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Research Article

Serum Levels of Prostate Specific Antigen and Specific Reproductive Hormones Among Male Subjects with Benign Prostate Hyperplasia in Port Harcourt, Nigeria

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Abstract:

Benign prostate hyperplasia (BPH) is a medical condition in elderly men in which there is proliferation and enlargement of the prostate gland. This study evaluated the levels of male reproductive hormones among subjects with BPH. The study involved 150 subjects aged 40 years and above, comprising 80 BPH subjects attending the urology clinic and 70 control subjects. Five millilitres (5ml) of venous blood were collected from each subject into plain bottles for the determination of prostate-specific antigen (PSA), testosterone, prolactin, and estradiol, using the ELISA technique. The mean values of PSA (16.68±10.96 ng/ml), estradiol (71.03±18.56 pg/ml) and for the BPH subjects and prolactin (9.38±4.51 ng/ml) were significantly higher compared to the mean values of PSA (0.48±0.25ng/ml), estradiol (51.33±7.13npg/ml) and prolactin (6.92±1.93ng/ml) of the control subjects. However, the mean testosterone value of the BPH subjects (5.02±1.93 ng/ml) was significantly lower than the mean value for the control (6.57±3.48ng/ml). The BPH who used to consume alcohol had higher PSA (24.26±8.33ng/ml) and testosterone (7.68±3.41ng/ml) compared to the PSA (16.34±3.22ng/ml) and testosterone (4.95±3.62ng/ml) of those who never consumed alcohol. The BPH had significantly altered hormone parameters as well as raised PSA levels. Including hormonal parameters in diagnosing and managing BPH could be an important consideration in our population.

Keywords: Prostate-specific antigen, hormones, prolactin, Benign prostate hyperplasia, testosterone, Port Harcourt, Nigeria

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1. Introduction

Benign Prostate Hyperplasia (BPH) is a medical condition that is characterized by the proliferation and enlargement of the tissues of the prostate gland and is commonly associated with elderly men (1). The symptoms associated with the condition include urinary reluctance, frequent urination, weak stream, and nocturia (2).

The human prostate is made up of both glandular and fibromuscular tissues and has three histological zones, namely the central zone and the peripheral zone (3). The peripheral zone is where prostate cancer primarily occurs, while the transition zone is where virtually all clinically significant BPH develops in the transition zone of the prostate (4). Clinical BPH develops when the hyperplasia of the epithelial tissue and stromal tissues coalesce to form microscopic and macroscopic nodules in the prostate gland. As age increases, every man will eventually develop microscopic nodules under normal physiological function. However, not every man will develop the macroscopic nodules (3). It is the macroscopic growth of the

transition zone that potentially causes the narrowing of the urethra as it passes through the prostate, eventually leading to a bladder outlet obstruction (BOO), which affects urine flow.

Within the transitional zone of the prostate, the proliferation of both epithelial and stromal cells occurs (5). Due to this accumulation of cells in the prostate, prostatitis and fibrosis could develop, which eventually lead to lower urinary tract symptoms (6). It has been established that age is the principal factor for the development of BPH. However, it has also been suggested that androgens can also lead to the condition, in addition to age; androgens are needed for the normal physiological functions of the prostate, but the exact role of androgens in BPH is not clearly understood (7).

The pathogenesis of BPH is yet to be clearly understood (2). However, it is associated with increases in dihydrotestosterone (DHT) levels, which is synthesized from testosterone by the 5α-reductase enzyme within the prostate glands (7). The increased accumulation of DHT in the prostate with ageing leads to an increase in cell growth and hyperplasia (6) because the DHT has a greater effect on the prostate cells than testosterone, principally due to the increased affinity of DHT to the androgen receptors (AR) in the prostate tissue (7).

Generally, BPH can be seen as a result of an imbalance between the homeostatic processes of cell proliferation and cell death, which occur in the epithelial and stromal environments of the prostate. This homeostatic imbalance results in favour of the proliferation of the cells, thereby leading to BPH (8).

Oestrogens have also been associated with the development of BPH; Oestrogens act in ways similar to androgens but do so via different nuclear hormone receptors (Oestrogen receptor alpha- Erα and oestrogen receptor beta- Erβ). Further, testosterone testosterone can be converted to oestrogen by the enzyme aromatase (9).

It appears that the regulation of BPH by the hormones depends on both the androgen receptors and oestrogen receptors in the prostatic tissues (10). Given this, scientific research into the roles of the hormones and their receptors becomes necessary.

Prolactin is produced by prostate epithelial cells under normal physiological conditions in humans (11). It has been proposed that prolactin plays an important role in the development of the prostate gland and simultaneously inhibits apoptosis of the prostatic cells (12). It is reported that prolactin locally produced by the prostate cells can greatly affect the prostate epithelial compartment, resulting in the expansion of the basal and stem-like epithelial cells and marked proliferation of the epithelial cell (11). While some studies have implicated prolactin as a possible contributor to prostate cancer (12), its role in BPH is not clearly understood.

This study seeks to evaluate the levels of testosterone, oestrogen, prolactin and prostate-specific antigen in subjects with BPH.

2. Materials and Methods

I. Study Population

The study involved 150 male subjects, who were 40 years and above, comprising 80 male subjects with benign prostate hyperplasia and attending a clinic at the Rivers State University Teaching Hospital, Port Harcourt, and another 70 apparently healthy male subjects within the same age bracket who served as control subjects.

The sample size for this study was determined using G*Power 3.1.9.2, at a power of 0.8, alpha error probability of 0.05 and effect size of 0.5. The calculated sample size was 64 BPH subjects and 64 control subjects. However, this study adopted 80 male subjects with BPH and 70 male, apparently healthy control subjects.

The ethical approval for this study was obtained from the Rivers State Health Research Ethics Committee. Subjects who participated in this study also gave their oral informed consent to participate in this study.

II. *Eligibility Criteria*

i. Inclusion Criteria: Male subjects, who were 40 years and older, had been diagnosed with BPH (but did not have diabetes, infection of any kind or fertility therapy) and attended clinic at the time of this study. They also consented to participate in this study.

ii. Exclusion Criteria: Male subjects who were less than 40 years old, were on fertility therapy, or had any infection were excluded from this study.

III. *Sample Collection and Analysis*

For this study, 5 ml of venous blood was collected from each subject and put into plain bottles. The samples were spun at 3000rpm, and the serum was collected into another set of plain bottles and stored at -20^{o}C prior to analysis.

Samples were analyzed for prostate-specific antigen (PSA), prolactin, estrogen and testosterone using the ELISA technique for each.

IV. *Data Analysis*

The data from this study were analyzed using SPSS version 23. Results were expressed as mean ± standard deviation. Comparison of means was done using an independent t-test and one-way ANOVA, with p≤005 being considered statistically significant.

3. Results

I. *Comparison of Parameters among Subjects*

The BPH subjects had significantly raised prostate-specific antigen (PSA), estrogen, prolactin, estrogen/testosterone ratio and prolactin/testosterone ratio, but significantly lower testosterone compared to the control subjects.

Table 3.1: Comparison of Parameters among Subjects

	PSA (ng/ml)	**Testo (ng/ml)**	**Estro (pg/ml)**	**PRL (ng/ml)**	**ETR**	**PRT**
BPH Subjects	16.68±10.96	5.02±1.93	71.03±18.56	9.38±4.51	0.021±0.010	2.20 ±0.46
Control Subjects	0.48±0.25	6.57±3.48	51.33±7.13	6.92±1.93	0.011±0.007	1.44 ± 0.51
p-value	<0.001	0.006	<0.001	0.002	<0.001	0.013
t-value	10.444	2.837	6.148	3.195	1.348	1.608

Keys: BPH-benign prostate hyperplasia, PSA-Prostate specific antigen, Testo-testosterone, Estro-estradiol, PRL-prolactin, ETR-estrogen testosterone ratio, PRT- prolactin testosterone ratio

II. *Comparison of Parameters Based on Hypertension*

There were no significant differences in the mean values of estradiol, testosterone, prolactin and PSA between the BPH subjects who had hypertension and those who did not have hypertension.

Table 3.2: Comparison of Parameters Based on Hypertension

	Estradiol (pg/ml)	**Testosterone (ng/ml)**	**PSA (ng/ml)**	**Prolactin (ng/ml)**
Hypertensive	63.71±20.63	6.22±3.54	19.25±12.65	10.50±5.77
Non-hypertensive	65.88±16.08	6.86±4.16	17.50±10.84	10.02 ±4.26
p-value	0.639	0.669	0.395	0.791
t-value	0.475	0.435	0.866	0.268

PSA-Prostate Specific Antigen

III. Comparison of Parameters Based on Alcohol Intake

The BPH subjects who consumed alcohol had significantly raised testosterone and PSA compared to those who did not. There were no significant differences in the mean values of estrogen and prolactin between the BPH subjects who consumed alcohol and those who did not consume alcohol.

Table 3.3: Comparison of Parameters Based on History of Alcohol Intake

	Estradiol (pg/ml)	**Testosterone (ng/ml)**	**PSA (ng/ml)**	**Prolactin (ng/ml)**
No Alcohol	64.82±19.37	4.95±3.62	16.34±3.22	10.85 ±4.71
Alcohol	64.84±17.13	7.68±3.41	24.26±8.33	9.7 ± 5.88
p-value	0.998	0.041	0.007	0.596
t-value	0.003	2.145	1.984	2.598

PSA-Prostate Specific Antigen

IV. Comparison of Parameters Based on Area of Residence

The were no significant differences in the mean values of estrogen, testosterone, prolactin and PSA between the BPH subjects based on whether they lived in urban or rural settings.

Table 3.4: Comparison of Parameters Based on Area of Residence

	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
Rural	65.67±22.39	6.42±3.37	22.46±7.31	6.46±3.37
Urban	64.30±17.01	6.46±4.01	20.31±14.14	6.46 ±4.01
p-value	0.858	0.976	0.293	0.976
t-value	0.181	0.030	1.071	0.300

PSA-Prostate Specific Antigen

V. Comparison of Parameters Based on Previous Urinary Tract Infections

The were no significant differences in the mean values of estrogen, testosterone, prolactin and PSA between the BPH subjects based on their history of previous urinary tract infections.

Table 3.5: Comparison of Parameters Based on Previous Urinary Tract Infections

	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
Previous UTI	66.79±20.71	6.68±3.83	21.08±12.52	9.50 ±4.35
No previous UTI	69.68±15.27	6.09±3.66	18.07±11.38	11.64 ±6.35
p-value	0.235	0.671	0.496	0.318
t-value	1.265	0.431	0.691	1.029

PSA-Prostate Specific Antigen, UTI- urinary tract infections

VI. Comparison of Parameters Based on Body Mass Index (BMI)

There were significant differences in estrogen and PSA levels among the different BMI classifications. However, there were no significant differences in the mean values of testosterone and prolactin.

Table 3.6: Comparison of Parameters Based on Body Mass Index (BMI)

Body mass index (kg/m²)	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
18.5-24.5	67.33±19.52[a]	6.29±5.81[a]	19.14±7.79[a]	10.70±5.83
25-29.5	57.44±16.76[b]	6.93±3.07[a]	17.92±4.69[b]	9.19±1.14
30 & above	44.72±28.90[c]	5.29±1.37[b]	16.17±3.64[c]	10.99±4.69
p-value	0.005	0.638	0.025	0.617
f-value	3.316	3.885	3.806	3.340

Values with different superscripts are significantly different from each other.

Key: PSA-Prostate Specific Antigen

4. Discussion

This study evaluated prostate-specific antigen (PSA), testosterone, estrogen and prolactin in male subjects with benign prostate hyperplasia (BPH). The BPH subjects had significantly raised mean values of PSA, estradiol, and prolactin but significantly reduced testosterone compared to the control subjects. The raised levels of PSA in the BPH subjects could be attributed to the inflammation in the system. Inflammation is one of the key factors in BPH (13). Although the exact mechanism of how inflammation increases PSA levels is clearly understood, it is hypothesized that inflammation causes injury to the epithelium of the prostate, leading to the release of PSA into circulation (14). It has also been reported that men with larger prostate size (such as seen in BPH) produce higher levels of PSA (15). This finding agrees with an earlier work (16).

The testosterone levels were significantly reduced in the BPH subjects compared to the control subjects. This finding agrees with the work of another researcher (17)(16). Testosterone decreases with increasing age (18), with men in their 20s having higher testosterone levels than those in their 30s, 40s, and so on. Thus, the low level of testosterone seen in the subjects in this study could be due to age. It is also known that testosterone can be converted to estrogen by the action of the enzyme aromatase, and this accounts for a large amount of circulating estrogen (19). Testosterone is also converted to dihydrotestosterone by the enzyme 5α reductase (20). These two processes may be responsible for the decreased testosterone in the BPH subjects.

The results from this study also showed that the BPH subjects had significantly raised estradiol and significantly reduced testosterone compared to the control subjects. These findings are in agreement with an earlier study (21). The significantly raised level of estradiol in the BPH subjects may be due to the conversion of testosterone to estradiol. This is probably because, in older men, about 80% of the estradiol is almost exclusively synthesized via the aromatization of testosterone (17). The testes also synthesize some amount (about 20%) of estradiol (19). These processes may explain the high estradiol levels in BPH subjects.

The BPH subjects had significantly higher levels of prolactin compared to the control subjects. This is probably because the levels of prolactin increase with increasing age (22). Also, estrogen stimulates the pituitary gland to release prolactin, which in turn stimulates prostate enlargement (3). However, the exact mechanism of how this effect of prolactin on the prostate occurs in BPH is still under study (23).

The BPH subjects in this study also had significantly higher estrogen-to-testosterone ratio as well as prolactin-to-testosterone ratio compared to the control subjects. The decrease in testosterone and an increase in estrogen in BPH brings about an imbalance between the two hormones, which shifts towards estrogen dominance, as seen in the increased ETR. This increased estrogenic stimulation in the prostate can lead to hyperplasia (24). A similar observation is found with the prolactin-to-testosterone ratio, indicating a raised prolactin level in BPH subjects, probably arising from the stimulation of the pituitary gland by estrogen and local synthesis of prolactin in the prostatic cells.

The hormone parameters did not differ significantly between the BPH subjects who had hypertension and those who did not. This may imply that hypertension does not affect prostate health. Both hypertension and BPH have some features in common, though they are different disease entities; they are age-related conditions in older men, they involve the sympathetic nervous system and treatment for both involves alpha-adrenergic blockers (25). Our finding here may be because the two conditions do not share the same pathophysiological mechanisms (26). Similarly, this study found no significant differences in the hormone parameters among the BPH subjects based on area of residence (urban/rural) and previous urinary tract infection history.

The BPH subjects who used alcohol had significantly raised PSA levels compared to those who did not drink alcohol. A previous study had earlier reported a similar finding (27). There was also a significantly raised testosterone in the BPH who used alcohol compared to those who did not. A previous study in China (28) had reported a similar finding. However, another study (29) reported that there is an association between modest alcohol intake and decreased benign prostatic hyperplasia diagnosis. It is, therefore, possible that the effect of alcohol on BPH could be dose-dependent, with moderate intake giving beneficial effects. The raised testosterone in this study is probably because alcohol acts as a hormone disruptor in males (28).

Results from this study showed that, among the BPH subjects, the estradiol, testosterone and PSA decreased significantly with increasing body mass index (BMI). This finding has been reported by an earlier study (30). Obesity is known to increase the risk of BPH (31). This association between BMI and decreased PSA levels among our subjects may be due to lower testosterone serum levels (32) or probably due to plasma hemodilution because obesity causes larger plasma volume compared to non-obese individuals (33).

5. Conclusion

The data from this study indicate that BPH subjects had significantly raised PSA, estradiol, prolactin, estradiol/testosterone ratio and prolactin/testosterone ratio. However, they had significantly reduced testosterone levels. There were no differences in the hormone parameters among the BPH subjects based on area of residence (urban or rural) and previous history of urinary tract infections or hypertension. However, previous alcohol consumption increased testosterone and PSA levels compared to those who never consumed alcohol. Based on BMI classification, estradiol, testosterone, and PSA levels significantly reduced as BMI increased. Hence, it is important to consider hormone parameters when managing BPH.

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