# CORRELATION BETWEEN THE POST 5ARI SYNDROME AND DEHIDROEPIANDROSTERONE LEVELS IN PATIENTS WITH BPH

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**Abstract:** Conservative or non-surgical treatment of benign prostatic hyperplasia relies on the use of mainly two groups of medicines: selective alpha blockers and 5 alpha reductase inhibitors (5ARI). The most efficient non-surgical treatment is combination therapy of these medicines but occasionally after the introduction of 5ARI in the treatment, certain adverse effects that include sexual disturbances and depression may appear that are known as "post-5ARI syndrome". The purpose of this study is to show the significance and role of the dehydroepiandrosterone as an important predictor of post-5ARI syndrome in patients with BPH who are treated with 5ARI. In this randomized controlled prospective pharmaco epidemiological study, we investigated 120 patients with BPH combination therapy (tamsulosin and dutasteride) versus control group that consisted of 130 patients with monotherapy for BPH (tamsulosin).The correlation between both erectile dysfunction and depression on one side an serum dehydroepiandrosterone levels on the other was investigated at the time of active use of therapy in period of 6 months. We evaluated two groups of patients through 3 questionnaires: IPSS (International Prostate Score System) to evaluate the symptoms of benign prostatic hyperplasia (BPH), IIEF (International Index for Erectile Function) questionnaire for erectile dysfunction (ED) and a Beck depression inventory (BDI). We concluded that there is a law-proportionate correlation between appearance of post 5ARI syndrome and dehydroepiandroserone levels in patients with BPH.
**Keywords:** BPH, erectile dysfunction, depression, dehydroepiandrosterone, post 5ARI

## 1. INTRODUCTION

Post 5 ARI syndrome initially known as "postfinasteride syndrome" since 2012 relates to all adverse effects of 5 alpha reductase inhibitors (5ARI), mainly erectile dysfunction and depressive disorders[1]. The basis of its occurrence is the inhibition of 5 alpha reductases enzymes thus blocking the conversion of testosterone to dihydrotestosterone (DHT) as well as catalyzing the biosynthesis of powerful neurosteroids from their precursor dehydroepiandrosterone. Analysis of the literature indicates that after 2 years of treatment with 5ARI, approximately 12% of patients must discontinue treatment with these medicines due to adverse effects, particularly erectile dysfunction[2]. Research also suggests that 5ARI not only inhibits the process of conversion of testosterone to dehydrotestosterone, but they also cause a reduction in nitric oxide synthetase (NOS) activity, and therefore the erection of cavernous bodies in these individuals is compromised[3]. The 5 alpha reductase inhibitors are a group of drugs that not only enable conversion of testosterone to dihydrotestosterone but also enable the conversion of other steroids and neurosteroids that act as antiepileptic, antidepressants and anxiolytics to brain tissue. In that way 5 ARI are responsible for the production of several neuroactive steroids[4].

From the physiological point of view both testosterone and dihydrotestosterone also modulate the neuroendocrine stress response and are inversely proportional to depressive disorders[5]. The neurosteroids such as alopregnanolones are produced in the brain with mediation of 5-alpha reductase enzyme and shows lower values in men with

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depressive symptoms[6]. Patients with clinical depression have also been shown to have lower values of 5-alpha reductase enzymes in the prefrontal cortex[7].

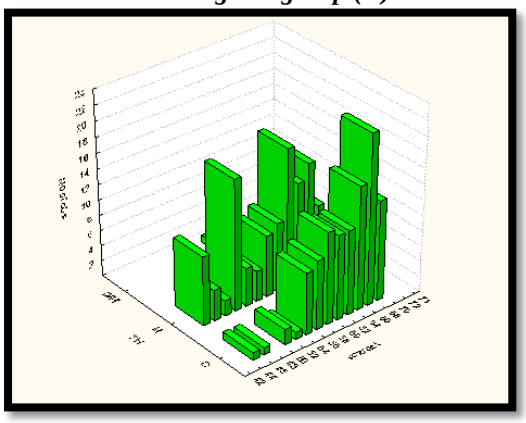
Dehidroepiandrosterone (DHEA) is steroid precursor and its sulfated depot in the human body is DHEA-S, excreted by zona reticularis of the adrenal gland. It also has been proven both as a direct stimulator to NOS activity in the endothelium and as neuromodulator in the brain. Genetic studies have shown 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 ultimate 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[8]. Several studies have reported a reduced serum level of DHEA in patients with erectile dysfunction (ED), which suggests that decreased DHEA and DHEA-S secretion are important risk factors for ED in aging men[9].

These lower levels of serum DHEA in addition with decreased levels of DHT in BPH patients, raises the possibility of appearance of post 5ARI syndrome in those patients who are treated with 5ARI.

## 2. MATERIAL AND METHODS

In this randomized controlled prospective pharmaco-epidemiological study, a total of 250 outpatients with diagnosis of BPH were followed for 6 months in a specialist urological clinic. The research procedures were in line with ethical standards and the 1975 Helsinki Declaration, which was revised in Seoul in 2008. Patients were divided in two groups: control group that consisted of 130 patients treated with monotherapy for BPH (tamsulosin) and investigated group of 120 patients treated with BPH combination therapy (tamsulosin and dutasteride).The correlation of post 5ARI syndrome on one side and serum dehydroepiandrosterone levels on the other, were investigated at the time of active use of medicinal anti BPH therapy, in period of 6 months after starting the therapy.

***Graph 1. Bivariant histogram of patients with BPH by age and therapy they receive; a control group (M) and an investigated group (D)***



We evaluated two groups of patients through 3 questionnaires: IPSS (International Prostate Score System) in order to evaluate the symptoms of benign prostatic hyperplasia (light, medium or severe), IIEF-5 (International Index for erectile function-5) to determine erectile dysfunction (ED) and a Beck depression inventory to evalu ate patients` psychological status.

Inclusion criteria for the study were men with diagnosis of BPH aged 45 to 70 years, prostate volume equal to or greater than 40cm3, prostate specific antigen (PSA) less than or equal to 4ng/ml, IPSS from 12 to 26, IIEF-5 equal to or greater than 21and Beck depression index (BDI) equal to or greater than 11.

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Exclusion criteria were dementia, deafness, medical history of mental disorders, vascular diseases, and myocardial infarction and prostate cancer.

Diagnosis of BPH was established by routine analysis of prostate volume by transabdominal echosonography, prostate specific antigen (PSA) determination, and lower urinary tract symptoms (LUTS) evaluated by IPSS. At the same time serum levels of dehydroepiandrosterone were measured in the same laboratory between 8 and 9 a.m in all 250 patients at the point of introduction of anti BPH medicinal therapy.

After the patients signed consent to use the data for the study, the urologist determined the IPSS score and the degree of ED through a questionnaire and gave them a self-assessment questionnaire for depression i.e BDI. Self-evaluation is considered to provide a more objective insight into the degree of depression, as the patient is not ashamed to give an objective response when self-evaluating, which would be the case if confronted with a physician. The urologist notes and interprets the final score of the questionnaires.

## 3. RESULTS

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

The score obtained from the IPSS questionnaire classifies all patients with BPH into three groups: patients with mild (1-7), moderate (8-19) and severe (20-35) symptoms as showed in table 1.

***Table 1: Number of patients classified according the lower urinary tract symptoms and IPSS***

| IPSS | Nº of patients | Percentage of patients% | Description of symptom score |
|---|---|---|---|
| (7-15) | 117 | 46,8 | mild |
| (16-20) | 106 | 42,4 | moderate |
| (21-35) | 27 | 10,8 | severe |
| Total 250 | | | |

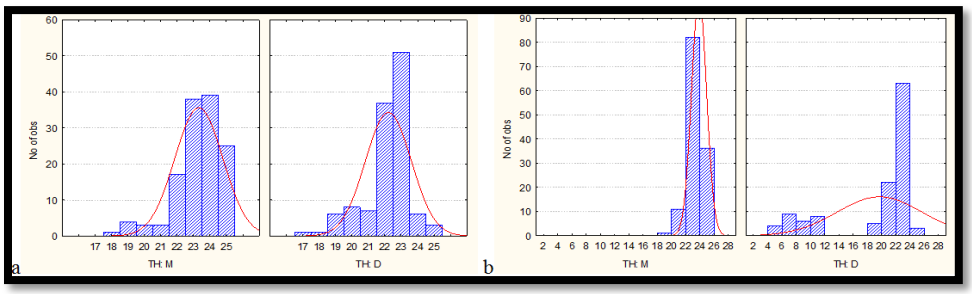
The IIEF-5 erectile function questionnaire contains 5 self-evaluation questions interpreted by an urologist. According to the obtained score, patients were classified in five groups: no ED (22-25), minor ED (17-21), mild ED (12-16), moderate ED (8-11), severe ED (5-7) as shown in table 3.

***Table 2: Number of patients classified according to IEFF-5 for erectile dysfunction at the beginning of the study***

| IIEF-5 | Nº of patients | Percentage of patients% | Description of symptom score |
|---|---|---|---|
| 20-25 | 249 | 99,6 | NO ED |
| 17-21 | 1 | 0,4 | Minor ED |
| 12-16 | 0 | | Mild ED |
| 8-11 | 0 | 0 | Moderate ED |
| 5-7 | 0 | 0 | Severe ED |

As shown in graph 1.erectile function at the point of starting BPH medicinal therapy ranged from 17 to 25 in the control group (1a) which means that none of these patients suffered from impaired erectile function. As for the examined groip (D) at the beginning of the therapy patients had satisfying erectile function as well ranging from 17 to 25. After 6 months of BPH therapy (1b), patients in the control group (M) remain with satisfying erectile function, while there was a decreasing of erectile function index in some patients of the examined group (D). Total of 26 patients in the examined group had IIEF score from 4 to 12 points and experienced ED.

***Graph 2: Categorized histogram of IIEF-5 in control group (M) and examined group (D) at the beginning of the study (a) and after 6 months of receiving anti BPH therapy (b)***



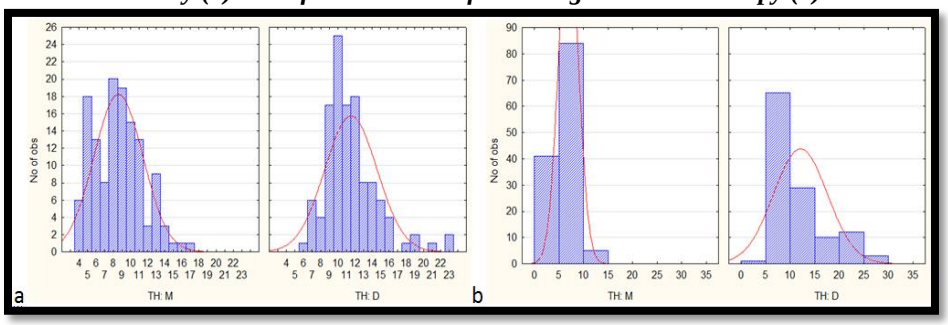
We evaluated the symptoms of depression by administering a Beck Depression Inventory containing 21 items and self-evaluating patients. Scoring and interpretation of the results were done by an urologist, according to whom patients were classified as: normal oscillations (1-10), moderate oscillations (11-16), borderline clinical depression (17-20), moderate depression (21-30) and severe depression (> 40) as shown in table 2.

***Table 3: Number of patients classified according to IEFF-5 for erectile dysfunction at the beginning of the study***

| BDI | N° of patients | Percentage of patients% | Description of symptom score |
|---|---|---|---|
| 1-10 | 227 | 90,8 | Normal oscillations |
| 11-16 | 23 | 9,2 | Physiologic oscillations |
| 17-20 | 0 | 0 | Borderline clinical depression |
| 21-30 | 0 | 0 | Moderate clinical depression |
| 31-40 | 0 | 0 | Severe depression |
| > 40 | 0 | 0 | Extreme depression |

As shown in graph 3. BDI index at the point of starting BPH medicinal therapy ranged from 4 to 18 in the control group (1a) which means that none of these patients suffered from depressive disorder. As for the examined group (D) at the beginning of the therapy only few patients had mild mood disorders due to impaired sleep because of the symptoms of BPH. After 6 months of BPH therapy (1b), patients in the control group (M) had an improve of the psychological status due to improvement of BPH symptoms and overnight sleep, while there was a worsening of BDI index in some patients of the examined group (D). Total of 26 patients in the examined group had BDI score from 20 to 30 points and expressed clinical signs of depression.

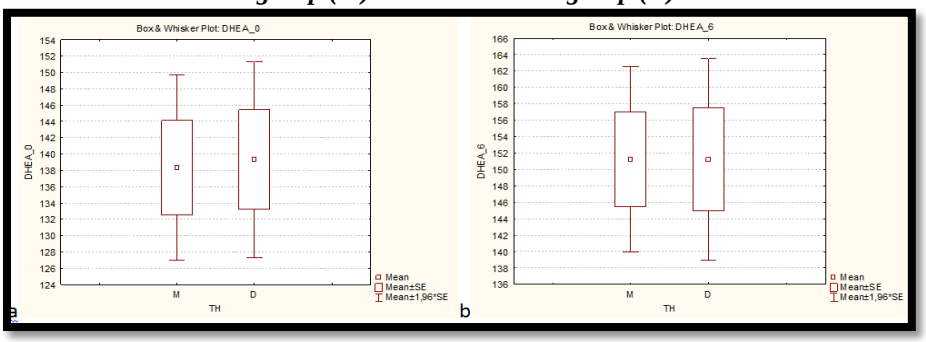
***Graph 3: Categorized histogram of BDI in control group (M) and examined group (D) at the beginning of the study (a) and after 6 months of receiving anti BPH therapy (b)***




From the analysis of the obtained data, we made a brake throw the insights of the impact of anti BPH therapy on the sexual function and psychological changes in patients with BPH and correlation of their appearance and the serum levels of DHEA. Processing consists of tabular and graphical representation of statistical series according to defined variables.

The serum level of DHEA at the beginning of the study ranged from 15 to 290 in both control and examined group as seen from Graph 4.

***Graph 4: Serum DHEA levels at the beginning of the study (a) and after 6 months of the study(b) in control group (M) and in examined group (D)***



With regard to DHEA values in both groups of patients, as shown in graph 2, it is evident that there were no significant differences in the DHEA serum values of the two groups at the beginning of the study.
After 6 months of BPH therapy serum DHEA measurements showed no significant oscillations compared to the original taken at the beginning of the study (graph 4).
In order to determine the possible correlation of erectile dysfunction with DHEA levels, a Spearman rank correlation was performed. It showed a significance ($p < 0.05$) in the correlation of dehydroepiandrosterone levels with erectile dysfunction and mood disorders.
Patients who had low levels of DHEA (below physiological limits) in the study showed lower IIEF-5 score and expressed ED. The results of this correlation are shown in Table 4.

***Table 4: Correlation of DHEA levels with erectile function***

| | IIEF_0 m. | IIEF_6 m. |
|---|---|---|
| DHEA_0 | -,0126 | ,4400 |
| | p=,843 | p=,000 |
| DHEA_6 | ,0049 | ,4450 |
| | p=,939 | p=,000 |

DHEA levels throughout the study showed a significant correlation ($p < 0.05$) with a rise in the Beck Depression Index and mood disorders. The values of this correlation are shown in Table 5.

***Table 5: Correlation of testosterone and DHEA levels with Beck`s depression index***

| | BDI_0m. | BDI_6m. |
|---|---|---|
| DHEA_0 | ,0628 | -,3954 |
| | p=,323 | p=,000 |
| DHEA_6 | ,0599 | -,4011 |
| | p=,345 | p=,000 |

The above results indicate that serum DHEA levels are significantly correlated with erectile function and psychological status in the patients included in this study.

## 4. DISCUSSION

Summarized data from a large number of clinical trials that were processed during the development of this study clearly showed that some patients with BPH, after pharmacological treatment with 5ARI, experienced adverse reactions such as erectile dysfunction and mood disorders.
The role of DHEA/ DHEA-S is still unclear but several studies have reported a reduced serum level of DHEA / DHEA-S in patients with ED, meaning that reduced synthesis of these pro hormones is a significant risk factor in the development of ED in older men. Reduced levels of DHEA-S, especially in young men with ED, may be an etiological factor for the occurrence of ED. However, patients treated with DHEA had a statistically significant increase in all domains of IIEF-5 compared to the placebo group[9].
The prevalence of depressive symptoms in the Polish cohort study of patients with BPH, PolSenior (2007-2012), revealed that only 13.6% of the elderly included in the study were initially diagnosed with depression. Following the introduction of 5ARI in the treatment of BPH, the incidence of mood disorder and DS in BPH patients in their study was approximately 26%, excluding patients who previously had a depressive condition[10]. This is in support of the hypothesis in this study that after the introduction of 5ARI in the treatment of BPH, there is a possibility of post-5ARI syndrome, and its symptoms correlate with each other and change the quality of life of those patients in whom they occur.
The most relevant finding is the association between BPH pharmacotherapy and DSs occurrence is demonstrated in a study that shows that the use of a 5ARI is associated with a 1.52-fold higher prevalence of depressive symptoms[11]. It is in line with a study showing that the use of finasteride, a 5ARI might induce development of depression[12].

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There is experimental evidence for the direct effects of DHEA on the brain. The elucidation of the role of DHEA in sexual function is confirmed by the administration of DHEA which results in the biosynthesis of active androgens that act on tissue target targets without repercussions at their level in the peripheral circulation[13].

## 5. CONCLUSION

In this study it is concluded that 5ARI therapy has a negative effect on erectile function and psychological health only in a limited number of patients with BPH, (2 out of 10 BPH patients), receiving combination therapy of alpha 1 blocker and dutasteride.

The analysis in this study provided conclusion that patients with negative effects of 5ARI (dutasteride) i.e the expression of post-5 ARI syndrome have lower serum levels of DHEA-S that deviate from normal, physiological age ranges. In a situation where conversion of testosterone to its more potent androgen DHT is inhibited by the action of 5ARI, DHEA/DHEA-S acts as a secondary conditional androgen and is the only steroid that can express its positive effect on erectile and psychological function. The reason lies in the fact that 5 alfa reductase enzymes does not have any effect in the biochemical changes of DHEA and its sulfurated depot, DHEA-S. In a condition where DHEA/DHEA-S serum values are within physiological limits they have a direct impact in both erection of cavernose bodies and act as neurosteroids in the brain. This study showed that when DHEA-S values were lower than normal, physiologically ranges for the appropriate age, in patients treated with 5ARI, BPH patients expressed a post-5ARI syndrome.

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