ASSOCIATION OF THE TREATMENT WITH 5 ALPHA-REDUCTASE INHIBITORS WITH THE PSYCHOLOGICAL WELL-BEING OF PATIENTS WITH BENIGN PROSTATE HYPERPLASIA

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Abstract: Benign prostatic hyperplasia is defined as a disorder, which has different ways of treatment depending on the symptomatology, the response to drug therapy, and the occurrence of complications. Pharmacological treatment of benign prostatic hyperplasia involves the use of mainly two groups of drugs: alpha 1 blockers and 5 alpha-reductase inhibitors (5ARIs). Side effects commonly occur during treatment with 5ARIs such as erectile dysfunction, decreased libido, and deterioration of psychological well-being. This paper aims to determine the association between DHEAS deficiency and the occurrence of side effects of 5ARI therapy that relate to the psychological well-being of patients with BPH. The analysis included 250 patients with benign prostatic hyperplasia (BPH), of whom 130 were treated with an alpha 1 blocker, while 120 patients were treated with a combination of tamsulosin and 5ARIs. The evaluation was conducted through questionnaires: IPSS (International Prostate Scoring System) to quantify BPH symptoms and PhQ-9 questionnaire for self-evaluation of depressive symptoms. The results showed that impaired psychological well-being occurred in 26 patients (22.5%) in the study group after 6- and 12-month therapy, which was statistically significant in this group ($p<0.05$). In these patients, there were also initially reduced serum values of dehydroepiandrosterone sulfate (DHEAS) ($p<0.05$). In this analysis, we concluded that the occurrence of impaired psychological well-being in patients treated with 5ARIs correlates with initially lower serum values of DHEAS before the start of therapy, which should be taken into account when using these medications.
Keywords: benign prostatic hyperplasia, side effects, psychological well-being

1. INTRODUCTION

Comparative knowledge and definition of benign prostatic hyperplasia is a disorder of the division of stem cells in the prostate where the "sleeping" stem cells are awakened and cells capable of division are created, increasing their number, and thus causing an increase in the volume of the prostate. When proliferating cells mature through the process of terminal differentiation, they have a limited lifespan before programmed cell death occurs (Bushman, 2009). Alpha-adrenergic blockers and 5α-reductase inhibitors and their combination are the "gold standard" in the medical treatment of BPH (EAU Guidelines, 2022). Inhibition of 5α-reductase results in almost complete and consistent suppression of the conversion of serum testosterone and dihydrotestosterone and more than 85% of men treated, results in a reduction of the serum level of more than 90% within 4 weeks (Roehborn et al ., 2010).

The view of the nature of BPH has recently broadened to include comorbidities and treatment effects. From the moment of starting the therapy with dutasteride, research is directed toward the occurrence of side effects which confirmed that the negative effects of the drugs used for the treatment of BPH and surgical procedures are risk factors for the development of erectile dysfunction and depressive state. (Roehrborn et al., 2002, McConnell et al., 2003).

The mood disturbance induced by 5ARIs may be attributed to their inhibitory effect on androgen and steroid 5α-reduction in the brain. Since dutasteride is a potent dual inhibitor, it also has inhibitory effects on the brain-predominant 5ARI type 1 (Harris, 1992). Mechanisms of occurrence of these mood disorders that depend on neurosteroid interactions and synthesis have been elucidated and well-known through the biosynthesis and conversion of steroids mediated by 5 alpha reductases. Neurosteroids can be formed from their parent steroid hormones directly in the brain or synthesized in peripheral tissues (Reddy, 2010). Although steroid precursors of neurosteroids are mainly synthesized in the gonads, adrenal gland, and fetoplacental unit their conversion occurs in peripheral tissues such as reproductive endocrine tissues, liver, and skin which are rich in both types of 5 alpha-reductase required for their conversion. (Do Rego et al., 2009). Steroid precursors also readily enter the brain, so precursor bases synthesized in the periphery are readily available for the local biosynthesis of neurosteroids. Five alpha-reductase activity has been identified in both neurons and glial cells in the brain (Melcangi et al., 2013).

The lack of neurosteroids has a key role in the occurrence of depression. Animal studies have shown that fluoxetine, a selective serotonin inhibitor and widely used antidepressant, increases allopregnanolone levels in the brain (Uzunova et al., 1996). Testosterone in the brain is transformed into estradiol by the enzyme aromatase and into dihydrotestosterone (DHT) by 5α-reductase, after which it binds to androgen receptors. The complete absence of an

association between circulating estradiol and mood outcomes does not rule out the hypothesis that testosterone's influence on mood is mediated by estradiol aromatization (McEwen, 1981). The sulfurized neurosteroids pregnenolone sulfate (PS) and DHEAS, as well as DHEA, have clear antidepressant effects (Reddy et al., 1998).
Dehydroepiandrosterone and its precursor DHEAS have been widely investigated as novel antidepressants. Their importance as neurosteroids is all the greater because their synthesis and further action in brain tissue do not depend on the activity of 5α-reductase (Wolkowitz et al., 1999).
This paper aims to determine the association between DHEAS deficiency and the occurrence of side effects of 5ARI therapy that relate to the psychological well-being of patients with BPH.

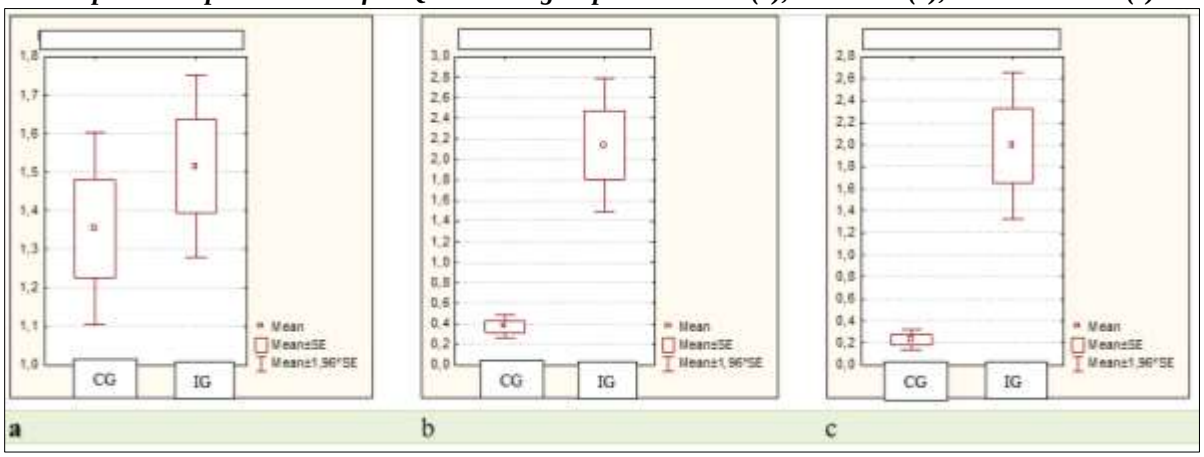
2. MATERIAL AND METHODS

In this prospective study, we evaluated the adverse effects of the 5-ARIs (dutasteride) in patients diagnosed with benign prostatic hyperplasia (BPH) by following the ethical standards of the Helsinki Declaration revised in Seoul in 2008. Patients included in this study signed a written informed consent to participate and the study was approved by the ethics committee at the institution where it was conducted.
A total of 250 patients met the inclusion criteria of the study, age from 40 to 70 years, prostate volume more than 40ml, total PSA serum levels less than 4ng/ml and first visit to a urologist due to different degrees of lower urinary tract symptoms (LUTS). Quantification of LUTS was done with the International Prostate Symptom Score (IPSS) questionnaire. Exclusion criteria were dementia, deafness, medical history of mental disorders, vascular disease, myocardial infarction, diabetes mellitus, and prostate cancer Patients were randomized into two groups depending on the BPH therapy they were prescribed in a control group(CG) of patients treated with alpha tamsulosin (n=130/250) and an investigated group (IG) that were treated with a combination of tamsulosin and dutasteride (n=120/250).
At the beginning of the study, all patients included had normal psychological status without signs of depression, measured by the PhQ-9 self-evaluation questionnaire. The PHQ-9 (Patient health questionnaire-9) questionnaire is a standardized and validated self-assessment tool that consists of nine short and simple questions that are built on the criteria for depression identified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Determination of mood disorder in all patients was done at the beginning of the study and two control points after 6 and 12 months of continuous drug treatment. All patients who had mood swings and clinically significant mood swings were excluded at the start of the study.

3. RESULTS

The obtained values from the studied parameters were entered into the database of the program Statistics 7 and processed with it. Evaluation of the obtained data provided insight into the impact of BPH therapy on the mental state of patients. The depression self-assessment questionnaire (PHQ-9) presented non-significantly different sums between the two groups of patients before therapy (p=0.17) (graph 1a) and significantly different after 6 months (p=0.011) (graph 1b) and after 12 months of therapy (p=0.046) (graph 1c), as a result of significantly higher scores for the questionnaire obtained in patients on dual therapy.

Graph 1. Box presentation of PhQ-9 in both groups at 0-month (a), 6th month (b), and 12th month (c)



The mean PHQ-9 score was 2.14 ± 3.6 in the investigated group of patients treated with combination therapy, 0.38 ± 0.7 in the group treated only with an alpha1 blocker after 6 months from the start of therapy, and 1.99 ± 3.7 and 0.23 ± 0.5, consistently in the group of patients treated with monotherapy and combination therapy (table 1).

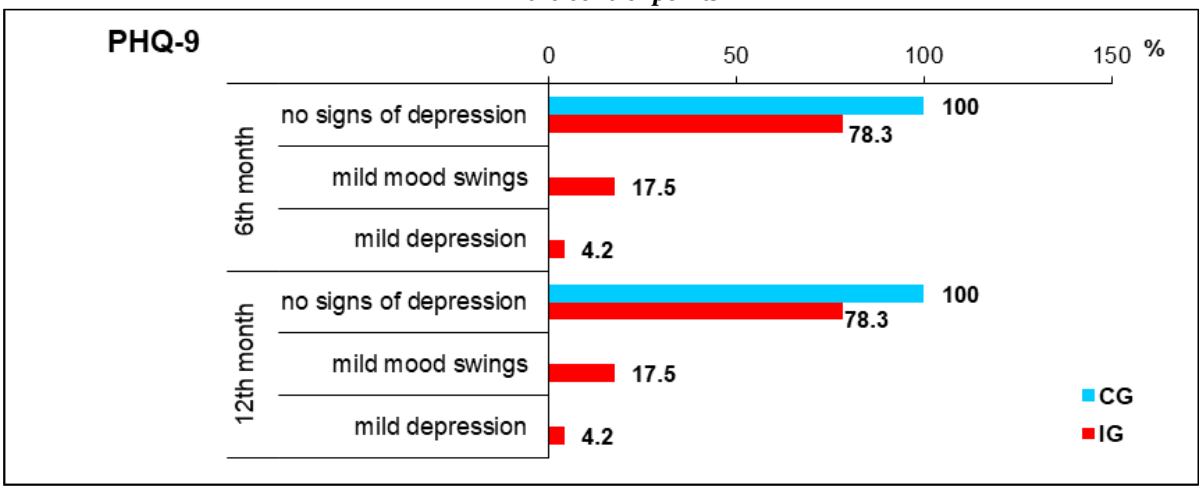
Table 1. Comparative analysis of the control group (CG) and investigated group (IG) to PHQ-9 score (Z - Mann-Whitney)

Group	PHQ-9 (mean ± SD)	PHQ-9 median (IQR)	p value
0 - month			
CG	1.35 ± 1.4	1 (0 – 3)	Z=1.38 p=0.17 ns
IG	1.52 ± 1.3	1 (0 – 2.5)	
6th month			
CG	0.38 ± 0.7	0 (0 – 1)	Z=2.52 p=0.011 sig
IG	2.14 ± 3.6	0 (0 – 1)	
12th month			
CG	0.23 ± 0.5	0	Z=1.82 p=0.046sig
IG	1.99 ± 3.7	0 (0 – 1)	

From the analysis, it is evident that after 6 and 12 months of therapy for BPH 26 patients treated with combination therapy expressed mood disorders of varying degrees. This indicates that the type of drug therapy significantly affects the mood disorder of patients.

According to the results, during the treatment period, depressive symptoms were not registered in any patient from CG, while in IG 21 (17.5%) patients manifested weak mood deviations, and 5 (4.2%) patients had mild depression (graph 2).

Graph 2. Percentage presentation of patients with different degrees of mood disorder in two patients groups in the control points



Regarding patients` age, mood disorders were most common in patients aged between 51 and 60 years (77.78%), in one patient under the age of 51 (3.7%), and 5 (18.52%) patients aged between 61 and 70 years (table 2).

Table.2 Number of patients with MD concerning the age of the patients

Age	**MD 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)

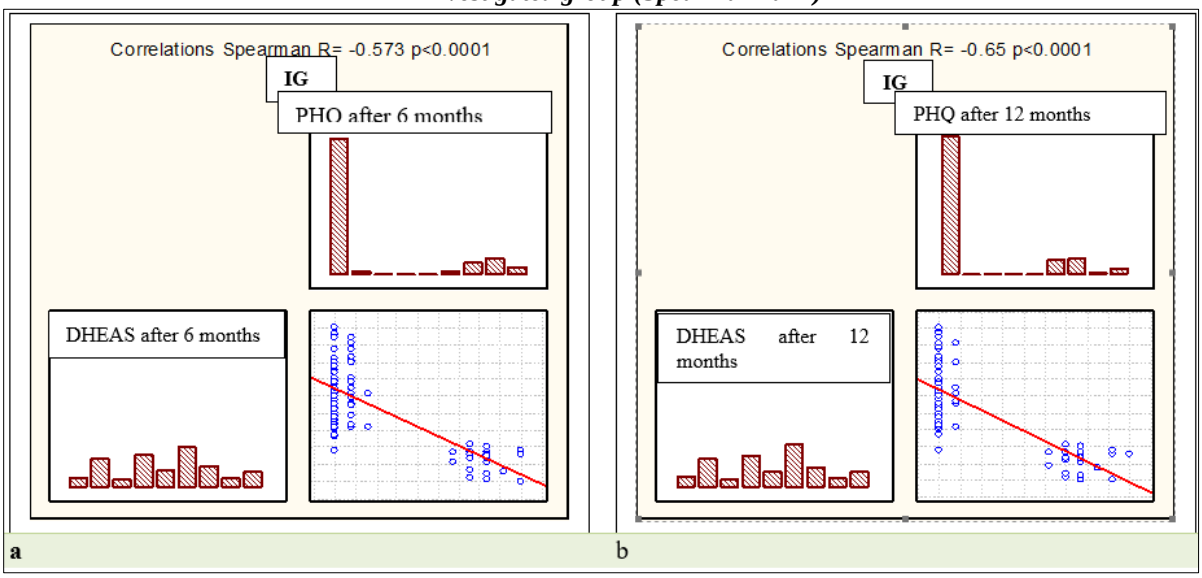
The correlation between the PHQ-9 scale and serum DHEAS level after 6 and after 12 months of therapy in CG (p=0.86 and p=0.82 respectively did not show significance. The correlation between the PHQ-9 scale and the serum level of DHEAS showed significance (p<0.0001) in the group treated with combination therapy, which is shown in table 3.

Table 3. Correlation between PHQ-9 and serum DHEAS values in both groups at both control points

DHEAS & PHQ-9	CG		IG	
	Spearman R	**p-level**	**Spearman R**	**p-level**
6th month	0.016	0.86 ns	-0.573	0.000 sig
12th month	0.019	0.82 ns	-0.649	0.000 sig

In the investigated group that was treated with combination therapy, the correlation was significant at both time points (p<0.0001), with Spearman's coefficient values of R = -0.573 and R = -0.649, respectively after 6 and 12 months from the start of therapy, which indicate a negative, indirect correlation (graph 3).

Graph 3. Negative, the indirect correlation between PHQ-9 and DHEAS after 6 (a) and 12 (b) months in the investigated group (Spearman rank)



As the serum DHEAS level decreased, the PhQ-9 sum increased and vice versa. Patients treated with combination therapy for BPH that has had initially lower serum DHEAS values had a worse PHQ-9 depression questionnaire score and vice versa.

4. DISCUSSION

Based on the results of the PHQ-9 questionnaire, patients from the control group had no symptoms of depression or disturbance of psychological well-being during the entire follow-up period after the beginning of therapy.

Disturbance of psychological well-being was registered in 26 patients from the study group, of which 21 (77.8%) had a mild mood disorder, and 5 (18.5%) had mild depression after 6 and 12 months of medical therapy for BPH. All 26 patients who at the beginning of the research were in a completely normal psychological state, after the medical treatment with 5ARI showed a certain degree of disturbed mood and depression. At the same time, these patients showed significantly lower initial values of DHEAS. Patients on combination medical therapy for BPH with lower serum DHEAS values (below 80 μg/dL) exhibited varying degrees of depression.

The results of this analysis pointed towards finding that patients who have low serum DHEAS values and are susceptible to the action of dutasteride (5ARIs) are more prone to deterioration of their psychological well-being than patients treated with tamsulosin alone.

Serum DHEAS levels decrease with aging and reference values are adjusted to the age. However, in some individuals, this drop in the level of DHEAS is greater than expected and could precipitate conditions related to its deficiency. Dehydroepiandrosterone sulfate is the only steroid in the human body on which 5α-reductases do not influence the processes of bioconversion. In conditions where 5α-reductases are inhibited by 5ARIs due to the treatment of BPH, the biosynthesis of these neurosteroids in the brain remains impaired. On the other hand, DHEAS is been proven to have direct antidepressant and cognitive properties and is also known as a neurosteroid that can increase feelings of well-being and is useful in ameliorating atypical depressive disorders (Stárka et al., 2015).

The impaired bioconversion of steroids due to the inhibition of 5α - reductase on the one hand and the low serum values of DHEAS, as a direct neurosteroid, contributes to the manifestation of depressive symptoms and impaired psychological well-being of patients.

The most relevant finding on the association between BPH pharmacotherapy and the occurrence of a depressive state is a study that confirmed that the use of 5-ARIs was associated with a 1.52-fold higher prevalence of depressive symptoms (Pietrzyk et al., 2015). However, the authors do not explain the reason for the occurrence of depression in these patients, which is achieved in our analysis.

It is important to stress the role of 5α-reductase in the biotransformation of steroids into neurosteroids as a very important biological process in establishing good mental status and psychological well-being. By inhibiting 5α-reductase, 5ARIs not only inhibit the conversion of testosterone to dihydrotestosterone but also affect the reduced synthesis of neurosteroids. This results in varying degrees of mood disorders and depression (Rahimi-Ardabili, 2006). We find this important and suggest the exogenous substitution of DHEA in patients with low serum levels (below 80 μg/dL) to maintain psychological well-being while treated with 5ARIs due to BPH.

The analysis of the results in this paper explains the reason for the occurrence of mood disorders associated with the use of 5ARIs by determining the association with serum levels of DHEAS. Its importance is to clarification of the potential negative side effects of inhibitors that target 5 alpha reductases for the treatment of benign hyperplasia of the prostate.

5. CONCLUSION

Low DHEAS values in conditions of inhibited activity of 5α-reductases and disturbed biosynthesis of other neurosteroids lead to varying degrees of mood disorders. When determining the duration of pharmacological treatment of patients with BPH, it is necessary to monitor the serum values of DHEAS, considering that this study proved that initially low values are the cause of mood disorders in patients with BPH who are on pharmacotherapy with 5ARIs.

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