and increased prostate-related diseases with age attracted the concern of the association between testosterone use and prostate diseases and the safety of these drugs. In this study, we found that TRT had a slight but not greater association with preneoplastic changes. In addition, subjects receiving dutasteride treatment with TRT were found to have lower preneoplastic parameters compared with those on TRT treatment arm only.

These findings are very significant given the ongoing debates about TRT and its benefits and risks when considering the recent reports about the increased use of TRT in the world (Layton et al., 2014). TRT can improve the effects of hypogonadism such as fatigue, sexual function, bone mineral density, lean body mass and cognitive function. It may also have some benefits on cardiovascular risk factors. On the other hand, the dark side of TRT may cause liver toxicity, gynaecomastia, erythrocytosis, testicular atrophy and

TABLE 2 Histopathological characteristics of prostate specimens

	No finding	Focal	1+	2+	3+	4+	Total	*p*
Glandular dysplasia, *n* (%)								
Orchidectomy + T + dutasteride	4 (33.3)	1 (8.3)	3 (25.0)	1 (8.3)	2 (16.7)	1 (8.3)	12 (100.0)	>0.05[a]
Orchidectomy + T	9 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100.0)	>0.05[b]
Only Orchidectomy	6 (54.5)	0 (0)	3 (27.3)	2 (18.2)	0 (0)	0 (0)	11 (100.0)	<0.05[c]
Control group	2 (13.3)	3 (20.0)	4 (26.7)	1 (6.7)	5 (33.3)	0 (0)	15 (100.0)	
Total	21 (44.7)	4 (8.5)	10 (21.3)	4 (8.5)	7 (14.9)	1 (2.1)	47 (100.0)	
Cellular stratification, *n* (%)								
Orchidectomy + T + dutasteride	2 (16.7)	4 (33.3)	6 (50.0)	0 (0)	–	–	12 (100.0)	0.019[d]
Orchidectomy + T	0 (0)	0 (0)	8 (88.9)	1 (11.1)	–	–	9 (100.0)	
Only orchidectomy	11 (100.0)	0 (0)	0 (0)	0 (0)	–	–	11 (100.0)	
Control group	6 (40.0)	1 (6.7)	7 (46.7)	1 (6.7)	–	–	15 (100.0)	>0.05[e]
Total	19 (40.4)	5 (10.6)	21 (44.7)	2 (4.3)	–	–	47 (100.0)	
Glandular epithelial nuclear pleomorphism, *n* (%)								
Orchidectomy + T + dutasteride	7 (58.3)	4 (33.3)	1 (8.3)	–	–	–	12 (%100.0)	0.007[f]
Orchidectomy + T	0 (0)	7 (77.8)	2 (22.2)	–	–	–	9 (100.0)	
Only orchidectomy	11 (100.0)	0 (0)	0 (0)	–	–	–	11 (100.0)	
Control group	15 (100.0)	0 (0)	0 (0)	–	–	–	15 (100.0)	
Total	33 (70.2)	11 (23.4)	3 (6.4)	–	–	–	47 (100.0)	
Glandular epithelial nuclear hyperchromasia, *n* (%)								
Orchidectomy + T+ dutasteride	8 (66.7)	3 (25.0)	1 (8.3	–	–	–	12 (100.0)	0.024[g]
Orchidectomy + T	1 (11.1)	7 (77.8)	1 (11.1)	–	–	–	9 (100.0)	
Only orchidectomy	11 (100.0)	0 (0)	0 (0)	–	–	–	11 (100.0)	
Control group	15 (100.0)	0 (0)	0 (0)	–	–	–	15 (100.0)	
Total	35 (74.5)	10 (21.3)	2 (4.3)		–	–	47 (100.0)	
Presence of nucleoli, *n* (%)								
Orchidectomy + T + dutasteride	0 (0)	7 (58.3)	5 (41.7)	–	–	–	12 (100.0)	<0.05[h]
Orchidectomy + T	0 (0)	0 (0)	9 (100.0)	–	–	–	9 (100.0)	<0.05[i]
Only orchidectomy	11 (100.0)	0 (0)	0 (0)	–	–	–	11 (100.0)	
Control group	9 (60.0)	1 (6.7)	5 (33.3)	–	–	–	15 (100.0)	<0.05[j]
Total	20 (42.6)	8 (17.0)	19 (40.4)	–	–	–	47 (100.0)	
Increase in number of nucleoli, *n* (%)								
Orchidectomy + T + dutasteride	11 (91.7)	1 (8.3)	–	–	–	–	12 (100.0)	0.016[k]
Orchidectomy + T	3 (33.3)	6 (66.7)	–	–	–	–	9 (100.0)	
Only orchidectomy	11 (100.0)	0 (0)	–	–	–	–	11 (100.0)	
Control group	15 (100.0)	0 (0)	–	–	–	–	15 (100.0)	
Total	40 (85.1)	7 (14.9)	–	–	–	–	47 (100.0)	

[a]Binary comparison of Groups III and IV.
[b]Binary comparison of Groups I and III.
[c]Binary comparison of Groups I and IV.
[d]Binary comparison of Groups I and II.
[e]Binary comparison of Groups I and IV.
[f]Statistical difference between Groups I and II.
[g]Statistical difference between Groups I and II.
[h]Statistical difference between Groups I and II.
[i]Statistical difference between Groups I and IV.
[j]Statistical difference between Groups II and IV.
[k]Statistical difference between Groups I and II.

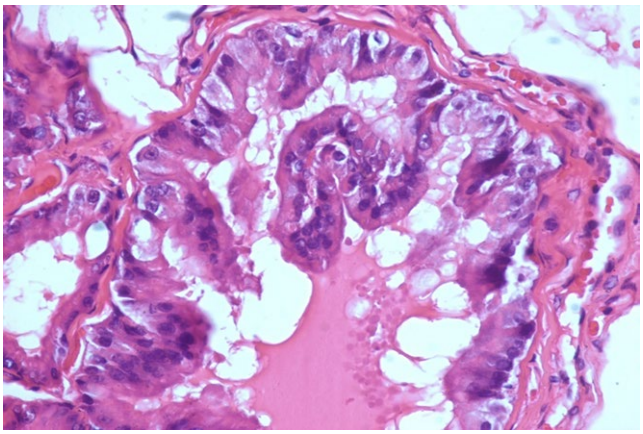

FIGURE 3 Presence of nucleoli, nuclear pleomorphism and cellular stratification (HE, ×400)

infertility, skin diseases and sleep apnoea and may stimulate the growth of breast and prostate cancers (Traish, Melcangi, Bortolato, Garcia-Segura, & Zitzmann, 2015).

Prostate cancer is well known to be an androgen-dependent disease in most cases, and medical or surgical castration has been a first-line treatment of advanced PCa. None of the benefits mentioned above might be worthwhile if T therapy is associated with the increased risk of PCa. Recent studies demonstrated little or no relationship between serum T concentrations and PCa (Cooper et al., 1998; Marks et al., 2006; Shabsigh, Crawford, Nehra, & Slawin, 2009). Most recent meta-analyses also support this information, but the individual trials in those meta-analyses had some limitations including short follow-up and the small sample sizes (Bruzzese et al., 2014; Cui et al., 2014). Otherwise, a recent meta-analysis demonstrated a significantly greater combined rate of prostate events in testosterone-treated men than in placebo-treated men (Calof et al., 2005). However, treatment arm was more likely to have a prostatic biopsy, which is a limitation of this study. Similarly, Bosland showed testosterone as a weak complete carcinogen and a strong tumour promoter for the rat prostate (Bosland, 2014). But, this paper has received a few negative reviews due to its methodology. In our study, although castrated groups receiving supraphysiological T (I and II) showed more preneoplastic features, some preneoplastic parameters including ASAP, glandular atypia and stromal hyperplasia were not shown in any subject. Our findings can be explained by the saturation model. According to this model, PCa growth is extremely sensitive to alteration in the serum T concentrations at or below the near-castrate range and is insensitive to T alterations above this concentration. More descriptively, there is saturation point below some critical T serum concentration and the effects of T and DHT on the prostate can be seen up to this saturation point. The change in the serum T levels above this point, such as administration of supraphysiological testosterone, has little or no effect on benign or malignant prostate growth (Morgentaler & Traish, 2009).

It has been demonstrated previously that DHT contributes to the growth and progression of PCa (Zhang, Zhang, Plymate, & Mostaghel, 2016). Dutasteride—a dual inhibitor of 5-ARI—inhibits the transformation of circulating T to DHT and is reportedly effective in the treatment of benign prostatic hyperplasia and in preventing prostate cancer (Andriole, et al., 2010; Thompson et al., 2003). Besides, Azuma, Matayoshi, Sato, and Nagase (2018) demonstrated that dutasteride may also be a therapeutic option in the treatment of castration-resistant prostate cancer. In this study, we also questioned the effect of dutasteride treatment on castrated rats receiving supraphysiological concentrations of T and indicated that rats receiving dutasteride treatment with T showed less preneoplastic histopathological signs compared to those receiving only T. However, dutasteride treatment could not prevent all the preneoplastic changes in the prostate tissue. According to the hormonal changes, testosterone concentrations are almost 550 times higher in the group receiving dutasteride, whereas those in the castrated group are 30 times lowered compared to the control group (Table 1). We can also explain these results with the saturation model. While in T-dependent phase (after castration), prostate tissue is extremely sensitive for T and its metabolite DHT, so both optimal prostate growth and histopathological changes can occur until saturation phase. After this point, circulating concentration of T is not important. However, if dutasteride is added, T concentrations retreat below the saturation point back and dutasteride does its work causing less preneoplastic changes and prostate volume. In the PCPT, the saturation model also works as PCa rates decreased by 25% in the finasteride-treated group compared to the placebo group (normal androgens), which may be related to the decreasing androgen levels below the saturation point (Thompson et al., 2003). This can also explain why young men do not have huge prostate sizes and prostate cancer, even though they have testosterone peak.

In several studies, prostate volume was shown to be decreased when combining the 5-ARI with TRT (Amory et al., 2004; Borst et al., 2007; Yarrow et al., 2017). Besides, in a recent meta-analysis, short-term testosterone plus 5α-reductase inhibitor therapy was demonstrated to not lead to prostate growth (Cui et al., 2014). However, only a few studies have histologically examined the prostate to determine whether premalignant changes occurred. In addition, it was shown that as circulating testosterone concentrations are increased from physiological to supraphysiological, testosterone alone can maintain prostate volumes even when 5α-reductase activity is suppressed effectively, which is compatible with our finding (Bhasin et al., 2012).

The present study has some limitations. First, it is an experimental animal study; therefore, it may show some differences compared to humans. In addition, we did not use any immunohistochemical analyses to detect intraprostatic T and DHT levels. Lastly, we performed this study with supraphysiologic testosterone dose and there should be a physiological dose group to strengthen the current study. Nevertheless, a less premalignant lesion was shown in orchidectomised rats receiving dutasteride and a high dose of testosterone compared to the other study groups.

In conclusion, dutasteride was demonstrably effective in preventing premalignant histopathological changes in rats and may be a promising therapeutic option for patients who are at risk of PCa and using TRT. To confirm this effect of dutasteride, prospective randomised studies are necessary.

CONFLICT OF INTEREST

None of the authors has any conflict of interest, financial or otherwise.

ORCID

Mehmet Akif Diri http://orcid.org/0000-0002-0413-4802

REFERENCES

Amory, J. K., Watts, N. B., Easley, K. A., Sutton, P. R., Anawalt, B. D., Matsumoto, A. M., … Tenover, J. L. (2004). Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *Journal of Clinical Endocrinology and Metabolism*, *89*(2), 503–510. https://doi.org/10.1210/jc.2003-031110

Andriole, G. L., Bostwick, D. G., Brawley, O. W., Gomella, L. G., Marberger, M., Montorsi, F., … REDUCE Study Group (2010). Effect of dutasteride on the risk of prostate cancer. *New England Journal of Medicine*, *362*(13), 1192–1202. https://doi.org/10.1056/NEJMoa0908127

Azuma, T., Matayoshi, Y., Sato, Y., & Nagase, Y. (2018). Effect of dutasteride on castration-resistant prostate cancer. *Molecular and Clinical Oncology*, *8*(1), 133–136. https://doi.org/10.3892/mco.2017.1480

Bhasin, S., Travison, T. G., Storer, T. W., Lakshman, K., Kaushik, M., Mazer, N. A., … Basaria, S. (2012). Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: A randomized controlled trial. *JAMA*, *307*(9), 931–939. https://doi.org/10.1001/jama.2012.227

Borst, S. E., Conover, C. F., Carter, C. S., Gregory, C. M., Marzetti, E., Leeuwenburgh, C., … Wronski, T. J. (2007). Anabolic effects of testosterone are preserved during inhibition of 5alpha-reductase. *American Journal of Physiology. Endocrinology and Metabolism*, *293*(2), E507–E514. https://doi.org/10.1152/ajpendo.00130.2007

Bosland, M. C. (2014). Testosterone treatment is a potent tumor promoter for the rat prostate. *Endocrinology*, *155*(12), 4629–4633. https://doi.org/10.1210/en.2014-1688

Bostwick, D. G., Qian, J., & Schlesinger, C. (2003). Contemporary pathology of prostate cancer. *Urologic Clinics of North America*, *30*(2), 181–207. https://doi.org/10.1016/S0094-0143(02)00189-1

Bruzzese, D., Mazzarella, C., Ferro, M., Perdonà, S., Chiodini, P., Perruolo, G., & Terracciano, D. (2014). Prostate health index vs percent free prostate-specific antigen for prostate cancer detection in men with "gray" prostate-specific antigen levels at first biopsy: Systematic review and meta-analysis. *Translational Research*, *164*(6), 444–451. https://doi.org/10.1016/j.trsl.2014.06.006

Calof, O. M., Singh, A. B., Lee, M. L., Kenny, A. M., Urban, R. J., Tenover, J. L., & Bhasin, S. (2005). Adverse events associated with testosterone replacement in middle-aged and older men: A meta-analysis of randomized, placebo-controlled trials. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*(11), 1451–1457. https://doi.org/10.1093/gerona/60.11.1451

Clark, R. V., Hermann, D. J., Cunningham, G. R., Wilson, T. H., Morrill, B. B., & Hobbs, S. (2004). Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. *Journal of Clinical Endocrinology and Metabolism*, *89*(5), 2179–2184. https://doi.org/10.1210/jc.2003-030330

Cooper, C. S., Perry, P. J., Sparks, A. E., MacIndoe, J. H., Yates, W. R., & Williams, R. D. (1998). Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *Journal of Urology*, *159*(2), 441–443. https://doi.org/10.1016/S0022-5347(01)63944-2

Cui, Y., Zong, H., Yan, H., & Zhang, Y. (2014). The effect of testosterone replacement therapy on prostate cancer: A systematic review and meta-analysis. *Prostate Cancer and Prostatic Diseases*, *17*(2), 132–143. https://doi.org/10.1038/pcan.2013.60

Dohle, G. R., Arver, S., Bettocchi, C., Jones, T. H., Kliesch, S., & Punab, M. (2016). *Guidelines on male hypogonadism 2015*. European Association of Urology. Retrieved from https://Uroweb.Org/Wp-Content/Uploads/EAU-Guidelines-Male-Hypogonadism-2015.Pdf

Huggins, C., & Hodges, C. V. (2002). Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *Journal of Urology*, *167*(2), 948–951. https://doi.org/10.1016/S0022-5347(02)80307-X

Layton, J. B., Li, D., Meier, C. R., Sharpless, J. L., Stürmer, T., Jick, S. S., & Brookhart, M. A. (2014). Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *Journal of Clinical Endocrinology and Metabolism*, *99*(3), 835–842. https://doi.org/10.1210/jc.2013-3570

Loeb, S., Folkvaljon, Y., Damber, J.-E., Alukal, J., Lambe, M., & Stattin, P. (2017). Testosterone replacement therapy and risk of favorable and aggressive prostate cancer. *Journal of Clinical Oncology*, *35*(13), 1430–1436. https://doi.org/10.1200/JCO.2016.69.5304

Marks, L. S., Mazer, N. A., Mostaghel, E., Hess, D. L., Dorey, F. J., Epstein, J. I., … Nelson, P. S. (2006). Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: A randomized controlled trial. *JAMA*, *296*(19), 2351–2361. https://doi.org/10.1001/jama.296.19.2351

Morgentaler, A., & Traish, A. M. (2009). Shifting the paradigm of testosterone and prostate cancer: The saturation model and the limits of androgen-dependent growth. *European Urology*, *55*(2), 310–320. https://doi.org/10.1016/j.eururo.2008.09.024

Prehn, R. T. (1999). On the prevention and therapy of prostate cancer by androgen administration. *Cancer Research*, *59*(17), 4161–4164.

Shabsigh, R., Crawford, E. D., Nehra, A., & Slawin, K. M. (2009). Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *International Journal of Impotence Research*, *21*(1), 9–23. https://doi.org/10.1038/ijir.2008.31

Thompson, I. M., Goodman, P. J., Tangen, C. M., Lucia, M. S., Miller, G. J., Ford, L. G., … Coltman, C. A. (2003). The influence of finasteride on the development of prostate cancer. *New England Journal of Medicine*, *349*(3), 215–224. https://doi.org/10.1056/NEJMoă60

Traish, A. M., Melcangi, R. C., Bortolato, M., Garcia-Segura, L. M., & Zitzmann, M. (2015). Adverse effects of 5α-reductase inhibitors: What do we know, don't know, and need to know? *Reviews in Endocrine and Metabolic Disorders*, *16*(3), 177–198. https://doi.org/10.1007/s11154-015-9319-y

Uemura, M., Tamura, K., Chung, S., Honma, S., Okuyama, A., Nakamura, Y., & Nakagawa, H. (2008). Novel 5 alpha-steroid reductase (SRD5A3, type-3) is overexpressed in hormone-refractory prostate cancer. *Cancer Science*, *99*(1), 81–86. https://doi.org/10.1111/j.1349-7006.2007.00656.x

Yarrow, J. F., Phillips, E. G., Conover, C. F., Bassett, T. E., Chen, C., Teurlings, T., … Ye, F. (2017). Testosterone plus finasteride prevents bone loss without prostate growth in a rodent spinal cord injury model. *Journal of Neurotrauma*, *34*(21), 2972–2981. https://doi.org/10.1089/neu.2016.4814

Zhang, A., Zhang, J., Plymate, S., & Mostaghel, E. A. (2016). Classical and non-classical roles for pre-receptor control of DHT metabolism in prostate cancer progression. *Hormones and Cancer*, *7*(2), 104–113. https://doi.org/10.1007/s12672-016-0250-9

How to cite this article: Diri MA, Diri B, Yildiz L, Büyükalpelli R. The effect of dutasteride on microscopic and macroscopic changes of testosterone replacement treatment on prostate tissue. *Andrologia*. 2018;e13110. https://doi.org/10.1111/and.13110