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Lipids and Testosterone Levels in Benign Prostatic Hyperplasia versus Prostate Cancer Patients attending Federal Teaching Hospital, Ido Ekiti, Nigeria.

Adebayo TO[1,2], Abidoye OJ.[1], Olaniyan OO.[2], Ajayi AA.[3], Oyetunji FS.[4], Obot AS.[5]

[1]*Department of Medical Laboratory Science, Achievers University, Owo, Nigeria.*
[2]*Department of Chemical Pathology and Immunology, Osun State University, Osogbo, Nigeria.*
[3]*Department of Family Medicine, Osun State University, Osogbo, Nigeria.*
[4]*St Luke's Specialist Hospital, Ijebu Ode, Nigeria.*
[5]*Department of Medical Laboratory Science, University of Uyo, Uyo, Nigeria*

Abstract:
Background*: Prostate Cancer (PCa) a cancer of global health concern needs to be differentially diagnosed from benign prostatic hyperplasia (BPH). Prostate specific antigen (PSA), the most widely used biomarker for PCa is unsatisfactory. This research is aimed at improving the differential diagnosis of PCa from BPH by comparing serum lipid profile, testosterone, and prostate-specific antigen levels between PCa and BPH patients.*
Materials and Methods*: The study enrolled 40 cases of histologicaly diagnosed prostate cancer (PCa), 40 cases of benign prostatic hyperplasia (BPH), and 40 healthy individuals without prostate cancer and Benign prostatic hyperplasia. The study was conducted at Federal Teaching Hospital (FTH), Ido- Ekiti, and samples were collected randomly from the interested individual. The levels of the parameters were measured using the ELISA technique and Spectrophotometry. Lipids, testosterone, and prostate-specific antigen levels were statistically compared between PCa and BPH patients.*
Results*: Prostate cancer patients had significantly higher levels of total cholesterol (6.28±0.62 mmol/L), triglycerides (2.53±0.24 mmol/L), low-density lipoprotein (4.75±0.69 mmol/L), testosterone (11.38±5.20 mg/mL), prostate specific antigen (32.35 ± 21.95 ng/mL) and a lower level of high-density lipoprotein (0.36±0.10 mmol/L) compared with benign prostatic hyperplasia patients which contributed to higher grades of the disease.*
Conclusion: *The results suggest changes in lipids, testosterone, could be used with prostate-specific antigen to improve the diagnosis of PCa. Thus, serum PSA assay currently remains an important investigation for detecting prostate cancer while lipid profile results can be a good index for disease progression, intervention, and management of benign prostatic hyperplasia and prostate cancer patients.*
Key Word*: Lipids, Tetosterone, Prostate, Hyperplasia, Cancer, Prostate specific antigen.*

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I. Introduction

Cancer is a term that describes the disease that results when cellular changes cause the unrestrained growth and division of cells. Some types of cancer cause rapid cell growth, while others cause cells to grow and divide at a slower rate[1]. Certain forms of cancer result in visible growths called tumors, while others, such as leukemia do not. Most of the body's cells have specific functions and fixed life-spans. While it may sound like a bad thing, cell death is part of a natural and valuable phenomenon called apoptosis[1].

Cancerous cells may appear in one area, then spread via the lymph nodes to other parts of the body. There are many causes of cancer, some are preventable, and these include: heavy alcohol consumption, excess body weight, physical inactivity, poor nutritional intake, etc. Other changes that can result in cancer take place in the chemical signals that regulate how the body deploys specific genes[2]. Cancer can be classified by its location in the body and the tissues that it forms. Common types of cancer include breast cancer, followed by lung and prostate according to the National Cancer Institute[3].

The prostate is a walnut-sized gland that is located below a man's bladder. It produces the fluid part of semen. The prostate wraps around the urethra (this is the tube that carries urine from the bladder out of the body)[2,3]. Prostate cancer is a disease common to elderly men; more than 75% of cancers being diagnosed are

seen in men over the age of 65. In recent years, the incidence has increased in younger age groups. In the earlier stages of the disease, prostate cancer rarely causes any specific symptoms[4]. Benign prostatic hyperplasia (BPH), on the other hand, is a non-cancerous enlargement/growth of the prostrate cell, and being benign, means it can't spread while Prostate cancer can spread to other parts of the body[5].

In both BPH and prostate cancer, the prostate gland gets larger, and their epidemiology is common in adult men. About 1 out of every 7 men will be diagnosed with prostate cancer, and half of men population in their 60s will have BPH. In Nigeria, the prevalence of reported prostate cancer was 8.8%[6] while, BPH was 23.7%[7] in men older than 50 years. BPH and prostate cancer have similar symptoms, so it's sometimes hard to differentiate between the two conditions[4,5]. As the prostate enlarges, it squeezes the urethra. This pressure prevents urine from getting down the urethra and out of the body. Prostate cancer symptoms often don't start until cancer has grown large enough to put pressure on the urethra[8].

The symptoms of both BPH and prostate cancer include; an urgent need to urinate, feeling the urge to urinate many times during the day and night, trouble starting to urinate or having to push to release urine, weak or dribbling urine stream, urine flow that stops and starts, feeling like your bladder is never fully empty. If an individual has prostate cancer, he might also notice painful or burning urination, blood in urine, trouble getting an erection, painful ejaculation, less fluid when you ejaculate, and blood in the semen[9].

Androgenic hormones have been widely accepted to regulate proliferation, apoptosis, angiogenesis, metastasis, and differentiation of prostate cancer in different ways. The relationships of androgenic hormones to prostatic tissue growth are however complex, but it is known that the prostate will not develop without the androgens and the gland will deteriorate if androgen support is withdrawn[9,11]. Testosterone, a male sex hormone, and androgen are produced in a man's testes, it helps to maintain sperm production, muscle and bone mass, facial and body hair and sex drive in a man[11]. Also, some studies have reported deranged lipid profiles which include a high serum triglyceride, a low or high serum high-density lipoprotein (HDL) cholesterol and a high total or low-density lipoprotein (LDL) cholesterol as a possible contributor to the development and or progression of both BPH and prostate cancer[10].

However, research has shown that lots of individuals with Benign prostatic hyperplasia are been classified wrongly as Prostate cancer patients while those with Prostate cancer are misdiagnosed as Benign prostatic hyperplasia because of Prostate-specific antigen which is a biomarker for the prostate gland is not specific. Therefore, this study, aimed at assessing the lipid profile and sex hormone levels of men with prostatic cancer and BPH as possible markers of differentiating between the two diseases.

II. Material And Methods

This Study was hospital based, and a cross-sectional design was conducted at a tertiary hospital in Nigeria. It comprises already diagnosed adult men (aged between 50 and 70 years) with enlarged prostate gland having either prostate cancer or BPH and attending the clinic at the Department of Histopathology, Federal Teaching Hospital, Ido- Ekiti between February and September 2021. The ethical approval for this study was approved by the ethical review board of the Federal Teaching Hospital FTH, Ido- Ekiti. The study population was randomly selected and grouped into three (3) categories: the first and second groups comprised histologically diagnosed prostate cancer (PC) subjects and benign prostate hyperplasia (BPH) subjects respectively, while the third group (control subjects) comprised age and sex matched individuals without BPH or prostate cancer. Patient/subject exclusion criteria include adult individuals who smoke, drink alcohol and those without any co-morbidity.

Sample Collection: Under strict aseptic precautions, 5ml of fasting venous blood was obtained from each of the participants into a lithium heparin bottle. Blood samples were then centrifuged at a speed of 3000 rpm for 5minutes and plasma was separated, the plasma recovered was transferred to a fresh plain tube for determination of lipid profile.

Biochemical Analysis: Triglycerides, total cholesterol, and HDL-c were determined by an enzymatic spectrophotometric method using commercially purchased kits (Randox, U.K), LDL-c. Briefly, Total cholesterol (TC), was determined by enzymatic hydrolysis and oxidation method, triglycerides (TG) were estimated by enzymatic hydrolysis method while precipitation method was used to determine high-density lipoprotein cholesterol (HDL-c). Friedewald *et al* formula, LDL- cholesterol (mmol/L) = total cholesterol – (T.G/2.2 + HDL cholesterol) was used to calculate low-density lipoprotein (LDL-c). The plasma concentration of prostate-specific antigen and testosterone were measured using Enzyme Linked Immunosorbent Assay (ELISA).

Study Duration: February 2021 to September 2021 (8 months).
Sample size: 120 patients.

Sample size determination: Convenience sampling method was used to select the study population as the target population consisted of men with prostate cancer, benign prostatic hyperplasia and those without both (control), the sample size was then calculated using Fisher's exact formulae.

Inclusion criteria: The people involved in this study were male, non smoker, non-alcoholic and individuals with no form of morbidity.

Exclusion criteria:
1. Female,
2. Smokers,
3. Alcoholics,
4. People with any form of morbidity.

Statistical analysis

Statistical analysis was done using IBM statistical package for the science solution (SPSS) version 25.0 software package and graph pad prism 5.0 to determine the means, standard deviation, correlations, and one-way analysis of variance (ANOVA) among study groups and $P<0.05$ was considered as the level of significance.

III. Result

A total of 120 subjects were enrolled in this study, 40 (33.3%) had prostate cancer (prostate cancer group) while 40 (33.3%) had benign prostatic hyperplasia (BPH group), and 40 (33.3%) healthy men without both disease conditions served as the control group.

The mean ages were 63.60 ± 7.43 years, 64.65 ± 8.69years, and 65.9 ± 8.43 years in the control, prostate cancer, and BPH groups respectively. Married men have the highest number of frequencies across all groups (65%, 85%, and 80%) in the control, prostate cancer, and BPH groups respectively as shown in Table 1.

Table 1: Shows Demographic Characteristics of Test and Control Subjects.

Parameter	CONTROL (n=40)	BPH (n=40)	PCa (n=40)	*P*-value
AGE	63.60 ± 7.43	65.35 ± 8.43	64.65 ± 8.69	0.799
MARRIED	26 (65%)	34 (85%)	32 (80%)	11.38
WIDOWER	14 (35%)	6 (15%)	8 (20%)	9.37

Values were expressed as mean ± standard deviation. BPH = Benign prostatic hyperplasia, PCa = Prostate Cancer. n=number of subjects. Significance level at $P<0.05$:

Table 2 however, reveals Total cholesterol level was significantly higher ($P<0.05$) in PCa (6.28 ± 0.62 mmol/L) patients as compared to BPH patients (5.08 ± 0.36 mmol/L), and a higher significant cholesterol level was observed in PCa (6.28 ± 0.62 mmol/L) in comparison to control subjects (4.33 ± 0.53mmol/L). HDL-c was significantly higher ($P=0.05$) in Control subjects (0.89 ± 0.15 mmol/L) as compared to PCa patients (0.36 ± 0.10 mmol/L) as compared to BPH patients (0.74 ± 0.18mmol/L). The triglyceride level was significantly lower ($P<0.05$) in Control subjects (0.82 ± 0.25mmol/L) in comparison to BPH patients (1.66 ± 0.32 mmol/L) and PCA patients (2.53 ± 0.24 mmol/L) respectively. The mean PSA level was significantly increased ($P>0.05$) in PCa patients (32.35 ± 21.95 ng/mL) in comparison to BPH patients (15.25 ± 12.55 ng/mL), and control subjects (1.72±1.40 ng/mL). The Testosterone level was also significantly higher ($P<0.05$) in PCa patients (11.38±5.20 mg/mL) compared to BPH subjects (9.37±6.32mg/mL), and a control subject (4.76±1.96mg/mL) (Table 2).

Table 2: Lipid Profile Level in the Test and Control Subjects.

Parameter	CONTROL (n=40)	BPH (n=40)	PCA (n=40)	*P*-value
TC (mmol/L)	4.33 ± 0.53	5.08 ± 0.36	6.28 ± 0.62	0.001
TG (mmol/L)	0.82 ± 0.25	1.66 ± 0.32	2.53 ± 0.24	0.001
LDL-C (mmol/L)	3.10 ± 0.52	3.58 ± 0.38	4.75 ± 0.69	0.001
HDL-C(mmol/L)	0.89 ± 0.15	0.74 ± 0.18	0.36 ± 0.10	0.001
PSA (ng/mL)	1.72 ± 1.04	15.25 ± 12.55	32.35 ± 21.95	0.001
Testosterone (mg/mL)	4.76 ± 1.96	9.37 ± 6.32	11.38 ± 5.20	0.001

Values were expressed as mean ± standard deviation. BPH = Benign prostatic hyperplasia, PCa = Prostate Cancer. n=number of subjects.TC=Total cholesterol, TG=Triglyceride, LDL-C=Low density lipoprotein cholesterol, HDL-C= High-density lipoprotein cholesterol. Significance level at $P<0.05$

Table 3: Table 3 shows the Pearson's correlation coefficients of the TC, TG, HDL-C, LDL-C, and Testosterone within the control subjects in this study. A positive correlation was observed between TC and LDL-C (r = 0.888, $P<0.01$). A negative correlation was observed between TC and Testosterone (r = -0.326, $P<0.01$). While no significant correlation was found between other parameters.

Table 3: Pearson's Correlation Coefficients of Biochemical Parameters within the Control Subjects**.**

PARAMETER	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	Testosterone (mg/mL)	PSA (ng/mL)
TC(mmol/L)	1	0.314	-0.125	0.888**	-0.326**	-0.035
TG (mmol/L)		1	-0.187	0.319	-0.286	-0.194
HDL-C (mmol/L)			1	-0.367	0.092	-0.001
LDL-C (mmol/L)				1	-0.240	0.044
Testosterone (mg/mL)					1	0.431
PSA (ng/mL)						1

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4 shows the Pearson's correlation coefficients of the TC, TG, HDL-C, LDL-C, and Testosterone within Benign Prostatic hyperplasia subjects in the study. A positive correlation was observed between TC and LDL-C (r = 0.779, $P<0.01$). A positive correlation was observed between Testosterone and PSA (r =0.872, $P<0.01$). While no significant correlation was observed in other parameters.

Table 4: Pearson's Correlation Coefficients of Biochemical Parameters within Benign Prostatic Hyperplasia Subjects

PARAMETER	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	Testosterone (mg/mL)	PSA (ng/mL)
TC (mmol/L)	1	-0.007	0.288	0.779**	0.302	0.246
TG (mmol/L)		1	0.083	-0.435	0.096	0.137
HDL-C (mmol/L)			1	-0.228	-0.234	0.357
LDL-C (mmol/L)				1	0.182	0.078
Testosterone (mg/mL)					1	0.872**
PSA (ng/mL)						1

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5 shows Pearson's correlation coefficients of the TC, TG, HDL-C, LDL-C, Testosterone, and PSA within prostate cancer subjects in the study.

A positive correlation was observed between TC and LDL-C (r=0.928, $P<0.01$). A negative correlation was observed between TG and LDL-C (r=-0.463, $P<0.01$). A positive correlation was observed between LDL-C and PSA (r=0.076, $P<0.01$). A positive correlation was also observed between Testosterone and PSA (r=0.559, $P<0.01$). While no significant correlation was seen in other parameters.

Table 5: Shows Pearson's Correlation Coefficients of Biochemical Parameters for Prostate Cancer Subjects.

PARAMETER	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	Testosterone (mg/mL)	PSA (ng/mL)
TC (mmol/L)	1	-0.246	0.001	0.928**	0.017	0.103
TG (mmol/L)		1	0.057	-0.463**	-0.123	0.126

HDL-C (mmol/L)	1	-0.147	0.025	-0.017
LDL-C (mmol/L)		1	0.075	0.076**
Testosterone (mg/mL)			1	0.559**
PSA (ng/mL)				1

**. Correlation is significant at the 0.01 level (2-tailed).

IV. Discussion

Patients in their sixth decade of life cumulatively accounted for 71.25% of the overall subject studied. These findings are similar to previously published data and confirm that prostatic diseases are significant problems for men in our region.

Benign prostatic hyperplasia is a common disease in elderly men, with lower urinary tract symptoms (LUTS) caused by hyperplasia of the prostatic epithelium and stromal cells[9]. In this study, it was observed that there were increases in levels of total cholesterol, triglyceride, low-density lipoprotein, and a decrease in high-density lipoprotein among BPH subjects this, however, suggests a derangement in lipid profile indices among BPH disorder.

Differences in serum PSA and testosterone levels are well known parameters that may differ between healthy individuals, BPH patients, and prostate cancer patients. This study has particularly put forth significant differences in lipid profile between prostate cancer and BPH.

From the results of this study, the serum PSA showed a significant difference in values in comparison and was higher in patients with prostate cancer when compared to those with BPH (P= <0.001 for serum PSA), these results are congruent with what has been seen in a study by Orakwe *et a*l[12]. In their study using supra-pubic prostatectomy specimens, Hill et al also demonstrated that the serum PSA was the best discriminator between those with and those without prostate cancer after they found that the serum PSA was significantly higher in those with prostate cancer (P< 0.00001, Mann–Whitney test)[13].

In this study serum testosterone showed a significant difference in values in comparison and was higher in patients with prostate cancer when compared to those with BPH (P= <0.001 for serum testosterone), although a study reported that the serum testosterone levels were found to be slightly lower in patients with prostate cancer but there was no statistically significant difference from the serum levels in BPH patients[12]. Heracek *et al* also compared serum androgen levels in patients with BPH and prostate cancer and found no significant difference in levels[14].

The changes in lipid profile parameters between the control, benign prostatic hyperplasia, and prostate cancer groups in various grades were statistically significant and were seen in the course of this study[13]. Moon and his colleagues presented a thesis that a high level of cholesterol increases the size of the tumor and that "cholesterol acts as a magnet, attracting the protein to the tumor cell surface," making it more aggressive[15]. These findings are similar to the results in this study, hypercholesterolemia was also observed in the prostate cancer subjects (6.28 ± 0.62 mmol/L).

High level of total cholesterol, LDL-cholesterol, triglyceride, and decreased level of HDL cholesterol has been seen to increase the risk of BPH, and cholesterol-lowering medication such as Statin may reduce the risk. Patsons *et al* compared fatty acid (FA) profiles in the serum of patients with prostate cancer and BPH and proposed that polyunsaturated FAs have certain relation with BPH and prostate cancer[16]. Higher serum LDL is associated with a greater risk of BPH and physical activity, while a decrease in the serum lipid level is associated with a decreased risk for BPH[17]. This has also been confirmed with this study thus reduction in the lipid levels of the body is critical in facilitating the treatment process in BPH condition.

A significant positive correlation was also found between PSA and TC, PSA and TG, and PSA and LDL with a correlation coefficient, (r: 0.540, 0.582, 0.483; P<0.05) and a significant negative correlation observed between PSA and HDL (r: -0.448; P<0.05) which is also strengthened by in vitro studies that suggested a definite relationship of lipids with prostate cell metabolism[18]. Therefore, more in vivo studies are required to understand the relationship between BPH and lipid profile and the level of correlation between lipid profile and prostate cancer.

V. Conclusion

Generally, the results of this study show that there is a derangement of lipid profile parameters in both BPH and prostate cancer subjects, with total cholesterol, triglycerides, and low-density lipoproteins significantly higher among the prostate cancer subjects as compared to the BPH subjects. Likewise, serum testosterone and PSA levels in prostate cancer patients were significantly higher than those in BPH subjects. Therefore, we can conclusively document that the PSA assay currently remains an important investigation for detecting prostate cancer while lipid profile analysis can be a good index to monitor the two diseases (benign prostatic hyperplasia and prostate cancer) progression, intervention, and management.

This study, however, recommends the use of lipid-lowering intervention drugs in both subjects undergoing therapy as this will go a long way to improve the quality of life in such patients and reduce mortality. A more robust study to include more populations of different ethnic groups is also suggested.

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