Assessment of Serum Lipid Profile and Apolipoproteins in Patients with Prostate Disorders in Nnewi, Anambra, South East Nigeria

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ABSTRACT

Background: Prostate cancer (PCa) is a common disease affecting men between the ages of 50 years and above and has a high incidence and mortality. It has been hypothesized that blood lipid levels might be associated with prostate cancer risk. **Objective:** The aim of this study is to determine the serum concentration of the various lipid indices and apolipoproteins in patients with prostate disorders. **Materials and Methods:** A total of one hundred and eighty male subjects participated in the study. This comprised of sixty patients with prostate cancer, sixty benign prostate hyperplasia patients and 60 apparently healthy men. Blood sample was collected from each subject for biochemical analysis using standard ELISA/colourimetric methods. Statistical analysis was carried out and level of significance was determined using KruskalWallis test. **Results:** The levels of both Apo A and Apo E were found to be significantly lower in the PCa group than in BPH and control subjects. Also, Apo A and Apo E were significantly lower in subjects with BPH when compared with values from controls. Meanwhile, Total cholesterol (TC) and Triglyceride (TG) were significantly higher in PCa patients compared to values seen in both BPH and control subjects. LDL-cholesterol was significantly lower in controls when compared with levels in PCa patients. **Conclusion:** The results obtained from this investigation suggest that altered lipid profile and Apolipoproteins A, and E levels might be associated with prostate cancer. Monitoring of these parameters could be helpful in the management of prostate disorders.

Keywords: Prostate disorders, Lipid profile, Apolipoproteins A and E

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INTRODUCTION

Cancer is a leading cause of death and an important barrier to increasing life expectancy in every country of the world. Prostate cancer is the 2nd commonest cancer worldwide after Lung cancer. PCa is the 5th cause of cancer death worldwide. [1,2]. Prostate cancer accounted for approx 1.4million new cancers and 375,000 deaths in 2020. Highest incidence of prostate cancer by race remains African Americans, 249/100,000. Overall, Black men are 1.7 times more

likely to be diagnosed with prostate cancer and 2.1 times more likely to die from prostate cancer than white men. [3, 4, 5] In Nigeria, the burden of prostate cancer is worrisome. [6] New cases of Prostate cancer was 15,306 (12.3% in Men) in 2020. It is the leading cause of cancer death in men in 2020 in Nigeria. [1]

Igbokwe et al in their 10 years retrospective study reported that a total of 4675 malignancies were histologicaly confirmed during the study period out of which Urological Malignances accounted for 420 (8.9%) of total malignancies. [7] There has been a growing discussion on the relationship between lipid profile and prostate cancer. Dyslipidaemia has been said to be a risk marker for the development of prostate cancer, prognosis and recurrence. [8] This link, however, has not been definitely established as different authors have come up with varying conclusions.

High circulating cholesterol and its deregulated homeostasis may facilitate prostate cancer progression. Genetic polymorphism in Apolipoprotein (Apo) E, a key cholesterol regulatory protein may affect changes in systemic cholesterol levels. [9] Apo E gene can trigger defective intracellular cholesterol efflux, which could promote aggressive prostate cancer. Ifere et al in their investigation also reported a relationship between prostate aggressiveness, Apo E isoforms and cholesterol imbalance.

Establishing dyslipidaemia as a true risk marker for prostate cancer development will help in the prevention, screening and treatment of prostate cancer. To the best of our knowledge, no such study has been done in our environment.

We set out to look at the relationship between total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), Apolipoprotein A (Apo A) and Apolipoprotein E (Apo E) in prostate cancer and benign prostate hyperplasia subjects resident in Nnewi, Anambra state, South-East Nigeria.

MATERIALS AND METHODS

Study Area

This study was carried out in Nnewi, Anambra state, South-East Nigeria. Geographically, Nnewi falls within the tropical rain forest region of Nigeria. It remains an area of rich agricultural produce and epicenter of business trade. Nnewi is the second largest and the second most populated city in Anambra State. The city is located east of the Niger River (6.01050N, 6.91030 N) and about 22 kilometers South East of Onitsha in Anambra State.

Study population

In this case-control study, a total of one hundred and eighty (180) adult males comprising of 60 prostate cancer (PCa) patients, 60 benign prostatic hyperplasia (BPH) patients and 60 apparently healthy men (control) of the same age range were recruited using consecutive sampling technique. All subjects were properly medically examined by the consultant Urologist at Nnamdi Azikiwe University Teaching Hospital, Nnewi (NAUTH). A structured questionnaire was administered to all participants which provided information concerning their age, sex, and other important bio-data.

Inclusion and exclusion criteria.

It is only patients suffering from prostrate disorders as confirmed by the consultant Urologist that were enrolled in this study. Patients with prostrate disorders on androgen deprivation therapy were excluded from the study.

Sample size Calculation

The minimum sample size for the study was determined using the following formula by Charan and Biswas, [10].

Where,

n = Minimum sample size in case group

r = Ratio of controls to cases (in this case1:1)

σ = Population standard deviation (this was calculated from pooled standard deviation obtained from the study by Adedapo et al. [11]

d = Expected mean difference between cases and controls based on previous study. [11]
Zα/2 = Standard normal deviate corresponding to the two-sided significance level of 5% (P < 0.05) = 1.96.
Zβ= Standard normal deviate corresponding to 100% - the power; for 80% power = 0.84
Pooled standard deviation was calculated using a formula by Cohen, [12]
52.41 mg/dl
Therefore, σ = 52.41
The mean difference between Prostate Cancer group and control group:
= 22.7mg/dl.[11]
Inputting all values into the first equation,
N = 41.79. Approx. 42 participants per group.
Therefore, minimum sample size = 126 participants (42cancer cases, 42 BPH cases and 42 controls).

Ethical approval;
Approval for this study was sought and obtained from the Ethical committee of Nnamdi Azikiwe University Teaching Hospital (NAUTH) on 29th July 2019 (Ref No NAUTH/CS/66/Vol.12/029/2018/012).

Sample collection: 6mls of fasting blood sample was collected from the newly diagnosed prostate disorder patients. The samples were allowed to clot for one hour and then centrifuged at 3000 rpm for 5mins. The serum obtained was used for assay of Apolipoprotein A, Apolipoprotein E, Total PSA, Free PSA and other fractions of serum lipids. Some demographic and anthropometric variables of the participants were obtained.

Method

Determination of Prostate Specific Antigen (PSA) and f-PSA were carried out according to the methods of Stowell et al [13] and Catalona [14] respectively. Human apolipoprotein A (Apo-A) was analyzed using ELISA technique (CAT NO. EKHU-1760) Melsin medical Co, Limited. Apolipoprotein E was also determined using ELISA technique, (ELISA KIT (CAT NO. EKHU-0763) Melsin Medical C. Limited.). The serum TC level was estimated using the enzymatic colourimetric method described by Naito. [15]. Serum HDL-C level was estimated by precipitation and CHOD-POD enzymatic colourimetric reaction, according to the method of Grove. [16]. Serum TG level was estimated by a GPO-POD enzymatic colourimetric reaction method. [17]. LDL-C was estimated by computation using a formula proposed by Friedewald et al. [18].

Statistical analysis
The statistical analysis was carried out using the statistical package for social sciences (SPSS). Data was analyzed using Kruskal Wallis test. Means of parameters were compared using the analysis of variance (ANOVA) test while significant intra group results were determined with pair wise comparison (post Hoc). Results were regarded as significant at $p<0.05$.
RESULTS
Table 1
Table 2
Table 3

RESULTS

The result obtained from this study, showed that the mean ages of those with PCa, BPH and controls were similar. The values of the mean height, weight, BMI, SBP and DBP in controls were also similar to those of PCa and BPH patients (Table 1). As expected, total PSA and %fPSA were significantly higher and lower respectively in PCa patients compared to corresponding values in controls and in patients with BPH ($p<0.001$ in each case). Similar significant differences were also observed when values in BPH patients were compared with controls ($P< 0.001$) in each case (table 2). It is also worthy of note that serum TC and TG were significantly higher ($p<0.001$) in those with PCa than that obtained from control subjects (Table 3). There were also significant differences in the levels of TG and TC between PCa and BPH, but

Table1. Medians of demographic and anthropometric variables and blood pressure measurements in all groups studied

Group	AGE	HGT	WGT	BMI	SBP	DBP
Control(A)	69.00	1.74	77.50	26.90	132.50	80.00
BPH(B)	68.50	1.69	85.25	28.58	132.50	77.50
PCa(C)	71.00	1.70	72.75	26.55	140.00	82.50
Kruskal-Wallis test	42.597	1.542	2.717	2.443	0.980	1.308
p-value	0.501	0.463	0.257	0.295	0.612	0.520
A vs B	0.401	0.573	0.766	0.268	1.000	1.000
A vs C	0.511	1.000	1.000	1.000	0.939	0.725
B vs C	0.499	1.000	0.175	0.343	0.725	0.769

HGT = Height WGT = Weight, BMI = Body mass index, PCa = Prostate cancer SBP =Systolic blood pressure, DBP = Diastolic blood pressure, BPH = Benign prostatic hyperplasia

Table 2.Serum levels of TPSA, FPSA a Nd %FPSA in control, BPH and PCa in all groups studied

Group	TPSA	FPSA	%FPSA
Control(A)	5.45	2.15	36.50
BPH(B)	28.00	1.37	20.50
PCa(C)	93.85	16.00	12.50
Kruskal -Wallis test	45.85	46.81	27.41
p-value	0.001	0.001	0.001
A vs B	0.001	1.000	0.001
A vs C	0.001	0.001	0.001
B vs C	0.001	0.001	0.001

Abbreviations:
TPSA = Total prostate specific antigen, FPSA = Free prostate specific antigen
%FPSA = percentage free prostate specific antigen
BPH = Benign prostatic Hyperplasia, PCa = Prostate cancer

Table 3. Serum levels of TC, TG, HDL-C, LDL-C, Apo A and Apo E in control, BPH and PCa in all groups studied

GROUPS	TC (mmol/l)	TG (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)	APO A mmol/l	APO E mmol/l
CONTROL (A)	4.37	0.91	1.30	2.42	111.00	1.10
BPH (B)	4.77	1.36	1.12	2.78	73.50	0.90
CAP (C)	5.37	1.74	1.17	3.15	60.50	0.80
KRUSKAL WALLIS TEST	22.053	34.245	5.706	10.59	66.032	52.510
p-value	<0.001	<0.001	0.058	0.005	<0.001	<0.001
A vs B	0.573	0.051	0.363	0.824	<0.001	<0.001
A vs C	<0.001	<0.001	0.116	0.003	<0.001	<0.001
B vs C	0.001	0.021	1.000	0.061	0.002	<0.001

Abbreviations:
TC = Total cholesterol, TG = Triglyceride, Apo A = Apolipoprotein A
HDL -C = High density lipoprotein -Cholesterol, Apo E = Apolipoprotein E
LDL -C = Low density lipoprotein -Cholesterol, PCa = Prostate cancer
BPH = Benign prostatic hyperplasia

none was observed between BPH and control values. Serum Apo A and Apo E were lowest ($p<0.001$) in patients with PCa compared with values from BPH and controls. Concentrations of Apos A (0.002) and E (<0.001) were also significantly higher in those with BPH compared to values obtained from those with PCa. Serum LDL-C was only observed to be significantly higher ($P<0.001$) in those with PCa compared to control values (Table 3).

DISCUSSION

Prostate disorders (Benign prostatic hyperplasia and prostate cancer) are highly prevalent disease amongst older men and a significant public health problem. [19].

In this study, total PSA level was significantly higher in both PCa patients and those with BPH when compared with values obtained from control subjects. PSA level was also significantly increased in PCa patients when compared with subjects with BPH. This simply suggests the presence of prostate disorders in the study population. There were significantly higher levels of total cholesterol, triglyceride and LDL-C in PCa compared to control. Also, TC and TG differed significantly between PCa and BPH. Low density lipoprotein was significantly higher in PCa when compared with the controls.

One of the mechanisms hypothesized for the relationship between total cholesterol and prostate cancer is that excessive accumulation of cholesterol shown in the cell membrane of prostate cancer cells form large lipid rafts which in the case of cancer cells, may facilitate pro-carcinogenic cell signaling. [20] However, the findings of dyslipidaemia in relation to prostate cancer have so

far shown confounding results. While some demonstrated a strong relationship between dyslipidaemia and prostate cancer, others say there is no relationship.

In the work by Kok *et al*. [21] where they prospectively studied 2842 Dutch men, they found that total cholesterol and low density lipoprotein were significantly associated with total prostate specific antigen and aggressive prostate cancer while high levels of high density lipoproteins were associated with non aggressive prostate cancer. In the same study, triglyceride was not significantly associated with increased prostate cancer risk. This was arrived at after eliminating confounding factors like, hypertension, diabetics, and patients on statins (lipid lowering drugs).

Montila et al. [22] doing another retrospective study on199 Puerto Rican men found high TG and Low HDL to be associated with aggressive PCa but unlike the findings from Kok et al [21], TC was not significantly associated with aggressive PCa. Mieke et al. [23] on the other hand reported a statistically significant relationship between HDL and PCa. Montila et al [22] in their study, also reported increased LDL serum levels were associated with a higher risk of prostate cancer in African American men but not in non-African American. Cholesterol has been regarded as a potential risk factor for prostate cancer; hence studies have suggested that hypercholesterolaemia increases the risk of prostate cancer. [24]

Reshu working in Indians noted that total cholesterol was significantly higher in prostate cancer and higher grade prostate cancer patients than in BPH patients. [25]. This was in agreement with our finding. He also reported that VLDL and triglyceride was significantly higher in PCa patients compared to BPH patient while HDL was insignificantly higher in PCa patients compared to BPH patients.

On the other hand, Sheng [26] who looked at the effect of lipid profile in prostate cancer recurrence after radical prostatectomy found that there was no relationship between prostate cancer recurrence and TC,TG, LDL and HDL. Liu *et al* [27], in their meta-analysis of 14 large prospective studies, observed that blood TC, HDL, and LDL levels were not associated with the risk of either overall prostate cancer or high-grade prostate cancer. Melvin however found a relationship between TG,TC, LDL and Low HDL and obesity related cancers which included PCa. All these show the inconsistencies in the relationship between lipid parameters and PCa. [28] From this present study Apo A and Apo E were statistically lower in PCa compared to BPH and controls. Also, Apo A and E levels were significantly lower in BPH than controls. The report of the effect or association of these apoliproteins in other works has also shown conflicting results. Jing *et al* showed that Apo A is upregulated in PCa and advanced PCa. [29]. Liwen in their review article on apolipoproteins, noted that the reduction of serum levels of apoA1 was an independent predictor for metastasis or unfavorable prognosis of many cancers, such as ovarian cancer, non-small cell lung carcinoma (NSCLC), nasopharyngeal carcinoma (NPC) colorectal cancer, lymphoma and prostate cancer but high in some other cancer like hepatocellular carcinoma (HCC). [30]. Apo E was highly expressed in the PC-3 human prostate cancer cell line and its expression was directly correlated with the Gleason score of prostate cancer tissues, hormone independence and local and distant metastasis.

Mari *et al.* [31] on the other hand found that apolipoprotein E levels were equal in the men with prostate cancer, those with BPH and the controls, arguing that there was absence of a relationship between Apo E and prostate cancer but Melvin et al [28] found reduction of Apo E to be associated with PCa with a relative risk of 1.42. Mieke *et al* [23] on the other hand noted that Apo A value was inversely associated with PCa risk.

Wolfer *et al* [32] studied Apo E looking at the various alleles namely Apo E 2, 3, and 4 and noted that the protective allele was the Apo E2 allele and that E3 and E4 encouraged cancer proliferation and metastasis of cancer and death. In our study we assayed for Apo E as one agent without looking at

the various alleles and by extension their phonotypical presentation. From the above it is evident that further investigation would still be required to fully understand the relationship between prostate cancer and lipid profile more especially with regards to the potential use of some fractions of lipids as agents for prognostification or diagnosis.

CONCLUSION

There were significant decreases of both Apo A and E in prostate disorders when compared to the control. Meanwhile TG and TC increased significantly in prostate cancer when compared to the control. Hence changes in serum levels of cholesterol, triglycerides and apolipoprotein may play a key role in prostate oncogenesis and severity. Long term prospective studies should be done along these considerations and unravel the true link and its clinical usefulness.

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Author contributions:

UKA, JEA, JAO and TUM conceptualized and designed the study. JMO and JEO contributed to implementation of the project and revision of the manuscript. All authors were involved in the writing and revision of the manuscript. UKA and CEO were involved in the sample analysis. JJN, TUM and BOO collected the samples. The authors read, approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability

The data generated in this study are available from the corresponding author upon reasonable request.

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Conflict of interest: None declared.

Ethical approval

The study was approved by the Institutional Ethics Committee with approval number: Ref No NAUTH/CS/66/Vol.12/029/2018/012).

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