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Research Article

Evaluation of Hormonal and Biochemical Risk Factors for Benign Prostatic Hyperplasia: A Possible Way for Management and Prevention of Benign Prostatic Hyperplasia

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ABSTRACT

Objective: To identify some risk factors that contributes to the development and severity of BPH among the elderly in Enugu state, Nigeria.

Study design: One hundred men aged 53 years-85 years were used for the study; the study was divided into two groups consisting of 50 male patients diagnosed with BPH and 50 healthy subjects.

Methods: Twenty millilitre of whole blood samples were collected from each patient and the following parameters were investigated; oestrogen, testosterone, lipid profile, PSA, PAP, TAP, electrolyte concentration and antioxidant biomarkers.

Results: It was found that increase in PAP, TAP, total cholesterol, TAG, LDL, oestrogen, potassium and sodium and decrease in levels of catalase, GP_x, selenium, HDL and testosterone are risk factors for the development and severity of BPH.

Conclusions: In view of this, modifiable lifestyles can be adopted for the prevention, management and treatment of BPH.

Keywords: Antioxidant biomarkers; Oestrogen; Risk factors; Lipid profile; Benign prostatic hyperplasia

INTRODUCTION

BPH is a common urologic condition in older men which affect the quality of life [1]. Commonly experienced symptoms include inability to delay urination, incomplete emptying of the bladder, frequent urination during the day and night, weak urine stream, urge incontinence or urine leakage and painful or bloody urination [2].

It is a major public health problem in developing countries where the incidence continues to increase and the mortality is still high [3]. It has been found that Africa carries an increasing BPH burden, and men of African heritage have been found to have earlier age of diagnosis of the disease and more advanced cases of the disease and are almost four times more likely to die of the disease when compared to their Caucasian male counterparts [4].

Age is the mostly implied factor in the prevalence of BPH. The prevalence is 25% among men 40 years to 49 years of age, 50% to 75% among men over 50 years of age and increases to about 80% among men 70 years to 80 years; it rises as high as 88% to 90% among men 81 years old and above [5].

BPH affect every three out of four men in their sixties. It was estimated that 612 million men had BPH globally in year 2018 [6]. In 2007, a total of 1.9 million visits to physicians' offices and more than 202,000 visits to the emergency department led to a primary diagnosis of benign prostatic hyperplasia, and 120,000 prostatectomies were performed for the disorder [7].

Despite the high impact of BPH on public health, however, the pathogenesis of BPH is still largely unresolved. Although ageing and genetic predisposition represent the central mechanism implicated, recent novel finding also highlighted the key role of hormonal alterations, metabolic syndromes and inflammation [8].

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Quantifying those with BPH and understanding the relationships between BPH and risk factors that contribute to the development and severity of BPH are central to distributing scarce resources for BPH management and developing appropriate prevention strategies [9]. Though many suggestions have been given about the risk factors of BPH, presently, there is controversy about the risk factors that contribute to the development and severity of BPH.

Therefore, this study investigated some of the suggested hormonal and biochemical indices as possible risk factors of BPH and their interconnectedness with BPH.

MATERIALS AND METHODS

Subjects and study design

One hundred men aged 53 years-85 years (average 69) were divided into two groups. Group 1 comprised 50 apparently-healthy subjects. Group 2 was made up of 50 male patients diagnosed with BPH whose clinical records were known. Groups 1 and 2 were age matched. For all the groups, the subjects were non diabetics, non-smokers and non-alcoholics and were not taking any medication that may interfere with the parameters studied.

Criteria for choosing subjects for the study

Data about the patients were obtained from administered questionnaire and also from their hospital folders. The study was conducted on the subjects after informed consent was obtained from each of them while the approval for the study was given by the ethical clearance committee of our hospital. Information about smoking status and other health and work related issues were obtained by a structured questionnaire.

Instruments/equipment

The instruments and equipment used in this study belong to the department of chemical pathology, university of Nigeria teaching hospital Ituku-Ozalla, Enugu. They include the following: Auto haematology analyzer, calimatic pH meter, chemistry auto analyzer, centrifuge, electrolyte analyser, incubator, water bath, weighing scale (All Beckman Coulter Co., Indianapolis, Indiana, USA), spectrophotometer, vortex mixer, colorimeter microplate reader, microplate washer (All Jenway Co., Stone, Staffordshire, UK).

Chemical/reagents

All chemicals used in this study were of analytical grade and products of Sigma-Aldrich, USA.

Determination of prostate specific antigen concentration and acid phosphatase activity

The serum concentrations of prostate specific antigen and acid phosphatase activity were determined using the ELISA method [10].

Determination of lipid profile

The lipid profile was determined using the Randox kits according to the method of Friedewald, WT [11].

Determination of serum calcium, sodium and potassium concentration

Serum calcium, sodium and potassium concentration was determined using the methods as described by Faulker WR [12].

Determination of serum testosterone concentration

Serum testosterone was determined spectrophotometrically with Diametra ELISA kit by the method of Ismail AA [13].

Determination of serum oestradiol concentration

Serum oestradiol (E2) concentration was determined by competitive enzyme immunoassay as contained in Biocheck Inc commercial test kits [14].

Assay of serum glutathione peroxidase activity and serum catalase activity

Serum glutathione peroxidase and catalase activities were determined using enychron glutathione peroxidase assay kits [15].

Determination of serum zinc concentration and serum selenium concentration

This was done following the method of Koracevic D [16].

Statistical analysis

This was done using Statistical Product and Service Solution (SPSS) version. Results were presented as means SD. One way Analysis of Variance (ANOVA) and student T-test were used to analyze the data. Multiple comparisons of the mean differences among the groups were done using the Least Square Differences (LSD) post hoc test. Differences were considered as significant when $p<0.05$ [17].

RESULTS

Prostate specific antigen concentration of normal and benign prostatic hyperplasia subjects

Prostate Specific Antigen (PSA) concentrations, total and prostatic acid phosphatases activities of normal and benign prostatic hyperplasia subjects are shown in Table 1. The result shows that PSA, Total Acid Phosphatase (TAP) and Prostatic Acid Phosphatase (PAP) of the subjects in group 2 are significantly ($p<0.05$) greater than subjects in group 1.

Table 1: Prostate specific antigen concentration, total and prostatic acid phosphatase activity of normal and benign prostatic hyperplasia subjects.

Experimental group	Prostate specific antigen (mg/ml)	Total acid phosphatase activity (IU/l)	Prostatic acid phosphatase activity (IU/l)
Group 1	1.12 ± 0.44[a]	4.82 ± 0.41[a]	0.40 ± 0.27[a]
Group 2	4.82 ± 0.96[b]	13.81 ± 1.78[b]	2.03 ± 0.38[b]

Note: Results are mean ± SD, n=50. Means having different superscripts in a column are considered significant ($p<0.05$).

Lipid profile of normal and benign prostatic hyperplasia subjects

The concentrations of total cholesterol, TAG and LDL of normal and benign prostatic hyperplasia subjects are shown in Table 2. The result shows that the concentrations of total cholesterol, TAG and LDL of subjects in group 2 were significantly ($p<0.05$) greater than the total cholesterol, TAG and LDL concentrations group 1 subjects. However, HDL concentrations of subjects in group 2 were significantly ($p<0.05$) lower than that of group 1.

Table 2: Lipid profile of normal and benign prostatic hyperplasia subjects.

Experimental group	Parameters (Lipid profile)			
	Total cholesterol (mg/dl)	TAG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Group 1	155.34 ± 32.04[a]	104.36 ± 53.62[a]	96.80 ± 23.48[a]	70.30 ± 15.34[a]
Group 2	186.90 ± 29.48[b]	111.14 ± 23.58[b]	53.78 ± 10.43[b]	84.06 ± 22.77[b]

Note: Results are mean ± SD, n=50. Means having different superscripts in a column are considered significant ($p<0.05$).

Antioxidant parameters of normal and benign prostatic hyperplasia subjects

The antioxidant enzyme activities and antioxidant metal concentrations of normal and benign prostatic hyperplasia subjects are shown in Table 3. The result shows that the catalase, glutathione peroxidase activities, zinc and selenium concentration of group 2 subjects was significantly ($p<0.05$) lower than the catalase and glutathione peroxidase activity of the group 1 subjects.

Table 3: Antioxidant parameters of normal and benign prostatic hyperplasia subjects.

Experimental group	Catalase activity (IU/l)	Glutathione peroxidase activity (IU/l)	Zinc conc (µg/dl)	Selenium conc (mg/dl)
Group 1	1.94 ± 0.63[a]	0.75 ± 0.08[a]	98.06 ± 4.88[a]	3.15 ± 0.76[a]
Group 2	1.10 ± 0.16[b]	0.39 ± 0.05[b]	103.96 ± 6.06[b]	1.68 ± 0.63[b]

Note: Results are mean ± SD, n=50. Means having different superscripts in a column are considered significant ($p<0.05$)

Hormonal and electrolyte concentrations of normal and benign prostatic

Hyperplasia subjects: The oestrogen, testosterone and electrolyte concentrations of normal and benign prostatic hyperplasia subjects are shown in Table 4. The result shows that the oestrogen and sodium ion concentration concentrations of group 2 subjects was significantly ($p<0.05$) greater than those of the group 1 subjects. However, no significant ($p>0.05$) difference was found between the testosterone, calcium and potassium ions concentrations of the subjects in group 2 and that of group 1 subjects.

Table 4: Hormonal and electrolyte concentrations of normal and benign prostatic hyperplasia subjects.

Experimental group	Oestrogen conc. (pg/dl)	Testosterone conc. (ng/ml)	Calcium ion (mg/dl)	Potassium ion (mmol/l)	Sodium ion (mmol/l)
Group 1	18.39 ± 0.40[a]	14.86 ± 1.28[a]	8.95 ± 0.51[a]	3.65 ± 0.18[a]	136.12 ± 2.37[a]

Group 2	33.95 ± 4.36[b]	10.66 ± 4.63[b]	9.02 ± 0.46[b]	4.80 ± 0.75[b]	186.12 ± 28.39b

Note: Results are mean ± SD, n=50. Means having different superscripts in a column are considered significant (p<0.05)

The interrelationship between some of the parameters determined and PSA

The interrelationship between some of the parameters determined and PSA are shown in Table 5. The result shows that there was significant (p<0.05) positive correlation between PSA in group 2 subjects and PAP, TAP, total cholesterol, TAG, LDL, oestrogen, potassium and sodium. Between PSA and HDL, catalase, GPx, selenium and testosterone, there was significant (p<0.05) negative correlation found. However, there was no significant (p>0.05) positive correlation between PSA and and calcium.

Table 5: Correlation of PSA and other parameters.

Patients no.	Parameters	Regression coefficient	p-value
BPH patients (50)	PSA *vs.* PAP	0.859	0
	PSA *vs.* TAP	0.877	0
	PSA *vs.* T. Cholesterol	0.408	0
	PSA *vs.* HDL	-0.722	0
	PSA *vs.* LDL	0.39	0
	PSA *vs.* Oestrogen	0.301	0.002
	PSA *vs.* Urea	0.82	0
	PSA *vs.* Creatinine	0.843	0
	PSA *vs.* Uric acid	0.819	0
	PSA *vs.* Potassium ion	0.642	0
	PSA *vs.* Sodium ion	0.034	0.034
	PSA *vs.* CAT	-0.346	0
	PSA *vs.* GPx	-0.549	0
	PSA *vs.* Selenium	-0.692	0
	PSA *vs.* Testosterone	-0.493	0
	PSA *vs.* TAG	0.603	0
	PSA *vs.* GHb	0.082	0.415
	PSA *vs.* Glucose	0.03	0.765
	PSA *vs.* Calcium	0.037	0.712
	PSA *vs.* Zinc	0.314	0

The interrelationship between PAP and some of the parameters determined

The interrelationship between some of the parameters determined and PAP are shown in Table 6. The result shows that there was significant (p<0.05) positive correlation between PAP in group 2 subjects and PSA, TAP, total cholesterol, LDL, oestrogen, sodium and potassium. Between PAP and catalase, GPx, selenium, HDL and testosterone, a significant (p<0.05) negative correlation was found. However, there were no significant (p>0.05) positive correlation found between PAP and

calcium. Also, a non-significant (p>0.05) negative correlation was found between PAP and TAG and zinc.

Table 6: Correlation of PAP and other parameters.

Patients no.	Parameters	Regression coefficient	p-value
BPH patients (50)	PAP *vs.* PSA	0.859	0
	PAP *vs.* TAP	0.864	0
	PAP *vs.* T. Cholesterol	0.394	0
	PAP *vs.* LDL	0.307	0
	PAP *vs.* Oestrogen	0.26	0.002
	PAP *vs.* Urea	0.813	0.009
	PAP *vs.* Creatinine	0.83	0
	PAP *vs.* Uric acid	0.78	0
	PAP *vs.* Potassium ion	0.662	0
	PAP *vs.* Sodium	0.092	0
	PAP *vs.* CAT	-0.508	0
	PAP *vs.* HDL	-0.741	0
	PAP *vs.* GPx	-0.56	0
	PAP *vs.* Selenium	-0.684	0
	PAP *vs.* Testosterone	-0.559	0
	PAP *vs.* TAG	0.117	0.246
	PAP *vs.* GHb	0.025	0.803
	PAP *vs.* Glucose	-0.065	0.52
	PAP *vs.* Calcium	0.079	0.434
	PAP *vs.* Zinc	-0.024	0.809

DISCUSSION

The incidence, characteristics and management of prostatic disease may vary according to region and race. Therefore this study was carried out to ascertain risk factors for development and severity of BPH among men in Enugu state, Nigeria in order to suggest some possible life styles that could be modified for the treatment and management of BPH.

First, investigation was done to know if increase in PSA concentration, total and prostatic acid phosphatases activities are risk factors in the development of BPH, the result showed that PSA concentration, total and prostatic acid phosphatases activities were significantly (p<0.05) high in BPH patients than in normal patients. This suggests that increasing PSA, total and prostatic acid phosphatases activities could be risk factors for development and severity of BPH. PSA is a protein produced by normal prostate epithelial cells. It has been suggested that PSA is an estimator for Prostate Volume (PV) due to the fact that prostrate epithelial cells are responsible for amount of circulating PSA [18]. Since a significant positive correlation has been found between PSA and prostate volume (PA), increasing PSA could mean increasing prostate volume which might eventually result to BPH if not prevented and managed on time [19]. The result of this study corroborates the result of Linton et al., who also found increase in PSA as a possible risk factor for development of BPH. On the other hand, prostatic acid phosphatase is an enzyme produced by the prostate and is believed to be a key regulator of prostate cell growth. Therefore, increasing total and prostatic acid phosphatases activities could lead to increased prostate volume, which will eventually result to BPH if no properly managed and prevented. This result corroborates the result of Muniyan et al., who also found out

that increased total and prostatic acid phosphatases activities are risk factors for the development of BPH.

Furthermore, investigation was done to ascertain if abnormal variation in lipid profile is a risk factor for the development of BPH. The result showed that concentration of total cholesterol, TAG and LDL of BPH patients were higher than that of normal patients while HDL concentrations of BPH patients were lower than that of normal patient. Since there were significant alterations in the normal lipid profile of the studied BPH patients, increased total cholesterol, Low Density Lipoprotetin (LDL) cholesterol, and triglycerides could be risk factors in the development and pathogenesis of BPH. This observation is consistent with the concept that cardiac risk factors are involved with BPH pathogenesis, and raises the possibility that modulation of LDL cholesterol, total cholesterol and triglycerides may possibly delay the development of BPH. The result of our study corroborates the result of Mitropoulos and Ploumidou who also found out that rats fed cholesterol rich diets exhibited both altered blood lipid profiles and hyperplastic changes in the prostate [20].

The oestrogen concentrations of BPH patients was significantly ($p<0.05$) greater than those of the non-BPH patients. However, no significant ($p>0.05$) difference was found between the testosterone concentration of the subjects in BPH patients and that of non-BPH patients. The increase in oestrogen suggests that oestrogen levels might play a role in the pathogenesis of BPH. In elderly men, the prevalence of fat tissue during ageing has been implicated in the expression of high concentrations of aromatase, which converts oestrogen to oestradiol, the major active form of estrogen. The increased oestrogen stimulation of the prostate in the ageing men influences prostatic growth. This corroborates with the results of Prins and Korach who also observed oestrogen induced aberrations in prostate epithelial growth in dogs and humans. In addition to epithelial effects, oestrogens also stimulate stromal cell proliferation. *In vitro* studies showed that upregulation of oestrogen receptor-α in cultured prostate stromal cell can be associated with upregulation of Fibroblast Growth Factor (FGF)-2 as well as other growth factors which could be implicated in BPH. Contrarily, the decreased testosterone concentration of the subjects in BPH patients suggests possible conversion of testosterone to Dihydrotestosterone (DHT) by type II 5-alpha-reductase, a major mechanism involved in the pathogenesis of BPH. This finding is consistent with the result of Prins and Korach which reported great decline in testosterone levels in older men. Also, several studies have shown that men with BPH/LUTS tend to have low levels of androgens and increased levels of oestrogens.

Changes in the serum electrolyte showed that sodium ion concentration in BPH patients was significantly ($p<0.05$) greater than that of non-BPH patients, whereas, no significant ($p>0.05$) difference was found between calcium and potassium ions concentrations of BPH patients and non BPH patients. Although the mechanism underlying changes in serum electrolyte concentration and development of BPH has not been fully elucidated, this study suggests that increase in sodium ion could be one of the possible outcomes of BPH. This result is comparable with the result of Altaf, et al., who also observed increase serum electrolyte in BPH patients before and after transurethral resection of the prostate. However, further investigation need to be carried out to understand the mechanism behind this so as to know possible ways of modulating sodium ion concentration for the management of BPH.

Decrease in enzymatic and non-enzymatic antioxidants of BPH patients were observed in the study. Decreases in catalase and glutathione peroxidase activity are makers of oxidative stress while increase in MDA is indicative of lipid peroxidation. Also decrease in zinc and selenium concentration signifies decrease in the antioxidant defence mechanism. Thus this result suggests that oxidative stress and lipid peroxidation may play role in the aetiology of BPH. In oxidative stress, there is imbalance between pro-oxidants and anti-oxidants which is usually in favour of pro-oxidants. Antioxidant enzymes and metals are depleted by pro-oxidants in their attempt to scavenge these oxidants or trap their intermediates. With decrease in enzymatic and non-enzymatic antioxidants, accumulation of free radicals such as $OH^{\cdot}$ might occur oxidizing DNA, lipid, proteins and other structures in the vicinity and thus leading to deleterious effects on the prostate such as hyperplasia as seen in BPH. This result corroborates the result of Aryal, et al., which also reported decrease in both enzymatic and non-enzymatic antioxidants. This also suggests that antioxidant supplements might be helpful in prevention and management of BPH in elderly men.

To confirm statistically the connectedness between PSA and some of the parameters analysed, the interrelationship between PSA and some parameters were determined using correlation. The result showed significant ($p>0.05$) positive correlation between PSA of BPH patients and parameters such as PAP, TAP, total cholesterol, TAG, LDL, oestrogen, potassium and sodium. Specifically, the positive correlation was stronger between PSA and oestrogen, potassium and sodium. However no significant ($p>0.05$) positive correlation between PSA and calcium exist. This suggests that increase in PAP, TAP, total cholesterol; TAG, LDL, oestrogen, potassium and sodium could cause an increase in PSA (the major biological maker for BPH). Whereas decrease in PAP, TAP, total cholesterol, TAG, LDL, oestrogen, potassium and sodium could cause a decrease in PSA.

A significant negative correlation was found between PSA and HDL, catalase, GP_x, selenium and testosterone. This suggests that increase in HDL, catalase, GP_x, selenium and testosterone could cause a decrease in PSA while decrease in HDL, catalase, GP_x, selenium and testosterone could cause an increase in PSA.

Apart from PSA, another biological maker used for the diagnosis of BPH is PAP; analysis was done using correlation to confirm the interconnectedness between PAP and other biochemical and hormonal parameters studied. The result showed a significant ($p<0.05$) positive correlation between PAP of BPH patients and their PSA, TAP, total cholesterol, LDL, oestrogen, sodium and potassium. This suggests that increase in PSA, TAP, total cholesterol, LDL, oestrogen, sodium and potassium could cause an increase in PAP while decrease in PSA, TAP, total cholesterol, LDL, oestrogen, sodium and potassium could cause a decrease in PAP. On the other hand, no

positive correlation was found between PAP and calcium. This suggests that increase in calcium does not cause an increase in PAP; hence not a risk factor in the development of BPH.

Finally, between PAP and catalase, GP_x, selenium, HDL and testosterone, a significant ($p<0.05$) negative correlation was found. This suggests that PAP is indirectly proportional to catalase, GP_x, selenium, HDL and testosterone; hence decrease in levels of catalase, GP_x, selenium, HDL and testosterone would cause an increase in PAP which would eventually result to the development of BPH. Thus, decrease in catalase, GP_x, selenium, HDL and testosterone are risk factors to the development and severity of BPH.

CONCLUSION

Since the incidence, characteristics and management of prostatic disease may vary according to region and race. Investigation was done to identify some risk factors in the development and severity of BPH among men in Enugu state, Nigeria so as to know modifiable life styles that could help in the management of BPH. It was found that increase in PAP, TAP, total cholesterol, TAG, LDL, oestrogen, potassium and sodium and decrease in levels of catalase, GP_x, selenium, HDL and testosterone are risk factors in the development of BPH in elderly men in Enugu state, Nigeria. In view of this, modifiable lifestyles that could help modulate this biochemical and hormonal parameters investigated can be adapted for the prevention, management and treatment of BPH among the elderly in Enugu state, Nigeria.

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