Does Tadalafil Increase The Uptake of Finasteride into Prostate Tissue? A Biochemical and Histological Evaluation in Rats

Alper Gök[1]*, Can Tuygun[1], Tugba Taskin Türkmenoglu[2], Gamze Gök[3], Gamze Avcıoglu[3], Cemil Nural[3], Ibrahim Güven Kartal[1], Azmi Levent Sagnak[1], Osman Raif Karabacak[1], Hikmet Topaloglu[1], Muhammed Abdurrahim Imamoglu[1], Hamit Ersoy[1]

Purpose: To histopathologically and biochemically evaluate the hypothesis that tadalafil increases the uptake of a second medication into the prostate tissue by increasing the blood supply in the prostate.

Methods: Forty 12-week-old Sprague Dawley male rats were equally divided into 5 groups and were administered drugs orally as follows: Group 1 – no drugs, Group 2 – 10 days of finasteride, Group 3 – 10 days of finasteride + tadalafil, Group 4 – 30 days of finasteride, and Group 5 – 30 days of finasteride + tadalafil. At the end of 10 days of drug administration in Group1, 2, and 3, and at the end of 30 days of drug administration in Group 4 and 5, blood samples were collected from rats and analyzed for serum androgen levels. In addition, prostate tissues were removed for histological examination.

Results: The mean DHT level as well as the minimum and maximum epithelial thicknesses in Group 3 were lower than those in Group 2. However, there was no statistical significant difference ($P = 0.989$, $P = 0.176$, and $P = 0.070$, respectively). The mean DHT level as well as the minimum and maximum epithelial thicknesses in Group 5 were lower than those in Group 4. However, there was no statistical significant difference ($P = 0.984$, $P = 0.147$, and $P = 0.478$, respectively). The mean minimum and maximum epithelial thicknesses in Group 3 and Group 4 were not statistically different ($P = 0.488$ and $P = 0.996$, respectively).

Conclusion: The similarity of the mean minimum and maximum epithelial thickness in Group 3 and Group 4 may be indicate that the combination therapy provides an early histological effect. However, the fact that there was no statistical significant difference between Group 2 and Group 3, and between Group 4 and Group 5, in terms of the mean DHT level and minimum-maximum epithelial thicknesses suggests that longer term studies with more rats are necessary to test the validity of our hypothesis.

Keywords: PDE5 inhibition; tadalafil; finasteride; prostate; benign prostatic hyperplasia; rats

INTRODUCTION

Androgen stimulation of androgen receptors (AR) causes a proliferative effect in prostate tissue[1]. The 5□-reductase enzyme (5-AR) is a nuclear-bound steroid enzyme that converts testosterone (T) to dihydrotestosterone (DHT), a potent androgen that has a higher affinity to AR than testosterone. There are two isoforms of 5-AR encoded by the SRD5A1 and SRD5A2 genes. While the type I 5-AR isoform is found in extraprostatic tissues (e.g., skin and liver), the type II 5-AR isoform is predominantly found in prostate tissue and other genitourinary tissues[2]. Finasteride (FIN) is a type II 5α-reductase enzyme inhibitor (5-ARI) that is used in the treatment of benign prostatic hyperplasia (BPH). FIN reduces serum and intraprostatic DHT levels, causing epithelial atrophy in the prostate tissue[3-6]. Clinically, FIN decreases both the prostate weight and the International Prostate Symptom Score (IPSS), while increasing Qmax[4,7-11]. It has also been reported that FIN reduces acute urinary retention (AUR) and the need for surgery in BPH patients[12-14]. However, these positive clinical effects of FIN occur only after 6-12 months of treatment.

In October 2011, the US Food and Drug Administration (FDA) approved tadalafil (TAD), a phosphodiesterase type 5 inhibitor (PDE5i), for the treatment of BPH. Inhibition of the intracellular enzyme phosphodiesterase type 5 (PDE5) reduces cGMP degradation. Increased intracellular cGMP levels cause a decrease in intracellular calcium levels and lead to the relaxation of the

[1]Department of Urology, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, 06110, Turkey.
[2]Department of Pathology, University of Health Sciences, Diskapii Yildirim Beyazit Training and Research Hospital, Ankara, 06110, Turkey.
[3]Department of Biochemistry, Yildirim Beyazit University, Ankara, 06800, Turkey.
*Correspondence: Diskapi Yildirim Beyazit Egitim ve Arastirma Hastanesi, Ziraat mahallesi, Ömer Halisdemir Caddesi, 06110, Diskapi/Altindag/Ankara
Phone: +90 532 603 11 81. Fax number: +90 312 318 66 90. Email: alper_gok@hotmail.com.
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Table 1. The distribution of the groups

Group 1 (n:8)	Control group (not given any drugs)
Group 2 (n:8)	10 days of 1 mg/kg/day FIN by gavage
Group 3 (n:8)	10 days of 1 mg/kg/day FIN + 2 mg/kg/day TAD by gavage
Group 4 (n:8)	30 days of 1 mg/kg/day FIN by gavage
Group 5 (n:8)	30 days of 1 mg/kg/day FIN + 2 mg/kg/day TAD by gavage

prostate's smooth muscle and vessels[15,16]. In a study by Morelli et al., lower genitourinary tract tissues were collected during urologic surgeries[17]. These tissues were compared in terms of PDE5 mRNA expression[17]. This study showed that PDE5 mRNA expression was higher in the prostatic arteries and corpus cavernosum tissues than other parts of male urogenital tract tissues[17]. This study also compared the prostate tissues of spontaneous hypertensive rats (SHR, characterized by reduced pelvic blood flow to the genitourinary tract) with healthy Wistar Kyoto rats, and found that SHR rats had dilated hypoxic glandular alveolas and decreased interstitial and stromal spaces in prostate tissue[17]. When the SHRs were treated with TAD starting at day 1, the blood supply and oxygenation of the prostate tissue began to improve; this was demonstrated by a significant decrease in hypoxyprobe immunopositivity, which was completely lost between the 7th and 28th day[17]. In addition, other studies have shown that PDE5i increases human and rat prostatic blood flow[15,17-19].

To our knowledge, our current study is the first to evaluate whether PDE5i, which has been shown to increase prostate blood flow, enhances the diffusion of a second medication into prostate tissue. Since the histological changes in the prostate caused by 5-ARI as well as its biochemical effects on serum are well known, we aimed to histologically and biochemically assess whether TAD increases the diffusion of FIN into prostate tissue in rats.

MATERIALS AND METHODS

This study was approved by the Local Ethics Committee of Kobay Deney Hayvanları Laboratuarı (221-20.01.2017) and by Scientific Research Board of Yıldırım Beyazıt Training and Research Hospital as a Scientific Research Project (62 / 02-09.02.2017).

This study included forty 12-week-old male Sprague-Dawley rats (Kobay Deney Hayvanlar Laboratuarı, Ankara, Turkey) weighing between 300-350 grams. Throughout the study, the rats were kept in a room with a temperature of 22 ± 2°C that was illuminated from 7 am to 7 pm. The rats were allowed to access water and food ad libitum.

The rats were equally distributed into groups given ± FIN ± TAD for 10 or 30 days to evaluate the hypothesis that the biochemical and histological changes caused by a combination of FIN+TAD are more pronounced than those caused by FIN alone. The distribution of the groups is shown in **Table 1**.

The rats were sacrificed by cervical dislocation after 10 days of drug administration in Group1, 2, and 3, and at 30 days of drug administration in Group 4 and 5. Blood samples were taken from the rats via cardiac puncture. All of the rats underwent laparotomy, and their prostate, bladder, kidney, testes, and liver tissues were removed and stored for further studies.

Biochemical evaluation

All blood samples were drawn into EDTA tubes and incubated for 20 minutes at room temperature, followed by centrifugation at 3000 rpm for 20 minutes. The supernatant (plasma) was stored in Eppendorf tubes at -20°C until further use. Immediately before use, the samples were thawed at room temperature, and then they were analyzed for dihydrotestosterone and testosterone via ELISA (EASTBIOPHARM Rat DHT and T ELISA Kit). Biochemical evaluation was conducted by 3 experienced biochemists and the researchers were blinded to the study groups.

Histological evaluation

Specimens were fixed with 10% neutral buffered formalin and embedded in paraffin. Slides were stained with Hematoxylin and Eosin and examined with a Nikon Eclipse Ni microscope (Nikon Corp, Japan). Images were captured digitally with the Nikon DS-Fi1c camera (Nikon Instruments, Japan). Measurements of minimum and maximum epithelial thickness were performed at a magnification of 400x from the ten most central acini (**Figure 1**). Histological evaluation was conducted by a pathologist experienced in prostate histology and the researcher was blinded to the study groups.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Descriptive statistics were expressed mean ± SD, and one-way ANOVA was used to determine the mean differences among groups. The post-hoc Tukey HSD test was used to determine which group differed from others. Values of p less than 0.05 were considered significant.

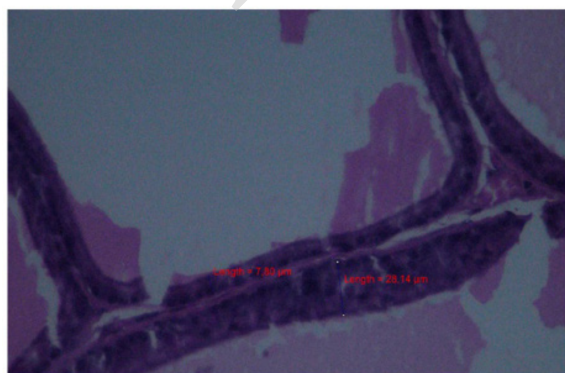

Figure 1. Measures from epithelial thickness

RESULTS

DHT levels were significantly different between the groups ($P = 0.007$). Specifically, the DHT levels of the control group (group 1) were higher than those of group 3 (10 days FIN+TAD), group 4 (30 days of FIN), and group 5 (30 days of FIN+TAD) ($P = 0.041$, $P = 0.010$, and $P < 0.001$, respectively). Although group 2 (10 days of FIN) had lower mean DHT levels than group 1 (control), this difference was not significant ($P = 0.118$). In addition, the mean DHT levels of group 3 (10 days FIN+TAD) were lower than those of group 2 (10 days of FIN), and the mean DHT levels of group 5 (30 days FIN + TAD) were lower than those of group 4 (30 days

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Table 2. Biochemical and histological measurements of the study groups

	Group 1 (Control)	Group 2 (10 days FIN)	Group 3 (10 days FIN+TAD)	Group 4 (30 days FIN)	Group 5 (30 days FIN+TAD)	*p*-value
DHT (pg/ml)	814.7 ± 533.6a,b,c	484.1 ± 190.1	420.3 ± 122.9a	391.2 ± 123.5b	321.6 ± 57.8c	0.030†
Testosterone (ng/ml)	2.17 ± 0.43a,b,c,d	4.56 ± 0.83d	4.50 ± 0.64a	5.19 ± 0.91b	5.22 ± 0.90c	< 0.001‡
Maximum epithelial thickness (µm)	47.3 ± 9.8a,b,c,d	37.1 ± 4.1d	30.3 ± 1.9a	31.2 ± 2.0b	27.0 ± 2.0c	< 0.001†
Minimum epithelial thickness (µm)	15.2 ± 2.3a,b,c,d	11.0 ± 2.3d	9.1 ± 1.0a	10.5 ± 0.7b	8.5 ± 1.3c	< 0.001†
Prostate weight (g)	0.72 ± 0.13b,c	0.56 ± 0.11d	0.57 ± 0.10a	0.54 ± 0.12b	0.53 ± 0.10c	0.016‡
Body weight (g)	325.4 ± 21.82	338.2 ± 11.47	334.9 ± 13.41	341.4 ± 10.93	339.1 ± 7.41	0.186‡

Data are expressed as mean ± SD, † Kruskal Wallis test, ‡ One-Way ANOVA, a: group 1 vs group 3 ($p < 0.05$), b: group 1 vs group 4 ($p < 0.05$), c: group 1 vs group 5 ($p < 0.05$), d: group 1 vs group 2 ($p < 0.001$).

FIN), but these differences were not significant (P = 0.989 and P = 0.984, respectively) (**Table 2**).

The mean testosterone levels were also significantly different between the groups ($P < 0.001$). The mean testosterone levels of all of the groups receiving drugs were higher than those of the control group (all P <0.001). However, the mean testosterone levels of groups 2 and 3 (10 days FIN and FIN+TAD) and groups 4 and 5 (30 days FIN and FIN+TAD) were similar (P = 1.000 and P = 1.000) (**Table 2**).

The mean maximum epithelial thickness levels in all of the groups receiving drugs were lower than those of the control group (P = 0.002 control vs group 2 (10 days FIN), P < 0.001 control vs all other groups). Although the mean maximum epithelial thickness levels were lower in the groups receiving a combination of FIN+TAD, these differences were not significant (P = 0.070 10 days FIN vs FIN+TAD and P = 0.478 30 days FIN vs FIN+TAD) (**Table** 2). Further, there was no difference in the mean maximum epithelial thickness between group 3 (10 days FIN+TAD) and group 4 (30 days FIN) (P = 0.996) .

The mean minimum epithelial thickness levels of all of the groups receiving drugs were lower than those of the control group (P < 0.001 for all). Although the mean minimum epithelial thicknesses of the groups receiving a combination of FIN+TAD were lower than those receiving FIN alone, these differences were not significant (P = 0.176 10 days FIN vs FIN+TAD and P = 0.147 30 days FIN vs FIN+TAD) (**Table 2**). In addition, there was no significant difference between group 3 (10 days FIN+TAD) and group 4 (30 days FIN) in terms of minimum epithelial thickness (P = 0.488).

Next, we compared mean prostate weights between the groups. The mean prostate weights of all of the groups receiving drugs were lower than those of the control group (P = 0.038 control vs 10 days FIN, P = 0.046 control vs 10 days FIN+TAD, P = 0.031 control vs 30 days FIN, and P = 0.020 30 days FIN+TAD). The mean prostate weights groups 2 and 3 (10 days FIN vs FIN+TAD) and between groups 4 and 5 (30 days FIN vs FIN+TAD) were similar (P = 1.000 and P = 1.000) (**Table 2**).

There were no differences between the groups in terms of mean body weights (P = 0.186) (**Table 2**).

DISCUSSION

In the prostate, androgen receptors (ARs) are predominantly located on the epithelial cells that lie on the inner surface of the glandular tissue, and therefore, the epithelial component of the prostate tissue is more sensitive to androgens than are its other components. FIN initiates prostate epithelial atrophy by reducing serum DHT levels by 62-82% and by reducing intraprostatic DHT levels by 92%[3-6]. Clinically, FIN provides a 15-21% reduction in prostate weight and a 13-38% reduction in IPSS, while increasing Qmax by 1.6-2.2 mL/s [4,7-11]. In addition to these effects, FIN also reduces risk of acute urinary retention (AUR) and the need for surgery in patients with BPH[12-14]. However, these positive clinical effects of FIN occur only after at least 6-12 months of treatment.

The expression of PDE5 in human prostate arteries is localized to endothelial and smooth muscle cells[18]. The expression of PDE5 in the prostate arteries is comparable to that in the corpus cavernosum, while several studies have shown the PDE5 expression in the prostate arteries is greater than its expression in other genitourinary tissues[17]. To assess possible hemodynamic changes in the prostate tissue caused by TAD, Bertolotto et al. evaluated 12 patients with BPH by transrectal contrast-enhanced ultrasound before and 90 minutes after TAD administration, and found that TAD led to increased blood flow in the prostate[15]. In rats, Morelli et al.[17] showed that inhibition of PDE5 increases prostate blood supply and oxygenation. In light of these studies, we hypothesized that since TAD increases prostate blood flow, a second drug given in combination with TAD may access the prostate more easily. Therefore, in the current study, we evaluated whether the combination of TAD and FIN, which is a 5-ARI, could increase biochemical and histological changes in the prostate. The rats were administered FIN at a dose of 1mg/kg/day based on previous studies showing that this dose caused significant changes in rat prostate tissue and serum DHT levels[1,20]. The rats were given TAD at a dose of 2 mg/kg/day based on the study of Morelli et al. (17), which showed that this dose increased the oxygenation of rat prostate tissue from day 1. Our hypothesis was supported by the findings that rats treated with a combination of FIN+TAD for 10 and 30 days had lower DHT levels and lower minimum-maximum epithelial thicknesses compared to rats that were treated with FIN alone. However, these differences were not significant ($p > 0.05$). In addition, the mean minimum and maximal epithelial thicknesses of group 3 (10 days FIN+TAD) were lower than those of group 4 (30 days FIN), but these differences were not significant (p = 0.488 and p = 0.996, respectively). This finding is important, and supports our hypothesis, as it suggests that the histologic effects achieved by FIN alone in 30 days was achieved

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by the combination of FIN+TAD in only 10 days. The mean prostate weights of groups 2 and 3 (10 days FIN vs FIN+TAD) and groups 4 and 5 (30 days FIN vs FIN+TAD) were similar. That is, the combination of FIN+TAD did not improve prostate weight compared to FIN alone. However, this result might have been impacted in that we used young rats with no BPH; if we had used older rats with BPH (e.g., having rich prostate epithelial tissues), we may have obtained a different result. The fact that there was no statistical significant difference between Group 2 and Group 3, and between Group 4 and Group 5, in terms of the mean DHT level and minimum-maximum epithelial thicknesses suggests may be a consequence of the small sample size. This could be considered a limitation to our study.
Unfortunately, there are limited studies in the literature examining the effects of FIN+TAD combination therapy in BPH patients[21-24]. One of these studies is an international, randomized, double-blind study conducted by Casabe et al.[21]. That study included a total of 695 patients over the age of 45 years with IPSS ≥13 and prostate volume ≥ 30 ml who were divided into two groups. The first group consisted of 350 patients treated with FIN+placebo and the second group consisted of 345 patients treated with FIN+TAD; both groups underwent treatment for 26 weeks[21]. The FIN+TAD group had an IPSS change of -4.0, -5.2, and -5.5 points with respect to baseline IPSS after 4, 12, and 26 weeks of treatment, while the FIN+placebo group had IPSS changes of -2.3, -3.8, and -4.5 points over the same weeks, respectively. The IPSS changes between the treatment groups were significantly different in each of the 3 periods ($P \leq 0.022$) [21], demonstrating that the combination of FIN+TAD resulted in earlier symptomatic improvement compared to FIN+placebo[21]. This earlier symptomatic healing may be due to the TAD-induced increase in blood flow, allowing more FIN to reach the prostate tissue, as outlined in our hypothesis. However, it is not possible to make a definite judgment, since the study by Casabe et al. did not measure the biochemical changes in the serum androgens, histological changes in prostate tissue or radiological changes in the prostate weight.

CONCLUSIONS

Although the results of the current study provide some evidence to support our hypothesis, we believe that more clinical, histological, biochemical, and radiological evaluations should be performed. If our hypothesis is validated by further studies, it can be said that an earlier and more effective treatment for BPH can be achieved with a combination of FIN+TAD. In addition, other prostate tissue diseases (e.g., chronic prostatitis, prostate cancer) may be treated more effectively by combining PDE5i with other suitable medications.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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