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ORIGINAL ARTICLE

Effects of dutasteride on sex hormones and cerebrospinal steroids in patients treated for benign prostatic hyperplasia

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Abstract

Purpose Neuroactive steroids may have a role in regulating sexual function. This case-control study assessed whether dutasteride, a 5α-reductase inhibitor used for treatment of patients with benign prostate hyperplasia (BPH), impacts on the levels of neuroactive steroids, leading to erectile dysfunction (ED) and/or hypoactive sexual desire (HSD).

Methods Forty patients with BPH and moderate-to-severe lower urinary tract symptoms (LUTS), pre-scheduled for prostate transurethral resection or open prostatectomy were enrolled. Twenty of these patients with prostate volume ≤40 mL were treated with α-blockers (Group A) and the remaining 20, with prostate volume >40 mL, with dutasteride plus α-blockers (Group B) for at least 6 months before surgery. Serum sex steroids and gonadotropin levels were measured the day before surgery, and the neuroactive steroid levels were assessed in the cerebrospinal fluid (CSF) collected during spinal anesthesia, at the day of surgery.

Results Before surgery, the International Index of Erectile Function 5-item score was higher in Group A that Group B (18.8 ± 4.8 vs. 15.1 ± 5.4, $p < 0.01$). Group A showed lower total testosterone (TT) (4.5 vs.6.4 ng/ml, $p < 0.01$) and 17β-estradiol (E_2) (24.3 vs.30.7 pg/ml, $p < 0.05$) serum levels than Group B. CSF levels of TT (1446.6 vs. 19.9 pg/ml, $p < 0.05$) and dihydrotestosterone (7.9 vs. 1.4 pg/ml, $p < 0.05$) were higher and CSF E_2 levels were lower (26.0 vs.36.0 pg/ml, $p < 0.01$) in Group A than Group B.

Conclusions A decrease of neuroactive steroids in the CSF of patients treated with dutasteride occurs. This may be one of the mechanisms by which dutasteride may cause ED and HSD.

Keywords Steroids · Prostate · Dutasteride · Erectile dysfunction · Libido

Introduction

Benign prostatic hyperplasia (BPH) is a common urological disorder that affects about 20% of American men aged 30–79 years. Its prevalence increases proportionally with increasing age [1]. Its pharmacologic treatment involves the use of α–blockers (AB) and/or 5α-reductase inhibitors (5ARI) [2]. The combined treatment has shown a greater efficacy in preventing the clinical progression compared to monotherapy, as showed by the amelioration of the international prostate symptom score (IPSS), uroflowmetry, the onset of acute urinary retention, urinary tract infections and/or incontinence [3]. However, medical treatment of BPH has some side effects. ABs often cause orthostatic hypotension and anejaculation. 5ARI can cause gynecomastia, erectile dysfunction (ED), decrease of sexual desire, and ejaculatory dysfunction. These side effects may be more pronounced when the combination therapy is prescribed [4].

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A previously published study carried out in patients with androgenetic alopecia (AGA) has shown similar effects also with the use of finasteride [5]. In addition, two meta-analyses documented that the use of 5ARI significantly increases the prevalence of ED and hypoactive sexual desire (HSD) in patients with BPH [6, 7].

The mechanism(s) by which 5ARI causes sexual dysfunction is not well known. Hypothetically, one of the mechanism involved may be the decreasing effect of dutasteride on neuroactive steroid levels in the central nervous system (CNS). In fact, the CNS is able to synthetize neuroactive steroids whose levels can, in turn, influence sexual desire [5]. 5ARI can hinder the effects of steroid metabolites involved in the regulation of sexual activity, within the CNS level [5]. In this regard, a recent study documented that an impairment of neuroactive steroid levels, associated with long-term sexual side effects as well as anxious/depressive symptoms, is still present in patients with AGA treated with finasteride even after the discontinuation of the treatment [5]. Therefore, this study aimed to evaluate the effects of dutasteride on CNS neuroactive steroid levels in patients with BPH and sexual dysfunction. To accomplish this, patients with BPH and sexual dysfunction were treated with ABs or ABs plus 5ARI before undergoing surgical treatment and the serum and CSF steroids were measured. A secondary aim was to analyze the correlation between the presence of ED and HSD in relationship to the treatment with 5ARI.

Patients and methods

Forty male patients with moderate-to-severe LUTS secondary to BPH, pre-scheduled for a transurethral resection of the prostate (TURP) or open prostatectomy, were enrolled in this study. Inclusion criteria were: sexually active patients (i.e., engaged in sexual activity with a partner during the past 4 weeks) aged ≥50 years, with a clinical diagnosis of BPH, an IPSS score ≥19 (at enrollment), a prostate volume of ≥30 ml [assessed using transrectal ultrasonography (TRUS)] and total serum prostate-specific antigen (PSA) levels ≤4 ng/mL. Patients suffering from a malignant tumor, hypogonadism and other endocrine diseases, anxious-depressive syndrome, central and peripheral nervous system disease, or any other condition capable of altering the levels of serum gonadotropins and sexual hormones and cerebrospinal neurosteroids (e.g., treatment with androgens and/or antiandrogens, antidepressants, antipsychotics) and patients who discontinued dutasteride treatment before surgery were excluded from the study.

Forty patients were finally enrolled. Those with a prostate volume ≤40 mL, were prescribed ABs (Group A, $n = 20$) and the remaining 20, with a prostate volume ≥40 mL, were treated with a combination of dutasteride and ABs (Group B) for at least 6 months before surgery.

Clinically, BPH were evaluated by DRE, serum PSA levels, IPSS, TRUS, and maximum urinary flow rate (Qmax) at uroflowmetry. In both groups the sexual function was evaluated before surgery by using the international index of erectile function- 5 (IIEF-5) questionnaire and the measurement of serum total testosterone (TT), luteinizing hormone (LH), 17β-estradiol (E_2), prolactin (PRL), and follicle-stimulating hormone (FSH). The presence of HSD in both groups was assessed by asking the following question: "Do you have a loss of sexual desire in the last 6 months?".

Blood samples were collected before any prostate evaluation, including DRE and TRUS, and were taken between 08.00 AM and 11.00 AM to minimize the confounding effects of diurnal variation in the hormone serum levels. The levels of PSA, TT, LH, FSH, PRL, and E_2 were measured by radioimmunoassay. After six months from therapy prescription, all patients underwent TURP or open prostatectomy. Both surgical procedures were performed under spinal anesthesia and, therefore, CSF was collected during the procedure. In both groups, the levels of the neuroactive steroids pregnenolone (PREG), progesterone (P), TT, dihydrotestosterone (DHT), and E_2 in the CSF were evaluated by ELISA (Abcam, Milan, Italy). After acquiring the patient's informed consent, the CSF samples were collected by the on-duty anesthesiologist during the operating session with a lumbar puncture performed immediately prior to the standard spinal anesthesia. A 25-gauge needle was inserted into the subarachnoid space at the L3-L4 interspace to collect 3 mL of CSF. Using the same needle, local anesthetics and narcotics were then injected in order to complete the procedure for spinal anesthesia and the subsequent surgery. The basal evaluation of CSF (i.e., glucose, protein and cells) was in the normal limits in all patients.

The study has been carried out according with the principles of Helsinki's declaration. A written informed consent was obtained from all participants.

The Student's t test was used for statistical analysis and a p value lower than 0.05 was considered significant.

Results

Clinical features of the patients at enrollment are listed in Table 1. Mean age, presence of comorbidities, body mass index, IPSS, and Qmax did not differ significantly between the groups. IIEF-5 score was significantly higher in Group A than Group B. Twenty-four out of 40 (60%) patients reported HSD; 10 (50%) in Group A and 14 (70%) in Group B, respectively ($p > 0.05$).

Table 1 Clinical characteristics of patients with benign prostate hyperplasia and sexual dysfunction at enrollment

	Group A ($n = 20$)	Group B ($n = 20$)
Age	65.5 ± 6.6	67.1 ± 7.1
BMI	27.0 ± 4.4	26.8 ± 3.4
Comorbidities		
Hypertension (*n*%)	17 (60.7)	11 (39.3)
Dyslipidaemia (*n*%)	5 (55.6)	4 (44.4)
Diabetes (*n*%)	4 (66.7)	2 (33.3)
Cardiovascular disease (*n*%)	9 (69.2)	4 (30.8)
HSD (*n*%)	10 (50%)	14 (70%)
Q_{max}	8.5 ± 2.9	9.1 ± 2.6
IPSS	23.4 ± 4.8	21.4 ± 4.11
IIEF-5	18.8 ± 4.8	15.1 ± 5.4*

Prevalence of HSD and IIEF-5 score were evaluated before surgery (following the 6-month-long therapy)

Patients were divided into two groups, that were prescribed α-blockers (AB) (Group A) or AB plus dutasteride (Group B)

BMI Body mass index, *HSD* hypoactive sexual desire, Q_{max} maximum flow rate, *IPSS* international prostate symptom score, *IIEF-5* international index of erectile function-5 questionnaire

*$p < 0.05$ vs. Group A. Results are expressed as mean ± standard deviation

Prostate volume, PSA, and serum concentrations of TT and E_2 are shown in Fig. 1. Prostate volume, PSA, preoperative serum levels of TT and E_2 were significantly different between groups. The mean prostate volume was lower in Group A than in Group B, whereas the mean serum levels of PSA was higher in Group A than in Group B. Group B had higher serum levels of TT and E_2 than Group A. Preoperative serum level of LH, FSH and PRL were similar between the two groups (Fig. 2).

The concentration of the neuroactive steroids in shown in Fig. 3. Higher CSF levels of TT and DHT were found in Group A than Group B. In contrast, CSF levels of E_2 values were significantly higher in Group B than Group A.

Discussion

This pilot study was aimed at assessing the effects of dutasteride on CNS neuroactive steroid levels in patients with BPH and sexual dysfunction. To accomplish this, patients with BPH and sexual dysfunction were treated with ABs (Group A) or ABs plus dutasteride (Group B) for six months before undergoing surgical treatment, and the serum and CSF steroid levels were measured. We found significantly lower IIEF-5 questionnaire scores in Group B than Group A, suggesting a better sexual function in the latter group. As expectable, significantly higher serum levels of TT and E_2 were found in Group B than Group A. Dutasteride is indeed an inhibitor of the 5-alpha reductase, which converts T in DHT. Its inhibition led to the accumulation of metabolites upstream of the biochemical pathway, such as TT and E_2. Interestingly, Group B showed significantly lower CSF TT and DHT levels, and significantly higher CSF E_2 levels than Group A, which may explain the poorer sexual function of Group B than Group A. Therefore, this pilot study provides evidence for the influence of dutasteride on CSF neurosteroids. This can serve as a further explanatory mechanism for the negative impact of dutasteride on sexual function.

Dutasteride and finasteride are drugs commonly used for the treatment of patients with BPH. Finasteride is also used to treat patients with AGA [8]. Both of these drugs share the same mechanism of action, which consists in the inhibition of the conversion of testosterone into DHT by blocking the 5AR enzyme. Dutasteride has been shown to decrease DHT production more efficiently than finasteride because it acts on both isoforms of the 5AR enzyme (types 1 and 2) [9]. Furthermore, some studies shown that the type 1 isoform is mainly expressed in the prostate tissue, while the type 2 is found also in the liver and the skin [10]. The efficacy and safety of these drugs for the treatment of BPH are confirmed by literature data and clinical practice guidelines [4]. A recent study carried out in 40 patients with BPH treated with dutasteride investigated their neuropsychological features by using the following questionnaires: Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Frontal Assessment Battery (FAB), Hamilton Anxiety Rating Scale (HAM-A), Beck Depression Inventory second edition (BDI-II), and Short Form-12 (SF-12). The authors found no significant changes in the scores of these questionnaires and concluded that dutasteride was safe on the mental profile [11]. However, some clinical studies and meta-analyses report an elevated chance of adverse effects on sexuality with their use [4, 6, 7].

Several studies have assessed the impact of 5ARI on sexual function providing conflicting results. For example, a study carried out by Wessells and collaborators reported a prevalence of ED of 15.8% in patients receiving finasteride compared to 6.3% in those treated with placebo [12]. Similarly, a placebo-controlled study with dutasteride reported ED, HSD and ejaculatory dysfunction in a higher portion of patients receiving dutasteride (7.3%, 4.2%, and 2.2%) than those receiving placebo (4%, 2.1%, and 0.8%, respectively) [13]. Other evidence suggests that the impact of 5ARI on the sexual sphere is transient. In this regard, the PLESS study, a placebo-controlled trial, showed that adverse effects on sexual function are more frequent in patients treated with finasteride than in the placebo group, during the first year of therapy (15% vs. 7%). However, after 2 years and up to 4 years of therapy, the prevalence of sexual adverse effects was similar between the two

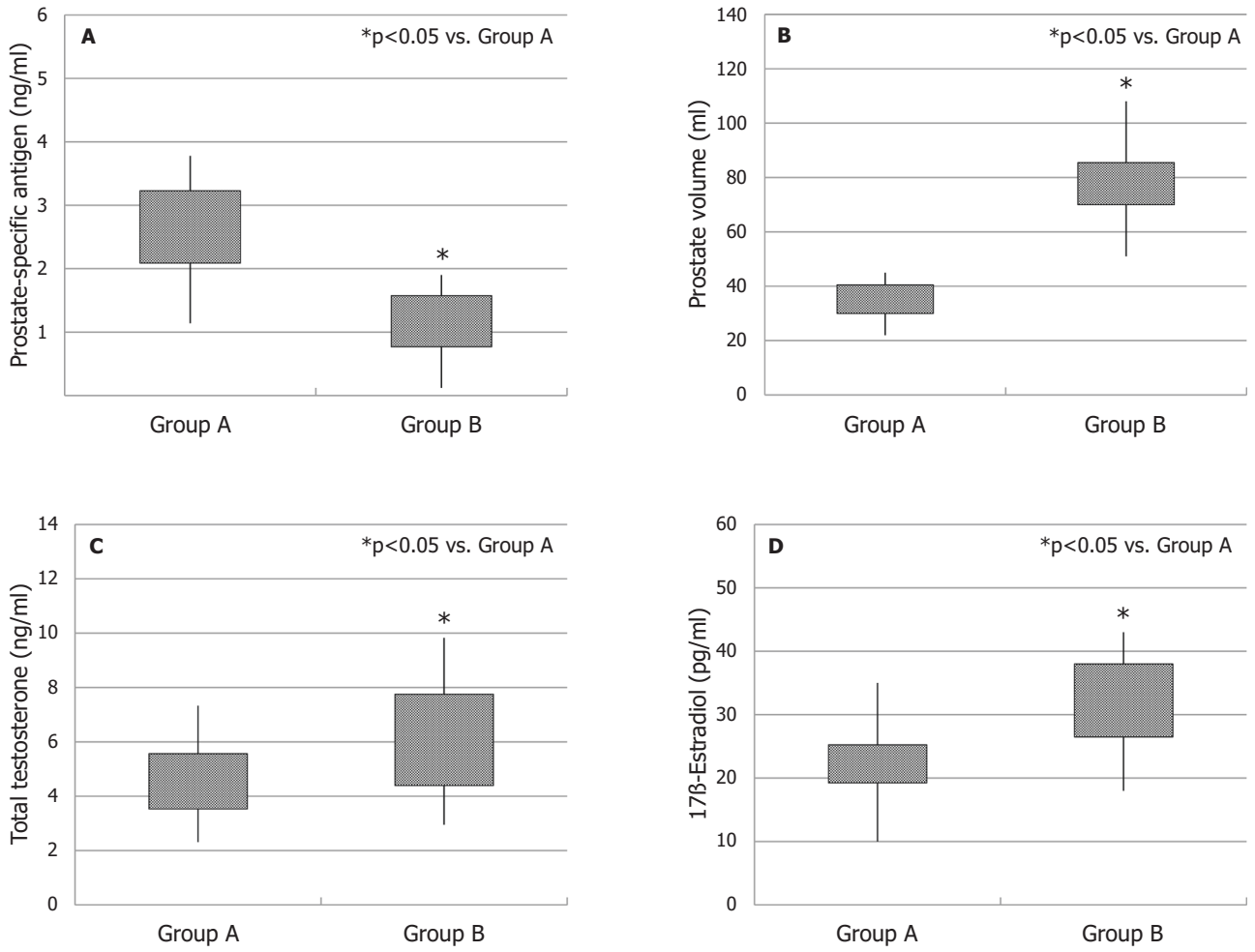

Fig. 1 Prostate-specific antigen (PSA), prostate volume and sex hormones. Differences in PSA (**A**), prostate volume (**B**), serum totaltestosterone (TT) (**C**), and 17β-estradiol (E_2) (**D**) in patients with benign prostate hyperplasia (BPH) and sexual dysfunction treated with α-blockers (AB) (Group A) or AB plus dutasteride (Group B) are shown

groups [14]. A possible "nocebo" effect must also be considered when the 5ARIs are used in patients adequately informed about possible sexual adverse effects [15]. In the present study, the prevalence of HSD did not differ significantly between patients treated with ABs plus dutasteride than in those receiving only Abs (70% vs. 50%). In contrast, the IIEF-5score was higher in Group A than Group B (Table 1). These findings might be consistent with a nocebo effect of dutasteride. In fact, all the patients were advised about the possible adverse effects of 5ARI before the treatment was started. However, it is noteworthy that a recent systematic review of 17 randomized controlled trials, including 17,494 patients, documented that the impact of 5ARI administration on sexual function was higher in patients with BPH than in those with other diseases. Indeed, these effects are less relevant when the same drugs are used for the treatment of alopecia. Hence, the effect could partly be dose-related [6]. Furthermore, the subgroup analysis of this study demonstrated that dutasteride had a higher impact on sexual impairment (in particular on the decline of sexual desire and ED), compared with finasteride [6].

Sexual function also worsens with time in patients treated with 5ARI. More in detail, this study shows that, in patients with BPH, there is a correlation between the duration of therapy with 5ARI and sexual adverse effects. In fact, the incidence of the adverse effects was higher for treatment lasting of at least one year compared to placebo. These data have not been reported in patients receiving 5ARI for alopecia [8]. Accordingly, another comprehensive review and meta-analyses showed that 5ARI significantly increased the newly onset of ED and HSD in patients with BPH [7].

The adverse effects of 5ARI on the sexual sphere are mainly ascribed to their known antiandrogenic properties. However, the possible mechanisms of action by which 5ARI cause adverse effects on sexuality have not still clearly elucidated. In fact, while they decrease circulating DHT levels with relative increase in serum TT, these drugs

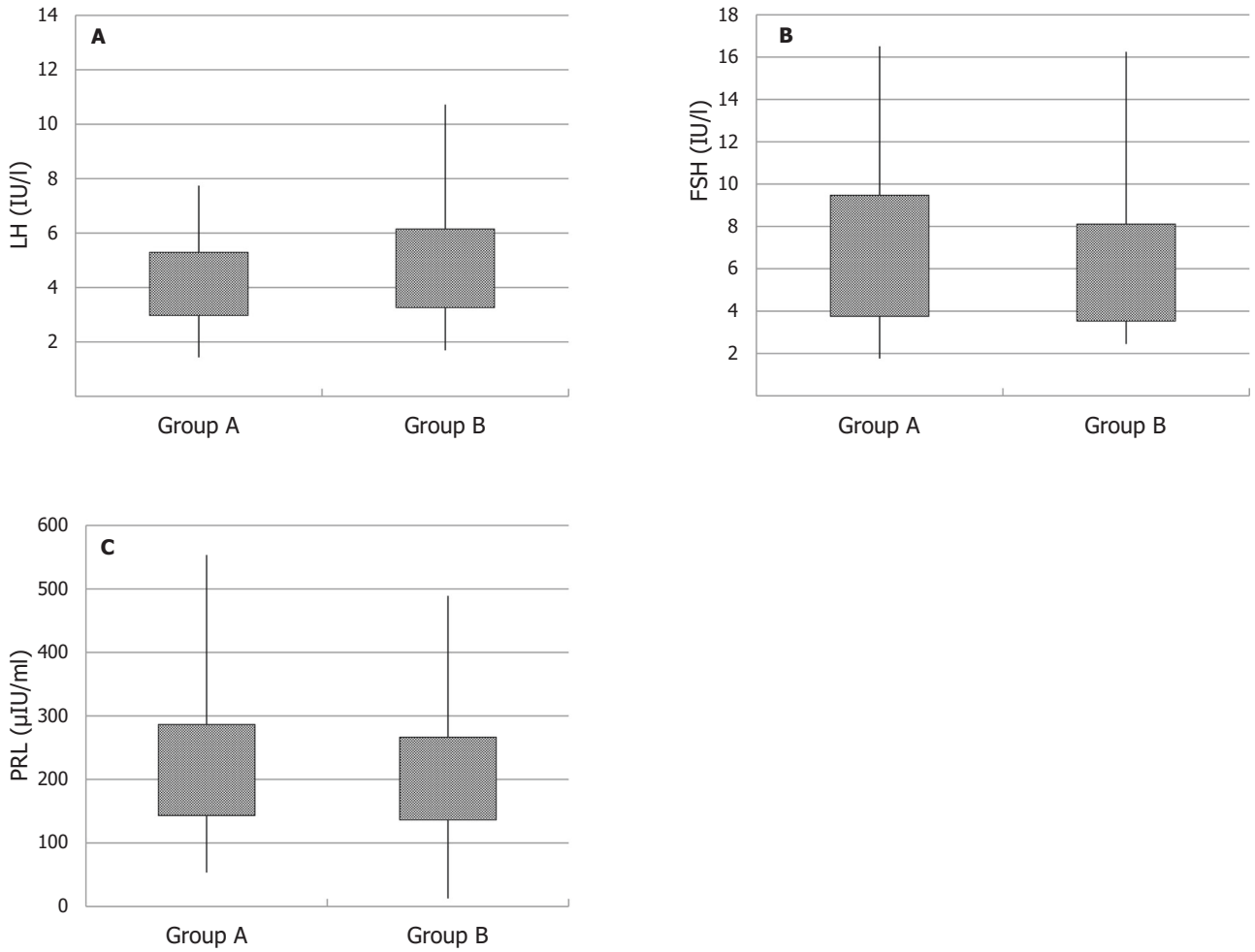

Fig. 2 Gonadotropin and prolactin serum levels. Differences in luteinizing hormone (LH) (**A**), follicle-stimulating hormone (FSH) (**B**), and prolactin (PRL) (**C**) in patients with benign prostate hyperplasia (BPH) and sexual dysfunction treated with α-blockers (AB) (Group A) or AB plus dutasteride (Group B) are shown

are often well tolerated by patients without particular negative effects on the sexual function [16, 17]. Experimental evidence conducted on both animals and humans have also suggested that the onset of adverse sexual effects after treatment with 5ARI may be partly attributable to their central effect and, in particular, to the 5ARI ability to inhibit the levels of some CNS neurosteroids probably implicated in the regulation of sexual desire and erection [18, 19]. In fact, a study performed in a small number of patients treated with finasteride for AGA has shown a decrease in CSF levels of neurosteroids [5]. These neurosteroids, which are produced by both the testis and the CNS, are implicated not only in the regulation of sexual function but also in cognitive, behavioral, and reproductive aspects, and possibly also in neurodegenerative diseases [20–22]. Although other animal and human studies have just shown that an alteration of neurosteroid levels can alter the sexual sphere, the present study highlighted, for the first time, the central effects of dutasteride when administered to patients with BPH. By acting on the two enzymatic isoforms of 5ARI, dutasteride could decrease in a more markedly CNS neurosteroids levels. We found that dutasteride administered to patients with BPH for almost 6 months decreases significantly CSF and serum levels of DHT but increases significantly CSF and serum levels of E_2. We also found significant differences in TT concentration between the two groups. In particular, TT levels were significantly higher in patients treated with dutasteride. Our findings are consistent with the inhibition of the conversion of T into DHT displayed by dutasteride. In contrast, CSF levels of TT were lower in patients receiving dutasteride compared with the patients who were given ABs alone. The role of the decreased levels of CSF TT during dutasteride treatment is unknown. We cannot exclude that this may have influenced the rate of ED in these patients.

Several limitations must be taken into account when analyzing the results of the present study. First, the lack of a finasteride-treated group does not allow to evaluate the

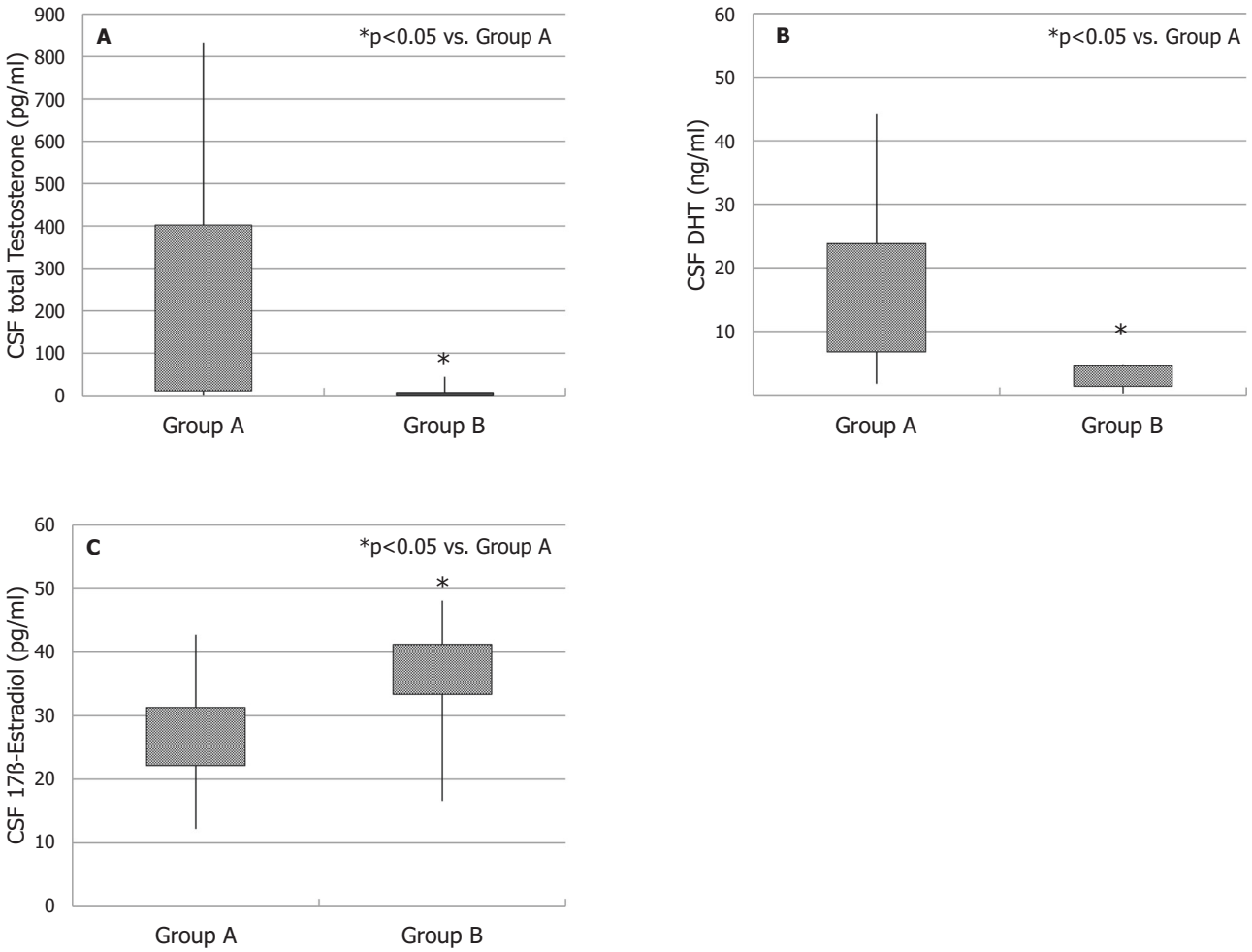

Fig. 3 Cerebrospinal fluid (CSF) sex hormone concentration. Differences in the CSF total testosterone (TT) (**A**), di-hydro-testosterone (DHT) (**B**), and 17β-estradiol (E_2) (**C**) in patients with benign prostate hyperplasia (BPH) and sexual dysfunction treated with α-blockers (AB) (Group A) or AB plus dutasteride (Group B) are shown

impact of single 5AR isoform inhibition on neurosteroids and serum sex hormone levels. A second limitation includes the small number of patients enrolled and the lack of randomization. At this regard, it must be emphasized that sexual hormones were dosed into the CSF. This is an invasive procedure, which limits the recruiting number. Third, a possible reversibility of the pharmacological effect of dutasteride on serum sex hormone levels and CSF neurosteroids after discontinuation of treatment could not be assessed.

Conclusion

In this pilot study, the effects of dutasteride on CNS neuroactive steroid levels in patients with BPH and its impact on sexual dysfunction was evaluated. Patients treated with dutasteride plus ABs showed a significantly lower IIEF-5 questionnaire score than those treated only with ABs, suggesting a better sexual function in the latter group. Expectably, patients treated with dutasteride had significantly higher serum levels of TT and E2 than the others. Importantly, they also had significantly lower CSF TT and DHT levels, and significantly higher CSF E_2 levels compared to patients treated only with ABs.

In conclusion, the present study shows, for the first time, that the administration of dutasteride for almost 6 months to patients with BPH and sexual dysfunction is associated with altered CSF neuroactive steroid and serum sex hormone levels. This may explain the development of ED and HSD. Further randomized, controlled trials are needed to confirm these findings.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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