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Evaluation of Sex Hormone Levels in Benign Prostatic Hyperplasia Patients Treated with 5 Alpha-Reductase Inhibitor (Finasteride) in Amara city/Iraq

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Abstract:

The present study aimed to determine the serum sex hormone levels among Benign Prostatic Hyperplasia (BPH) patients before and after 3 months of oral administration of 5- α reductase inhibitor (finasteride). Forty BPH patients and 40 healthy men from Amara city were involved in this study, their ages were between 40-59 year. They were all subjected to direct estimation of hormones by MinVidas method including Testosterone (T), Estradiol (E2), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL), and Dihydrotestosterone (DHT) before and after 3 months of treatment with 5 α -reductase inhibitor (finasteride) (the healthy individuals didn't take finasteride). The results showed that T level was significantly lower ($P < 0.05$) in pre-treated compared to the post-treated patients and control group, whereas no significant difference was observed between the two latter groups. Levels of E2 - and DHT were significantly lower ($P < 0.01$) in post-treated compared to the pre-treated patients with no significant difference with control group, while they were significantly higher ($P < 0.01$) in pre-treated patients compared to control group. FSH and LH levels showed no significant differences in the pre-treated in comparison with post-treated and control groups. PRL levels insignificantly higher in pre-treated in comparison with post-treated patients, while significantly higher ($P < 0.05$) in comparison with control group, with the later showing a significant lower ($P < 0.05$) in comparison with post-treated patients. It is concluded that 5 α -reductase inhibitor (finasteride) plays a role in decreasing levels of DHT and E2 which have vital roles in enlargement of prostate.

Key words: BPH, Dihydrotestosterone, Finasteride, 5- α reductase, Sex hormones.

Introduction:

Benign Prostatic Hyperplasia represents the most common nonmalignant condition of the abnormal growth of prostatic cells in aging men (1). It is considered as a common public health problem, causing high morbidity and essential worsening of men's quality of life (2), and could be evaluated clinically or pathologically. Clinically, BPH is generally viewed as a benign enlargement of the prostate, which shares in an array of urinary voiding difficulties that can range from bothersome to significantly influencing quality of life among older men (3).

Several hypotheses were found to explicate the development of BPH and the most accepted one is the DHT hypothesis. T converted by 5-alpha reductase (type II) to DHT, which is crucial to the early development and normal growth of the prostate (4). However, DHT was considered as the major cause of prostate gland enlargement (4, 5).

Benign Prostatic Hyperplasia develops from changes in the ratios of increasing prostatic cell growth compared to prostatic cell death (6, 7).

On other hand, finasteride has lately come to the forefront as an inhibiting agent for 5 α - reductase activity, especially type-II, which decreases intraprostatic DHT levels by 70% and reduces the size of the prostate by 27 % in patients with BPH, leading to alleviation of BPH symptoms (8,9). Finasteride showed effectiveness in long-term treatment of progression of disease (5,10). In view of controversy concerning the actual role of finasteride in controlling the levels of sex hormones, the present study was conducted in an attempt to shed some light on the effects of

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finasteride as an inhibitor for 5 α - reductase (Type II) activity. Therefore, the present study aimed to investigate reproductive (hormones) parameters for BPH patients before and after finasteride treatment, by the evaluation levels of hormones that include T, E2, FSH, LH, PRL, and DHT.

Materials and Methods:

Study population:

The present study involved 40 male BPH patients who attended to the Consultant Urologist at AL-Sadder Teaching Hospital (Al-Amara City, Iraq) through the period from April 2015 to April 2016. The ages were between 40 and 59 years old. Age matched healthy men (n=40) were included as a control group. Men who had a history of prostate cancer, prostate surgery, diabetes mellitus (DM), or hypertension were excluded.

Experimental Design:

Patients completed a previously validated baseline questionnaire. Prostatic size and configuration were determined by digital rectal examination (DRE) and ultrasonography (Shanghai Sunbright Industrial Co., Ltd, China). Patients were treated with a 5mg/day dose of finasteride for at least 3 month. Blood was collected from the patients (venous blood 5cc) before beginning of treatment (pre-treated) and after 3 month of the treatment (post -treated).

Collection of Blood Sample:

To minimize the confounding effects of diurnal variation in hormone concentrations, we collected 5 ml of blood from each patient at 8-10 AM. The blood sample was left for around 15 minutes to clot at room temperature, and then separated by centrifugation at 3000 rpm for 5 min. Serum was divided into several aliquots of 200 μ L labeled Eppendorf tubes and at stored-8 $^{\circ}$ C until used for estimation of hormones

Determination of Serum T,E2,FSH,LH,PRL levels:

Automated quantitative test with the VIDAS family instruments (bioMérieux, France) was applied for the quantitative measurement of T,E2,FSH,LH, and PRL in human serum, using the enzyme immunoassay competition method with the Enzyme Linked Fluorescent Assay (ELFA) technique.

Determination of Serum DHT level:

Competitive-ELISA was used for determination of DHT, by the available ELISA kit .The color change was measured spectrophotometrically at a wavelength of 450 \pm 2 nm. The level of DHT in the samples was then determined by comparing the OD of the samples to a standard curve.

Statistical Analysis:

The statistical analysis was performed using the statistical package SPSS version 17. The data were expressed as mean, and standard deviation (SD). ANOVA was used to analyze repeated measurements. Results were determined at highly significant (P<0.01) and significant (P< 0.05) difference levels.

Results and Discussion:

Testosterone (T)

The results revealed that T level in the post-treated patients (4.43 \pm 1.80 ng/ml) was significantly increased (P<0.01) compared to the pre- treated patients (3.68 \pm 1.49 ng/ml),with the latter being significantly decreased (P<0.01) compared to the control (5.09 \pm 1.70 ng/ml). There was no significant difference between the post-treated patients and the control as shown in Table 1 and Fig. 1.

The present results indicated that the level of T hormone was significantly associated with BPH disease, as observed from its significant decrease in the pre-treated patients compared to the control. This decrease might be resulted from the enzymatic activity of 5 α -reductase (converts T to DHT) which was reported to be about 7-folds higher in cultured BPH compared to normal, and the 17-hydroxysteroid dehydrogenase activity (metabolizes T to the inactive Δ 4-androstenedione) which was 250-folds more in BPH stromal cells (11,12). In addition, T level was significantly increased in the post-treated patients in comparison with the pre-treated patients after 3 month of finasteride treatment. Finasteride inhibits the synthesis of 5 α -reductase which is considered to be related to the reduction of Leydig cell activity, leading to increase T /DHT ratio.

These results are compatible with the results of other studies (13-17) that found that the mean of T was significantly lower in BPH patients than in control group. The increase in serum T and E2 levels were also shown to be associated with decreased BPH risk (18). Other studies reported that the high levels of T converted to DHT are significantly associated with the decreased risk of BPH (14,19).These steroids are mediating factors that explain the relationship of genetic or environmental features with BPH risk. Other studies found no difference in serum T and E2 between BPH patients and control subjects (20-23).

The present results are also consistent with previous studies on the effects of finasteride (13, 24, 25),which observed an increased serum T level after finasteride treatment. Previous investigations (26- 29) reported an approximately 6-fold increase

in intraprostatic T levels following finasteride treatment, while others (30-32) noted no significant differences in mean serum levels of T between finasteride treated and control groups. It was also state that studies reporting an increased risk of BPH

or LUTS with increased serum T levels are lacking (33). Furthermore, the proscar=finasteride (5mg/day) long-term efficacy and safety trial demonstrated low T level (<300ng/dl) in (21,7%)of aging men with BPH (33) .

Table 1. Effects of finasteride on serum E2,FSH,LH,PRL and ,DHT levels in patients with BPH

Groups Hormones	Patients group		control group	P value
	Pre-treated	Post-treated		
T (ng/ml)	b 3.68 ± 1.49	a 4.43 ± 1.80	a 5.09 ± 1.70	0.002**
E2 (pg/ml)	a 55.04 ± 9.9	b 40.26 ± 9.8	b 35.67 ± 4.09	0.0001 **
FSH (m.IU/L)	a 4.90 ± 1.99	a 5.58 ± 1.94	a 4.25 ± 1.92	NS 0.063
LH (m.IU/L)	a 3.67 ± 1.39	a 4.28 ± 1.87	a 3.25 ± 1.65	NS 0.064
PRL(ng/ml)	a 11.17 ± 4.51	a 10.42 ± 8.06	b 7.18 ± 3.17	0.020*
DHT(ng/ml)	a 148.16 ± 45.32	b 73.51± 16.88	b 63.69 ± 11.5	0.0001**

The values represent Mean ± SD.

Different letters refers to significant differences between groups.

Similar letters refers to no significant difference between groups.

NS refer to no significant differences among groups.

*refer to significant difference at the P <0.05 .

** refer to significant difference at the P <0.01.

Estradiol (E₂)

The E2 level was significantly decrease (P<0.01) in the post-treated patients (40.26 ± 9.8 pg/ml) in comparison with the pre-treated patients (55.04 ± 9.9 pg/ml). There was no significant difference in the level of E2 in the post-treated patients in comparison with the control group (35.67 ± 4.09 pg/ml).There was a significant increase in the level of E2 (P<0.01) in the pre-treated patients in comparison with the control as shown in Table 1 and Fig. 2. This might be due to the aromatase activity which is known to increase in BPH patients particularly in the proliferative stroma suggesting a local increase of estrogen levels (34). The reduction in E2 level in the post-treated patients in comparison with the pre-treated patients was possibly due to the inhibition of 5α-reductase activity by finasteride which may have affected lipid metabolism and thus aromatase activity. Estrogen effects on the prostate gland may also be indirectly mediated through alterations in other serum hormones leading to increase the E2/T ratio which is the most possible important etiological factor for BPH.

The present results are consistent with previous reports (35, 36, 37, 5, 15) which indicated mentioned E2 level increased significantly in BPH patients when compared with the control group. Similarly, a positive relationship between E2 and

incidence of BPH surgery was described, but only among men with low T and only after controlling for estrone (38), while E2 was found to be significantly and negatively correlated with BPH (21). The decrease in E2 level after finasteride treatment is not compatible with the results of a previous studies (29,32) which found no significant differences in mean serum E2 levels between finasteride-treated and control groups.

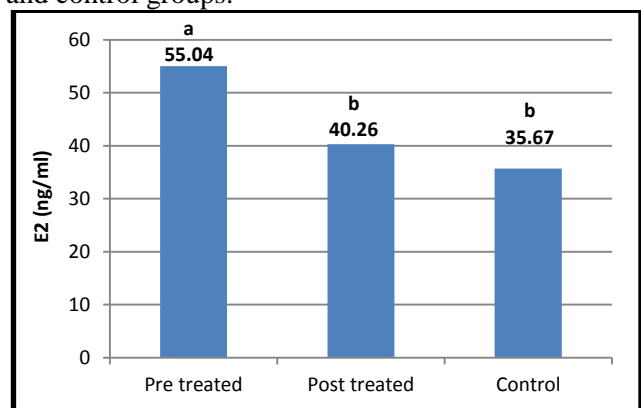


Figure 2. Effects of finasteride on serum E2 level in patients with BPH.

Follicle Stimulating Hormone (FSH)

The results revealed that the FSH level show no significant difference in the post-treated patients (5.58 ± 1.94 m.IU/L) in comparison with the pre-

treated patients (4.90 ± 1.99 m.IU/L) and the control (4.25 ± 1.92 m.IU/L) as shown in Table 1 and Fig. 3. The non-significant increase in FSH level in BPH patients as possibly a response to an increased pituitary and gonadal activities or altered steroid metabolism. In addition DHT has a minimal role in the negative feedback control of androgen secretion that results in affecting other hormones such as FSH (30).

The results are compatible with those of a previous study which reported that FSH level did not differ significantly between BPH patients and control group, but showed a significant increase with advancing age (13). While, another report showed a slight decrease in the mean FSH value in pre-finasteride as compared to post-finasteride groups of male patients(39). Furthermore, finasteride treatment was found to have no effect on FSH level (29).

On the other hand, two studies (40,41) found that FSH level was reduced by 24% after 3 and 6 months, respectively of finasteride treatment. While, it was also observed that, in spite of the compensatory feedback upregulation of T by PRL, FSH levels retained significantly suppressed levels (42).

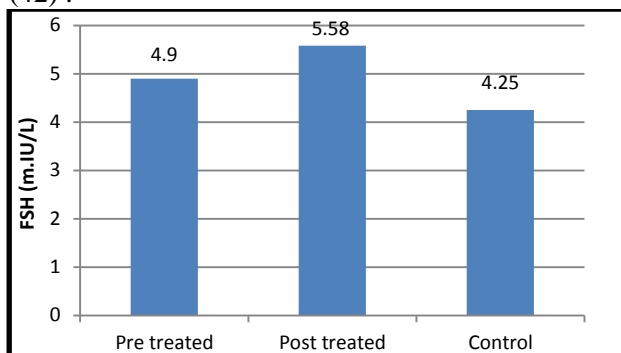


Figure 3. Effects of finasteride on serum FSH level in patients with BPH.

Luteinizing Hormone (LH)

The results revealed no significant difference in LH level in the pre-treated patients (3.67 ± 1.39 m.IU/L) in comparison with post-treated patients (4.28 ± 1.87 m.IU/L) and control group (3.25 ± 1.65 m.IU/L). Also there was no significant difference between post-treated patients and control group, as shown in Table 1 and Fig. 4. The results might be due to DHT which has a minimal role in the negative feedback control of androgen secretion, DHT has little effect on serum gonadotrophic levels or on the LH response to gonadotropin-releasing hormone, as demonstrated by earlier studies (30,43) which found a slight change in serum LH levels when serum DHT level was suppressed with 5α -RI.

Furthermore, the present results agree with other investigations, (13,29) who reported no

significant difference in LH level between BPH patients and control group.

The present results are also consistent with previous studies on finasteride therapy, reported small increase in serum LH level when serum DHT level was suppressed with finasteride (30,31). Also, it was demonstrated that increase in LH level in two groups of finasteride treatment (1mg, and 5mg) was significantly higher than in the placebo group (44,45). The mean LH values in pre-finasteride patients (5.6 IU/L in 9 men) was also shown to be increased to higher values in post-finasteride patients (6.3 IU/L in 8 men) (39).

In addition, other studies found about 16% reduction in LH levels after 3-6 months of finasteride treatment (40,41).

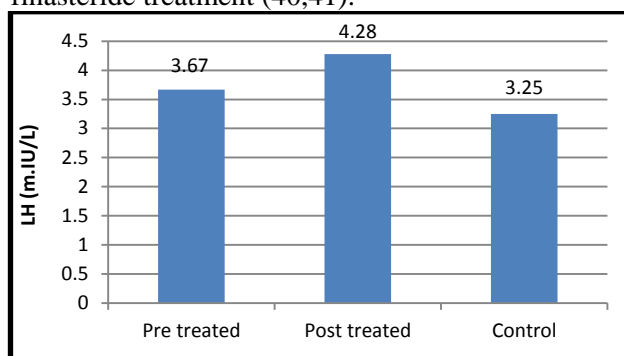


Figure 4. Effects of finasteride on serum LH level in patients with BPH.

Prolactin (PRL)

The results revealed that serum PRL level in the post-treated patients (10.42 ± 8.06 ng/ml) was non-significantly decreased in comparison with the pre-treated patients (11.17 ± 4.51 ng/ml) and significantly increased ($P < 0.05$) in comparison with the control (7.18 ± 3.17 ng/ml). Also, PRL level significantly increased ($P < 0.05$) in pre-treated patients in comparison with the control, as shown in Table 1 and Fig. 5.

The present results reveal a non-significant decrease in the post-treated patients in comparison with the pre-treated patients. This might be due to the significant decrease in the level of E2 which is considered as a stimulator to PRL secretion that occurs via estrogen response elements in the pituitary gland gene, resulting to infertility. Gonadal steroids, E2, and T together frame a long loop feedback mechanism for the regulation of PRL secretion at the hypothalamic-pituitary level. Whereas E2 or long-term deprivation of T stimulates the PRL secretion at the hypothalamic level, suggesting a positive long feedback (46).

Also, the prostate might not depend on pituitary PRL, which, however, can be produced by its secretory epithelium (47), while the adipose tissues itself functions as an endocrine organ that

leads to increase levels of PRL (48). Several endogenous factors were reported to induct of PRL secretion such as serotonin, thyrotropin-releasing hormone (TRH), luteinizing hormone releasing hormone (LHRH), substance P, vasopressin, EGF, FGF, cholecystokinin, angiotensin II, and prolactin releasing peptides (PrRPs) by direct effect at the pituitary level (49,46). Elevated levels of PRL have significant stimulatory actions on prostate ductal development and cause hyperplastic growth in the adult gland (50,51)

The results of the present study showed an increase in PRL level in BPH patients, which agreed with the results obtained by an earlier report (52) which found a clear difference in PRL levels among age groups and prostate gland status. An increased PRL level in prostatic secretions was observed both in advanced age and in BPH dogs. It was also shown that the prostate was enlarged in the laboratory rats treated with PRL, while low level of PRL resulted significant decrease in the prostate weight and seminal vessels(50,51) . Moreover, it was that PRL levels were reduced during finasteride treatment, thereafter PRL values were slowly and progressively decreased to normal during the next 6 months (53).

The present results are not consistent with those of a previous study (13) that reported no significant difference in PRL level between BPH patients and control group.

On other hand, other investigations reported no significant differences in serum PRL level after months of finasteride treatment in BPH patients(39,40,29) .

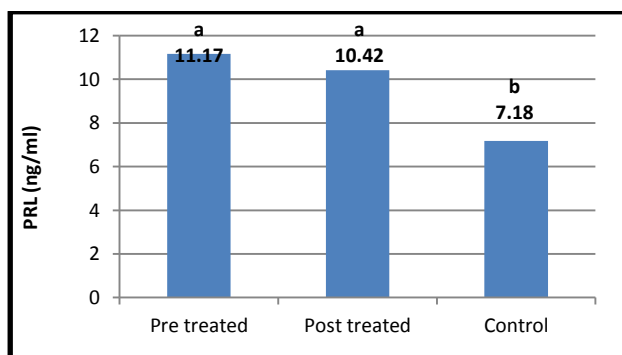


Figure 5. Effects of the finasteride on serum PRL level in patients with BPH.

Dihydrotestosterone (DHT)

The results revealed that DHT level was significantly decreased ($p < 0.01$) in the post-treated patients (73.51 ± 16.88 ng/dl) in comparison with the pre-treated patients (148.16 ± 45.32 ng/dl) ,with no significant difference between the post-treated patients and the control (63.69 ± 11.5 ng/dl),and a significant increase ($p < 0.01$) in pre-treated patients

in comparison with the control ,(Table 1 , Fig. 6). The significant reduction in the post-treated patients may be caused by inhibition of 5 α -reductase through the action of finasteride. High level of DHT in the pre-treated patients may be due to 5- α reductase activity and the continuous production and accumulation of DHT in the prostate ,which might promote the cells growth .

The present results are compatible with those of other studies (14,54,55) who reported that the increased androgen levels in BPH was due to 5- α reductase activity. It was reported that DHT activity is increased in BPH patients as related to that in normal prostate gland, acting as a permissive, rather than a transformative, mediator in the BPH development (21). Also, other studies, (33,55) observed that men who do not synthesis DHT do not develop BPH, and that those who had the highest midlife levels of DHT had nearly 3 times the risk of BPH compared to those with lowest levels .

The present results are in agreement with previous studies on finasteride therapy (25, 27, 30, 32, 56) which indicated reduction in serum DHT levels by70%-90%. It was also reported that there was a reduction in DHT by 60-93% from the baseline after 7-8 week of therapy in patients taking 5mg /day compared to those taking 1 mg/day(24), while finasteride was shown to slowly induce 50% decrease in serum DHT level (4). Moreover, (31) in finasteride-treated group, it was shown that no case had a DHT level less than 10pg/ml ,while only 9% had less than 50 pg/ml level at the end of 24 weeks of drug exposure (31).

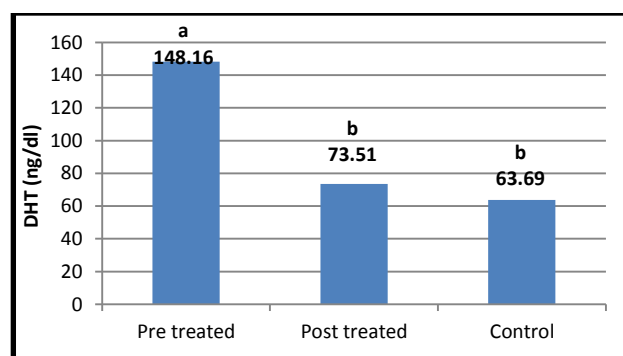


Figure 6. Effects of finasteride on serum DHT level in patients with BPH.

Conclusions:

This study concludes that BPH affects the hormonal parameters through a number of observed significant differences in sex hormones levels in pre-treated and post-treated patients compared to control group. Also, the 5-alpha reductase inhibitor (finasteride) causes significant decrease in the levels of DHT and, E2 which play vital roles in BPH development.

Conflicts of Interest: None.

The author has signed on animal welfare statement.

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تقييم مستوى الهرمونات الجنسية في مرضى تضخم البروستات الحميد المعالجين بمثبط 5- ألفا ريدكتيز (الفيناسترايد) في مدينة العمارة / العراق

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الخلاصة:

هدفت الدراسة الحالية لتقييم مستوى الهرمونات الجنسية لمرضى تضخم البروستات الحميد (BPH) قبل وبعد ثلاث اشهر من العلاج ب (5 α -reductase inhibitor (finasteride). تضمنت الدراسة 40 رجل مريض بحالة BPH و40 رجل سليم كمجموعة سيطرة من مدينة العمارة تراوحت اعمارهم بين (40-59) سنة. كلا المجموعتين تم قياس الهرمونات (التستوستيرون،الاستراديول، المحفز للجريبات، الهرمون اللوتيني، البرولاكتين و الديهايدروتستوستيرون) في كلا المجموعتين قبل وبعد 3 اشهر من العلاج بالفيناسترايد(لم تتناول مجموعه السيطرة العلاج). أظهرت النتائج انخفاض في مستوى هرمون التستوستيرون معنويا ($P<0.05$) في المرضى قبل المعالجة بالمقارنة مع المرضى بعد المعالجة ومجموعة السيطرة، في حين لم يكن هناك اختلاف معنوي بين مرضى بعد المعالجة ومجموعة السيطرة، بينما ارتفع مستوى هرموني الاستراديول و الديهايدروتستوستيرون معنويا ($P<0.01$) في المرضى قبل المعالجة مقارنة مع المرضى بعد المعالجة في حين لا يوجد فرق معنوي بين المرضى بعد المعالجة والسيطرة. كذلك اظهرت النتائج عدم وجود فروق معنويه في مستوى الهرمون المحفز للجريبات والهرمون اللوتيني بين المرضى والسيطرة، أما هرمون البرولاكتين فلم يختلف معنويا بين المرضى قبل وبعد المعالجة، في حين أظهر المرضى زيادة معنوية في مستوى الهرمون ($P<0.05$) مقارنة مع مجموعة السيطرة. يستنتج من ذلك ان مثبط 5 ألفا - ريدكتيز يلعب دورا في انخفاض مستوى هرموني الديهايدروتستوستيرون والاستراديول اللذان يلعبان دورا حيويا في الإصابة بتضخم البروستات الحميد.

الكلمات المفتاحية: تضخم البروستات الحميد، الديهايدروتستوستيرون، الفيناسترايد، 5-ألفا ريدكتيز، الهرمونات الجنسية.