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CONTENTS

THE ROLE OF DEHYDROEPIANDROSTERONE SULPHATE AND TESTOSTERONE IN ERECTILE DYSFUNCTION IN PATIENTS TREATED WITH 5 ALPHA REDUCTASE INHIBITORS

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Abstract: The pharmacological treatment of benign prostatic hyperplasia involves the use of mainly two groups of drugs: selective alpha 1 blocker and 5 alpha reductase inhibitors (5ARI). In patients who undergo 5ARI pharmaco-treatment, adverse effects such as sexual disturbances such as erectile dysfunction and decreased libido may occur. The purpose of this study is to investigate the occurrence of these side effects, particularly erectile dysfunction in order to predict and overcome them more easily. We conducted a controlled prospective pharmaco-epidemiological study to evaluate the side effects with the use of 5ARI in 250 men with benign prostatic hyperplasia (BPH). Erectile function was assessed at the time of the initiation of therapy and at the time of active use of therapy in two consecutive periods of 6 months and 12 months. We evaluated two groups of patients: the control group of patients treated with alpha 1 blocker (tamsulosin), and the investigated group of patients treated with combination therapy of alpha 1 blocker (tamsulosin) and 5 alpha reductase inhibitors (dutasteride). The evaluation was conducted through questionnaires: IPSS (International Prostate Score System) to calculate the symptoms of benign prostatic hyperplasia (light, medium or severe) and IIEF-5 (International Index for Erectile Function-5) questionnaire for calculating erectile function. During the study measurement of serum levels of testosterone and dehydroepiandrosterone sulphate were performed respectively. Statistical results of nonparametric group analysis showed that erectile dysfunction appeared in 27 patients (22.5%) in the investigated group after 6- and 12-months therapy respectively which was statistically significant ($p<0,05$). Twenty six of these patients (96,3%) have had lowered testosterone and dehydroepiandrosterone sulphate serum levels ($p<0,05$). As a conclusion we recommend investigation of testosterone and DHEAS serum levels prior to starting therapy should be considered valuable in order to avoid 5ARI related erectile dysfunction.
Keywords: BPH, erectile function, testosterone, dehydroepiandrosterone-sulphate

1. INTRODUCTION

Medical treatment of BPH as golden standard involves the use of mainly two groups of drugs: selective alpha 1 blockers and 5 alpha reductase inhibitors (5ARI). While selective alpha 1 blocker inhibits smooth muscle contraction within prostate and lower urinary tract resulting in fast lower urinary tract symptoms (LUTS) relief, 5ARIs inhibit the conversion of testosterone (TST) to dihydrotestosterone (DHT), thus reducing prostate growth and enlargement. Therefore, 5ARIs affect the reduction of the prostate volume up to 20-30% after 6 to 12 months therapy (Oelke et al.,2015).

The most common side effects of 5ARI include sexual dysfunctions such as erectile dysfunction, decreased libido and ejaculatory disorders (Motofei et al.,2018). Literature data shows that after 2 years of 5ARI therapy, about 12% of patients must discontinue treatment with these drugs due to side effects, especially erectile dysfunction Side effects induced with 5ARI therapy most often occur at the beginning of drug administration and are evidently reduced in intensity and frequency over time (Corona et al., 2017).

5ARIs not only block the conversion of testosterone (TST) to dihydrotestosterone (DHT), but they also directly reduce the activity of nitric oxide synthetase (NOA-S) in cavernous penile bodies, which compromises the erection in these individuals (Corona et al.,2020).

At the same time 5ARIs inhibit the bioconversion of other steroids in the body including neurosteroids that affects brain tissue activity; especially androstenedione conversion that has antiepileptic, antidepressive and anxiolytic function (Celec et al.,2015).

The only steroid that is not under 5 alfa reductase activity is dehydroepiandrosterone sulphate (DHEAS). It is a steroid precursor, excreted by zona reticularis of the adrenal gland. It also has been proven both as a direct stimulator to NOS activity in the endothelium and as neuromodulator in the brain. Genetic studies have shown that there is a precisely specific receptor (G-protein) on the plasma membrane to which DHEA binds. This DHEA receptor is functionally linked to all three subtypes of G-protein, which mediate the activation of nitric oxide synthetase (NOS). The released NO afterwards, causes a series of intracellular reactions, the goal of which is to decrease intracellular calcium which results in relaxation of the smooth muscle of the blood vessels and establishing erections of cavernous bodies (Zaric et al.,2020).

The aim of this study was to investigate the occurrence of erectile dysfunction as a side effect during 5ARI therapy in order to prevent and overcome its appearance.

2. MATERIAL AND METHODS

We conducted a prospective controlled clinical study to evaluate the side effects from the use of 5-alpha-reductase inhibitors (dutasteride) in men with benign prostatic hyperplasia (BPH). The research procedures were in line with ethical standards and the 1975 Helsinki Declaration, which was revised in Seoul in 2008. Each patient involved in this study agreed to participate and signed written consent. The study was approved by the ethical committee at the institution where it was conducted.

Two hundred and fifty patients aged 45 to 70 years with symptoms and signs for BPH that were referred to urologist for the first time were included in the study. The age framework was set widely in order to avoid age-related discrimination of sexually active male. The diagnosis of BPH was made by routine analysis of prostate volume with echotomography, prostate-specific antigen (PSA) determination, and lower urinary tract symptoms (LUTS) assessment with International Prostate Symptoms Score (IPSS) questionnaire. Inclusion criteria were prostate volume from 40 to 65 ml, PSA lower than 4ng/ml and IPSS between 12 and 26. Exclusive criteria were dementia, deafness, medical history for mental disorders, vascular disease and myocardial infarction, diabetes mellitus and prostatic cancer as well as the use of other medicines that may interfere with 5ARIs. All the patients included in the study were sexually active regardless of their marital status.

In this study we analyzed the control group of patients treated with tamsulosin as alpha 1 blocker (n=130/250) and the investigated group of patients treated with combination of tamsulosin and dutasteride (n=120/250).

International index for erectile function 5 questionnaire (IIEF-5) was used for the sexual function assessment. Patients fulfilled the questionnaire by their own as self-evaluation is considered to provide a more objective insight into the degree of symptoms, as the patient is not ashamed to give an objective answer when self-evaluating. The urologist afterwards interprets the final score of the questionnaire. During the study measurement of serum levels of testosterone and dehydroepiandrosterone sulphate were performed at the beginning of the study and after 6- and 12-months therapy, respectively.

3. RESULTS

The data obtained during the study were entered into the database and processed with the Statistica 7 program.

The evaluation of the obtained data gave an insight into the impact of the BPH therapy on the sexual function. The basic values of the analyzed variables are presented in (Table 1).

Table 1. Basic values of the examined variables at the beginning of the sudy

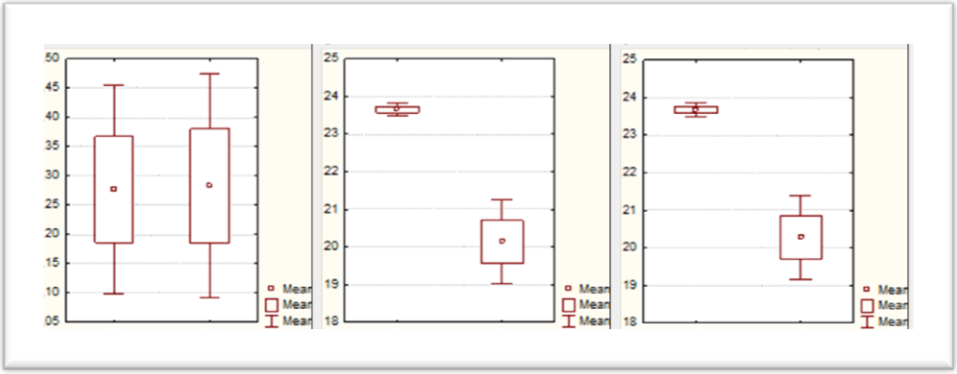
Beginning point of study		n=250
volP	mean ± SD; min-max	50.93 ± 13.4; 30-89
	median (IQR)	50 (39 – 60)
PSA	mean ± SD; min-max; min-max	1.83± 1.1;0.07-4.09
	median (IQR)	1.6 (1.05 – 2.67)
TST	mean ± SD; min-max	390.19±142.6;114-776
	median (IQR)	379 (270 – 494)
TST <270 ng/dL	n(%)	65 (26)
DHEAS	mean ± SD; min-max	151.82 ± 67.2; 15-290
	median (IQR)	155 (96 – 208)
DHEAS <80 ug/dl	n(%)	45 (18)
IPSS	mean ± SD; min-max	17.08 ± 2.8;12-26
	median (IQR)	17 (15 – 19)
IIEF-5	mean ± SD; min-max	23.28 ± 1.1; 22-25
	(median (IQR)	23 (22 – 24)

The patients from the control and study group had nearly identical result in terms of the erectile function ($p = 0.98$). Nonparametric analysis of the erectile dysfunction regarding differences in the two groups after statistical assessment showed significant difference ($p<0,05$) as shown in table 2.

Table 2. Mann-Whitney analysis of patients according to qualitative analysis of erectile function through IIEF-5 score in both groups.

Group	IIEF -5		p value
	mean ± SD	median (IQR)	
0-month			
CG	23.28 ± 1.03	23 (22 – 24)	Z=0.03
IG	23.28 ± 1.06	23 (22 – 24)	p=0.98 ns
6th month			
CG	23.65 ± 0.99	24 (23 – 240	Z=4.77
IG	20.14 ± 6.2	23 (21.5 – 24)	p=0.000002 sig
12th month			
CG	23.67 ± 1.1	24 (23 – 25)	Z=3.57
IG	20.28 ± 6.2	23 (20.5 – 24)	p=0.0004 sig

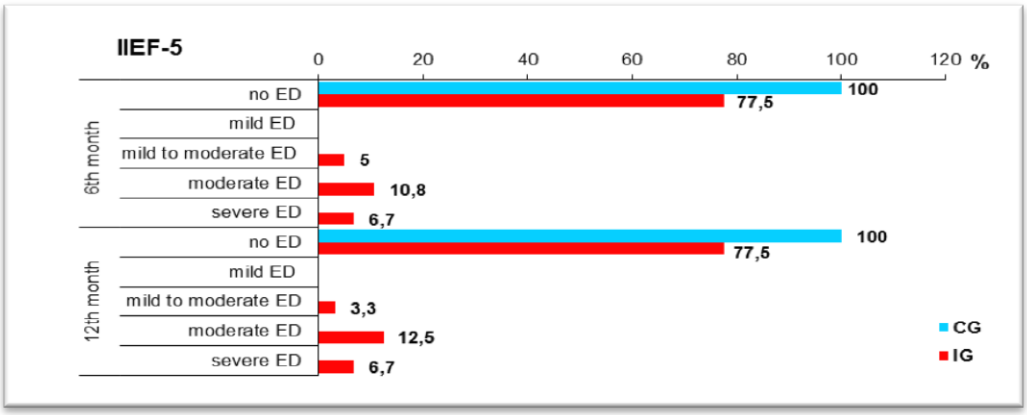
Figure 1. Graphic display of the IIEF-5 score in the control (CG) and test group (IG) at the beginning (a), after 6 months (b) and after 12 months (c).



As shown in table 2, the IIEF-5 in both groups of BPH patients before the start of therapy ranges from 22 to 25 i.e all the patients involved in the study had normal erectile function before therapy launching. After the introduction of therapy after 6 months (Figure 1b/M), erectile function improves in patients in the control group ($p<0,05$). In the second group (IG), patients that were receiving combination therapy showed lowering of IIEF-5 score in 27 patients (22,5 %) (figure 1b/D). There was no improvement of erectile dysfunction in these 27 patients from the IG after 12 months of therapy (figure 2c/D).

Statistical analysis confirmed a significantly higher incidence of erectile dysfunction in IG at 6 ($p<0.0001$) and 12 months from the start of treatment ($p <0.0001$). In both control time points after 6 and 12 months of therapy, the difference between the two groups was significant in terms of the degree of erectile dysfunction ($p <0.0001$) (figure 3).

Figure 3. Graphic representation of the percentage of patients with varying degrees of erectile dysfunction



Erectile dysfunction was most frequently represented in patients aged between 51 and 60 years (77,78%), in one patient aged under 51 years (3,7%) and in 5 (18,52%) patients aged between 61 and 70 years (table 3).

Table.3 Number of patients with ED regarding patients` age

Age (years)	Erectile dysfunction n (%)
45 – 50	1 (3.7)
51 – 60	21 (77.78)
61 – 70	5 (18.52)
(mean ± SD) (min – max)	(61.52 ± 5.2) (49 – 69)

DHEAS serum levels were measured in all patients in the same laboratory between 8 and 9 am at the beginning of therapy, and after 6 and 12 months, respectively.

Serum values of dehydroepiandrosterone sulfate at the start of therapy did not differ significantly between patients in the control and study groups (p = 0.82). The analysis did not find a statistically significant difference in the serum level of DHEAS between the two groups, after 6 months (p = 0.87) and 12 months after the start of therapy (p = 0.79)

Before the start of therapy and 6 months thereafter, 19 (14.6%) patients with CG and 26 (21.7%) within IG had decreased serum DHEAS values. At these two time points, a statistically significant difference was found between the two groups in terms of the prevalence of patients with normal and decreased serum DHEAS (p = 0.15). After 12 months of therapy, significantly lower serum DHEAS values were registered in patients with IG compared with CG (p <0.05) (table 5).

Table 5. Pearson Chi-square analysis of patients in both groups according to the values of dehydroepiandrosterone sulfate in the three time points of the research

DHEAS (µg/dL)	GROUP			p value
	n	CG n (%)	IG n (%)	
0 month				
<80	45	19 (14.62)	26 (21.67)	X^2=2.1
>80	205	111 (85.38)	94 (78.33)	p=0.15 ns
6th month				
<80	45	19 (14.62)	26 (21.67)	X^2=2.1
>80	205	111 (85.38)	94 (78.33)	p=0.15 ns
12th month				
<80	42	16 (12.31)	26 (21.67)	X^2=3.9
>80	208	114 (87.69)	94 (78.33)	p=0.048 sig

The erectile dysfunction scale correlated positively significantly with serum DHEAS levels after 6 and 12 months of therapy, in both CG and IG (p = 0.0002). In the IG, a stronger correlation was registered, (p <0.0001) in both control points (table 6).

Table 6. Spearman rank correlation between erectile function and DHEAS after 6 (a) and 12 (b) months

DHEA & IIEF-5	CG		IG	
	Spearman R	p-level	Spearman R	p-level
6th month	0.321	0.0002	0.614	0.000
12th month	0.269	0.002	0.650	0.000

During and after the treatment, no significant correlation was found in CG between the serum level of total testosterone and the score from the Index of Erectile Function ($p = 0.21$). In IG this analyzed correlation was significant both 6 months after the start of therapy and after the end of therapy ($p < 0.0001$) (table 7).

Table 7. Spearman rank correlation between erectile function and TST after 6 (a) and 12 (b) months

TST & IIEF	CG		IG	
	Spearman R	p-level	Spearman R	p-level
6th month	0.111	0.21	0.521	0.000
12th month	0.112	0.21	0.492	0.000

4. DISCUSSION

All patients participating in the study had normal sexual function before receiving BPH therapy and patients in the control and study groups had no significant differences in the IIEF-5 score ($p = 0.98$), but after 6 months of therapy in the study group patients treated with combination from tamsulosin and dutasteride a significantly lower IIEF-5 score was registered in 27 patients, ie the occurrence of erectile dysfunction in these 27 patients treated with combination therapy. Most of the literature data showed higher incidence of erectile dysfunction in patients treated with 5ARI versus placebo (Nickel et al.,1996, Skolarus et al., 2009, Edwards & Moore, 2002) or alpha blockers (Haque et al.,2018, López-Ramos et al., 2018).

The Korean study by Chi and Kim (2011) evaluates the effects of dutasteride were followed for one-year erectile function determined by the International Index of Erectile Function (IIEF-5) decreased significantly after 1 month and remained significantly reduced even after 12 months of treatment, as shown by the results in 27 men in this study. Methodologically, this study is close to the current research, in which the number of men with ED due to 5ARI therapy is 27 (22.5%).

In both groups, 75% of patients before and after BPH therapy had normal serum total testosterone levels. Decreased serum levels of total testosterone (<270 ng / dL) were reported in 34 (26.15%) CG patients and in 31 (25.8%) IG patients prior to therapy. In 26 patients from the IG who manifested erectile dysfunction after the treatment (96,3%), lowered levels of testosterone and DHEAS were obvious ($p<0,05$). The presence of low DHEAS values (<80mg/dL) in the control group without patients undergoing androgen blockade by dutasteride does not lead to obvious consequences regarding erectile function. In conditions when the androgenic function of testosterone is blocked, DHEAS as a primary steroid whose small but important role as a steroid is not subject to the action of 5ARI, assumes part of the role in the erection process. In these conditions erectile function is not disturbed.

Data from experimental and clinical studies show that DHEAS is a weak androgen that has no restorative effect on the erectile response but may contribute to the maintenance of erectile function in addition to the testosterone or dihydrotestosterone effect (Sahu et al.,2020).

DHEA has been shown to activate potassium channels by activating soluble guanylate cyclase and improving endothelial function by increasing nitric oxide (NO) synthesis and eventually dilating arteries and blocking vasoconstriction caused by hypoxia (Farukh et al, 1998).

Testosterone has an important and proven role in establishing the erection of the corpora cavernosa. Namely, its active isoform DHT stimulates the production of NO-synthetase in the corpora cavernosa, which enables the synthesis and release of NO in the endothelial cells of the blood vessels in the corpora cavernosa. The released NO causes a series of intracellular reactions, the goal of which is to reduce intracellular calcium as a result of which the smooth muscles of the blood vessels relax, dilate and establish an erection of the corpora cavernosa. Reducing the conversion of testosterone to dihydrotestosterone due to 5ARI inhibition reduces the amount of DHT that stimulates NO synthesis in the vascular endothelium of the corpora cavernosa. As a result, the amount of NO in the endothelial cells of the corpora cavernosa decreases, resulting in insufficient relaxation of the smooth muscle cells of the blood vessels in the corpora cavernosa and consequent insufficient erection of the same.

In conditions where DHT is reduced due to the blocked conversion of testosterone by 5ARI, the role of alternative stimulant of NO-synthetase is taken over by DHEA, which allows not to feel a drastic lack in stimulation of NO production in cavernous endothelial cells bodies. In cases where the amount of serum DHEAS is insufficient to cover the deficiency of DHT and as an alternative steroid to enable the release of NO in the corpora cavernosa, both the major and secondary biomechanisms of NO release are depleted. Due to this double lack of stimuli for NO

production, there is no relaxation of the smooth muscle cells of the blood vessels in the corpora cavernosa and as a result the erection process is unsatisfactory.

5. CONCLUSION

Summarizing the results of our study and data from the clinical studies it is clearly shown that in some patients, erectile dysfunction occurs after treatment with 5ARI. These side effects may not be significant in the comprehensiveness of the study, but for the individual patient this is a serious loss of quality of life and a serious individual approach should be taken before starting treatment with this type of drug.

Thus, investigation of testosterone and DHEAS serum levels prior to starting therapy should be considered valuable in order to avoid 5ARI related erectile dysfunction.

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