Asian Pac. J. Health Sci., 2015; 2(2): 48-55 e-ISSN: 2349-0659, p-ISSN: 2350-0964

Atherogenic lipid markers and testosterone levels in Nigerian men with prostate disorders

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ABSTRACT

Background: Prostate cancer is associated with increased cardiovascular risk.Atherogenic lipoprotein profile is an important risk factor for cardiovascular diseases. The aim of this study is to determine the atherogenic lipid markers and testosterone levels in Nigerian men with prostate cancer (PCa) and benign prostate hyperplasia (BPH) to evaluate their usefulness for predicting cardiovascular events in patients with prostate disorders. **Methods:** Study subjects consisted of 40 PCa patients, 32 BPH patients and 32 apparently healthy controls. Serum lipid profile, prostate specific antigen (PSA) and testosterone levels were determined using standard procedures. Atherogenic index of plasma (AIP) was calculated as log (triacylglycerol/high density lipoprotein-cholesterol). **Results:** The results from the study indicate that PCa and BPH subjects had significantly higher ($p < 0.05$) levels of total cholesterol (TC), low density lipoprotein- cholesterol (LDL-c), very low density lipoprotein-cholesterol (VLDL-c),Triacylglycerol (TAG) and AIP while high density lipoprotein-cholesterol (HDL-c) was significantly lower ($p < 0.05$) compared to the controls. However, PCa patients had significantly lower ($p < 0.05$) HDL-c and testosterone levels but significantly higher ($p < 0.05$) AIP levels compared to BPH patients. In PCa patients AIP, TC, and LDL-c showed significant positive correlations with PSA while a significant negative correlation was observed between HDL-c .and PSA. In BPH patients a significant positive correlation was observed between total testosterone and PSA. **Conclusions:** Prostate disorders are associated with altered lipid profile and atherogenic lipid markers. AIP may be useful in predicting the risk of cardiovascular diseases in Nigerian men with PCa and BPH.

Keywords: Atherogenic index of plasma, Atherogenic lipid markers, Nigeria, Prostate disorders, Testosterone.

Introduction

The morbidity and mortality of prostate cancer is rapidly increasing in the past decades especially in the developing countries like Nigeria. The reasons for this increase have not been fully elucidated. Several epidemiological studies have investigated the relation between prostate cancer incidence and a broad range of endogenous and exogenous factors, including lipids levels [1] but data on the prostate cancer-lipids relationship are inconsistent. Lipids comprise diverse classes of molecules with critical functions in cellular energy storage, structure, and signaling. They also might be associated with cancers because they play a key role in the maintenance of cell integrity [2]. Cholesterol and triglycerides which are important lipid constituents of cell carry out several vital physiological functions such as the maintenance of the structure and functional integrity of all biological membranes. Cholesterol is also involved in other biological functions including cell growth and division, the activity of membrane bound enzymes and stabilizing the DNA double helix. In plasma, triglycerides and cholesterol are packaged into lipoproteins which are then taken up and degraded by the cells. In the prostate gland, lipids promote the cellular proliferation, contractility and overall enlargement of the prostate and thus represent a potential risk factor for BPH and

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prostate cancer [3]. The prostate is a cholesterol-rich tissue; therefore elevated serum cholesterol may result in the accumulation of cholesterol in the cell membrane forming large lipid rafts [4]. These lipid rafts have been shown to have pro-carcinogenic cell signalling effects.

Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Altered lipid metabolism is increasingly recognized as a feature of cancer cells and blood cholesterol undergoes early and significant changes in some malignant diseases [5]. Low-density lipoprotein (LDL) can build up in the walls of the arteries that feed the heart and brain and form plaque—a thick, hard deposit that can clog those arteries, a condition known as atherosclerosis. Conversely, elevated levels of high-density lipoprotein (HDL) have been shown to prevent heart disease, while low HDL level increases the risk of heart attack and stroke [6]. In vitro reduction of cholesterol has been shown to induce apoptosis in prostate cancer [7], while treatment with statins leads to about a 50% reduction in the first cardiovascular event [8]. Elevated triglycerides may increase prostate cancer risk through lipoprotein signalling pathways. Hypertriglyceridemia results in the accrual of very low-density lipoproteins, chylomicrons, which are hydrolyzed, producing remnant lipoproteins. Lipoprotein remnants result in activation of Akt signal transduction, and mitogen-activated protein kinases, which increase prostate cancer cell proliferation. A high triacylglycerol level combined with a low HDL or high LDL can speed up the process of plaque formation in the arteries. Several studies have shown significant associations between high TAG levels and an increased risk of malignant tumours [2]. The potential mechanisms for the association between hypertriglyceridemia and cancer development include insulin resistance, infection, inflammation, and oxidative stress [6] [1].

Atherogenic lipoprotein profile of plasma is an important risk factor for cardiovascular disease which is characterized by a high ratio of LDL-cholesterol to HDL-cholesterol [9].

Atherogenic index of plasma (AIP) is the new marker of atherogenicity, given that AIP is related directly to the atherosclerosis risk. AIP is the ratio calculated as log (TAG/HDL- cholesterol) [10]. Existence of hypertriglyceridemia has been shown to increase the activity of hepatic lipase resulting in increased HDL-cholesterol catabolism. Susanti *et al*. [11] reported that each degradation of 1mg HDL- cholesterol will correlates with 2% increase in the risk coronary heart disease.Testosterone, a steroid hormone derived from cholesterol, occurs more abundantly in circulation among men. During the aging process, testosterone levels diminish gradually. This characteristic hormonal change of male aging is of interest because lower testosterone concentrations are commonly associated with a number of clinical conditions [12]. Evidence suggests that serum testosterone levels in men are negatively associated with LDL and triglycerides and positively related to HDL-cholesterol levels indicating that low serum total testosterone is associated with an unfavorable lipid profile [13]. Some studies now demonstrate that elevated risk is associated with low androgen states especially among men who have undergone androgen-deprivation therapy (ADT) for treatment of prostate cancer [14]. Interventional studies have also shown that testosterone replacement in hypogonadal men results in a significant decrease in total cholesterol, LDL cholesterol and triglycerides while serum HDL levels show an insignificant decrease [15].Despite widespread perception of a relationship between testosterone and prostate cancer risk, the majority of epidemiological studies are inconclusive. The role of testosterone in modifying lipoprotein function and cardiovascular risk in men remains highly uncertain and constitutes an intriguing area of emergent research. Also there is a paucity of studies on the usefulness of AIP as a tool for identification of the risk of cardiovascular disease in patients with prostate disorders. The aim of the present study is to determine the atherogenic lipid markers and testosterone levels in Nigerian men with BPH and prostate cancer in order to evaluate their usefulness for predicting cardiovascular events. Thus, the lipid profile analysis in patients with prostate disorders presents itself as a promising tool especially because of its potential contribution to a better management of prostate conditions since the majority of the cardiovascular signs and symptoms are associated with dyslipidemia.

Materials and methods

One hundred and four (104) human subjects within the aged 53-85years (average 69 years) participated in this study. They were sub-divided into groups A, B and C.

Group A were 32 apparently healthy subjects who served as the control subjects. They were age and sex-matched with the test subjects (B and C). Group B were made up of 32 patients diagnosed with benign prostate hyperplasia (BPH) and were attending urology clinics at the University of Nigeria Teaching Hospital Ituku/Ozalla, Enugu. Group C consisted of 40 prostate cancer patients who were either attending the urology clinic or were admitted at the wards at the University of Nigeria Teaching Hospital Ituku/Ozalla, Enugu and

whose clinical records were well known from their medical history. The patients were newly diagnosed cases, although some of them have advanced prostate cancer. They were not known to have any other acute or chronic medical problems and were therefore not yet on any known medication or supplements. They were yet to be placed on any form of therapy at the time of blood collection.

Exclusion criteria: 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.

Inclusion criteria: In each case, BPH or Prostate cancer was medically and histologically diagnosed in Chemical Pathology and Histopathology Departments of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu.

Information about smoking status and other health and work-related issues were obtained by a questionnaire and also from their hospital folders. The study was conducted at the Urology Clinic, Wards, Haematology and Chemical Pathology Departments of the University of Nigeria Teaching Hospital (UNTH), Ituku/Ozalla, Enugu.

The study was carried out 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 UNTH, Ituku /Ozalla.

Sample collection and treatment

Blood samples were collected from the subjects after an overnight fast (12hrs) and distributed into plain centrifuge tubes for determination of total prostate specific antigen (PSA), testosterone, total cholesterol, HDL-cholesterol and triacylglycerols. The samples were allowed to clot, spun at 4,000 rpm for 10 minutes in a Jenlab bench centrifuge, model 80-2 and the sera pipetted into serum bottles and analyzed.Serum total PSA concentration was estimated with ELISA kits produced by Diagnostic Automation / Cortez Diagnostics Inc. (Calabasas, California, USA) as described by. Serum total testosterone concentration was estimated with ELISA kits produced by DiaMetra (SEGRATE, M.I. Italy) by the method of [17].Total cholesterol concentration was determined as described by [18] using QCA commercial kits produced by BIOLABO (S.A. France). Triacylglycerol was estimated by the method of [19] using glycerol phosphate oxidase/peroxidase kits produced by Linear Chemicals, (Barcelona, Spain). HDL cholesterol was estimated by enzymatic colorimetric method of [20] with QCA reagent kits by BIOLABO (S.A. France). Serum LDL-cholesterol and VLDL were calculated using Friedewald's formula which is LDL-C = TC–(TG/2.2 + HDL-C) and VLDL = TG/2.2. [21-22]. The AIP was calculated as log (TG/HDL-c) using the Czech online calculator of atherogenic risk [10].

Data analysis

All statistical analyses were carried out using the statistical package program version SSPS 17.0 (SPSS, Inc., Chicago, IL, USA). Results were expressed as mean ± standard deviation. Level of significance between mean values of control and test groups was calculated and defined as $p < 0.05$.Correlation coefficient at 95% or 99% confidence interval between the parameters was also calculated.

Results

Table 1: Mean levels of PSA and testosterone in the BPH, PCa and control groups (A, B and C)

Groups	PSA (ng/ml)	Testosterone (ng/ml)
A n= 32	2.8 ±2.6	4.6±1.5
B n= 32	6.1±2.0[a]	4.1±1.4
C n= 40	34.5±26.8[ab]	1.7±1.1[ab]

KEY: A = Normal control group B = BPH group C = PCa group n = no of subjects,
a = $p < 0.05$ when compared with group A. ab = $p < 0.05$ when compared with groups A& B

Table 1 shows the mean levels of PSA in the BPH, PCa and control groups (A, B and C). The table indicates that relative to the mean level of PSA in both BPH (6.1±2.0ng/ml) and the control (2.8 ±2.8ng/ml) groups, that of PCa group (34.5±26.8 ng/ml) was significantly

higher ($p < 0.05$) and when the values for BPH and control groups were compared, that of BPH was also significantly higher ($p < 0.05$). However, when the test subjects were compared, the BPH group had significantly lower ($p < 0.05$) values than the PCa group.

The mean testosterone level in PCa group (1.7±1.1) was significantly decreased ($p < 0.05$) compared to those of BPH (4.1±1.4) and the control (4.6±1.5) groups but no significant difference ($p > 0.05$) was observed between BPH and the control groups.

Table 2: The mean concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, triacylglycerol and AIP in the different groups.

Groups	Total-c. (mmol/L)	HDL-c (mmol/L)	LDL-c. (mmol/L)	VLDL-c. (mmol/L)	T.G (mmol/L)	AIP
A n= 32	4.4± 0.9	1.1±0.3	3.1±0.8	0.4±0.1	0.8±0.2	- 0.11 ± 0.21
B n= 32	5.7±1.3[a]	0.7±0.2[a]	4.4±1.1[a]	0.6±0.3[a]	1.3±0.7[a]	0. 22 ± 0.24[a]
C n= 40	5.8±1.7[a]	0.5±0.2[ab]	4.6±1.8[a]	0.7±0.5[a]	1.6±1.0[a]	0.46 ± 0.31 [ab]

KEY: A= Control group, B= BPH group, C= PCa group, n= no of subjects, a= $p < 0.05$ when compared with group A; ab = $p < 0.05$ when compared with groups A and B;
AIP = Atherogenic index of plasma

Table 2 shows the mean levels of total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol, Triacylglycerol and atherogenic index of plasma of the prostate cancer, BPH and control groups. The levels of the total cholesterol (5.8±1.7 mmol/l), low density lipoprotein- cholesterol (4.6±1.8mmol/l), very low density lipoprotein- cholesterol (0.7±0.5 mmol/l) and Triacylglycerol (1.6±1.0 mmol/l) in prostate cancer group were significantly higher ($p < 0.05$) compared to the levels obtained in the control group (4.4±0.9, 3.1±0.8, 0.4±0.1, 0.8±0.2; respectively). Similarly, in the BPH group, the mean levels of total cholesterol (5.7±1.3 mmol/l), low density lipoprotein (4.4±1.1 mmol/l), very low density lipoprotein (0.6±0.3 mmol/l) and Triacylglycerol (1.3±0.7 mmol/l) were significantly increased ($p < 0.05$) compared to the control group. Although the levels of these lipid parameters were higher in the PCa group than in BPH group, the increase was not significant ($p > 0.05$). Conversely, the mean HDL levels were significantly lower ($p < 0.05$) in both BPH (0.7±0.2) and PCa (0.5±0.2) when compared to the values obtained for the control group (1.1±0.3) and the decrease was equally significant ($p < 0.05$) when the prostate cancer group was compared to the BPH group. The AIP of the PCa group (0.46 ± 0.31) was significantly higher ($p < 0.05$) than that of both BPH (0. 22 ± 0.24) and control group (- 0.11 ± 0.21); and also significantly higher ($p < 0.05$) when the values for BPH group was compared to that of the control group.

Table 3: Correlation between total cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerol testosterone, AIP and PSA in the BPH and Prostate cancer subjects.

Parameter	Control		BPH		PCa	
	r	**p-value**	**r**	**p-value**	**r**	**p-value**
T.cholesterol	0.2496	0.1684	-0.0622	0.7354	0.4588	0.0029**
HDL-cholesterol	-0.0399	0.8283	0.0317	0.8632	-0.5721	0.0001**
LDL-cholesterol	0.2738	0.1294	-0.1241	0.4985	0.4166	0.0075**

Triacylglycerol	0.1662	0.3632	0.1497	0.4135	0.2899	0.0696
Testosterone	-0.0489	0.7905	0.4716	0.0064*	0.0319	0.8450
AIP	0.125	0.495	0.132	0.471	0.532	0.000**

* = a significant correlation at $p < 0.05$ levels; ** = significant correlation at $p < 0.01$ levels.
T. cholesterol = Total cholesterol; r = Correlation coefficient

The correlation between lipid parameters, testosterone and prostate specific antigen in the test and control subjects are shown in Table 3. In the PCa subjects, a significant positive correlation was observed between total cholesterol, LDL- cholesterol and PSA ($r = 0.4588$, $p = 0.0029$, and $r = 0.4166$, $p = 0.0075$, respectively). Also there was a highly significant positive correlation existed between AIP and PSA ($r = 0.532$, $p = 0.000$) in the PCa group. Conversely, a highly significant negative correlation was observed between prostate specific antigen and HDL- cholesterol ($r = -0.5721$, $p = 0.0001$) in the prostate cancer subjects. For the BPH patients, a significant positive correlation was also found between PSA and testosterone ($r = 0.4716$, $p = 0.0064$).

Discussion

Blood lipid levels as part of the metabolic syndrome are thought to be linked to cancer risk [1]. The mean total cholesterol, LDL and triacylglycerol were not only significantly higher in patients with prostate cancer compared to controls, but also showed a positive significant correlation with PSA indicating that as the prostate degenerates and the cancer progressed, their levels increased. Likewise we also noted that HDL was significantly lower in the PCa subjects compared to BPH and control subjects and that HDL levels were negatively correlated with PSA. This observation agrees with the finding of [23], who reported a positive association between increasing total cholesterol level and overall risk of prostate cancer particularly in the advanced stage of prostate cancer. It is also supports the work of [24] who observed that men with higher cholesterol had a significantly increased risk of developing high grade disease than men with a desirable cholesterol level and that modifying cholesterol may reduce incidence of more aggressive disease. Several underlying mechanisms by which cholesterol and prostate carcinogenesis may be linked have been proposed. These researchers suggested that Prostate cancer cells tend to over-accumulate cholesterol in their cell membrane, forming large lipid rafts which, in the cancer cells may facilitate pro-carcinogenic cell signaling [25-26; 23].

Thus,having a lower cholesterol level may inhibit these pro-carcinogenic activities in the prostate cells. Similarly, this may be the same mechanism by which decreased HDL is associated with prostate cancer. Since HDL transports cholesterol from cells to the liver and other steroidogenic organs including the prostate thus removing harmful cholesterol from prostate tissue, thereby preventing the accumulation of cholesterol in the prostatic cell membranes [23], decreased HDL leads to the accumulation of cholesterol and formation lipid raft as stated above. Inflammation-related changes to HDL particles not only lower HDL cholesterol levels but also alter the anti-oxidant properties of HDL. It is thought that the lowering of HDL-cholesterol levels during inflammation is due to a reduction in cholesterol uptake by cells and an increase in their catabolism [27]. HDL inhibits oxidation and inflammation - properties which may also reduce prostate cancer risk [23]. However, our study differs from the findings of [28] which showed HDL did not cause any net change in the cholesterol content of the three prostate cancer cell lines examined, but rather induced the proliferation of androgen-independent prostate cancer cells. This may be because of the ability of HDL to also donate cholesterol to cells and the ability of cells to compensate for any loss of cholesterol by de novo synthesis [25].

A significant increase was also observed for triacylglycerol in this study between PCa and control group. This observation agrees with the finding of [29] who stated that high triacylglycerol levels correlated well with a higher incidence of prostate cancer and also more especially with aggressive PCa. They suggested that high triacylglycerol levels in elderly patients may provide the basis for developing prostate cancer with worse outcomes. Likewise, [30] observed high triacylglycerol concentrations among subjects with lung, thyroid and rectal cancer. The potential mechanisms for the association between hypertriglyceridemia and cancer development include infection, inflammation, and oxidative stress [27][31], although the contribution of chronic stress caused by

high triacylglycerol levels to prostate cancer development remains controversial [30]. The exact mechanisms by which lipids and lipoproteins may contribute to carcinogenesis are not clearly understood. Some studies suggest that LDL-cholesterol being more susceptible to oxidation in various pathologic conditions, generates higher lipid peroxidation during oxidative stress.The increased LDL-cholesterol observed in our study agrees with the findings of [32] who noted that LDL levels tend to be elevated in PCa due to its enhanced susceptibility to oxidation in prostatic cancer cells. Cholesterol-lowering treatment has been suggested to delay progression of prostate cancer by decreasing serum LDL [33]. Other researchers also have reported that higher LDL can increase the risk for some cancers, with the hormone-related cancers in men and women being especially affected [23][1]. Cholesterol availability is likely an important prerequisite for prostate cancer growth since reducing cholesterol levels was reported to have retarded prostate cancer growth in a prostate cancer xenograft model [34]. Some researchers have observed improved recurrence-free survival after radical treatment of prostate cancer among men using cholesterol-lowering statin drugs [35] while others noted that the use of statins after prostate cancer diagnosis was associated with a decreased risk in prostate cancer mortality [36]. Determining the plasma levels of cholesterol and its sub-fraction could also be used as biomarkers for prostate cancer since lowering cholesterol levels might be a good strategy to prevent and delay prostate cancer progression and reduce prostate cancer mortality. However, we observed no difference in the lipid levels between prostate cancer and BPH subjects. Although PCa is one of the leading causes of death in men, approximately half of the men with PCa die of non-cancer-related etiology. Co morbid conditions are common in this group, but a particularly strong association has been noted between the presence of cardiovascular disease and the eventual cause of death [15]. Atherogenic index of plasma, measured as the logarithmically transformed ratio of the serum triglyceride to HDL-cholesterol, may reflect the actual composition of the lipoprotein spectrum that might predict both the cardiovascular risk and effectiveness of therapy especially in cardiovascular disorders [37].This index has been shown to be a highly significant independent predictor of myocardial infarction, even stronger than TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios. AIP, a new marker of atherogenicity, is directly related to the risk of atherosclerosis hence people with high AIP have a higher risk of coronary heart disease than those with low AIP [9]. It has been reported that AIP has higher predicted value for atherosclerosis as compared to individual pro atherogenic markers alone [37]. In the this study, the AIP value for PCa patients was higher than those of BPH and the controls and this correlated positively with PSA indicating a higher risk for cardiovascular disease, while patients, with BPH showed medium risk. Considering the fact that AIP values from negative ones to 0.15 is "safe" from the aspect of atherogenicity [10], these findings indicate that AIP which reflects the plasma lipoprotein profile can be an objective indicator of the atherogenic risk in patients with prostate diseases. The present study also indicates that prostate cancer subjects have reduced testosterone levels compared to BPH and control subjects. Although the levels of total testosterone were low there was no correlation between prostate specific antigen and testosterone levels. This agrees with [38] who reported that serum testosterone levels were significantly lower in patients with prostate cancer than in the controls. Similarly, Morgentaler et al [39] found no correlation between endogenous testosterone concentrations and serum PSA levels in prostate cancer patients. They concluded that variation in endogenous testosterone concentration does not appear to influence PSA levels. Earlier prospective study by [40] that analysed the hormone levels of a cohort of patients followed for 15 years before they developed benign prostatic hyperplasia or prostate cancer, no significant association was found between serum testosterone levels and PSA levels. According to [41], this could be attributed to a possible inhibition of testosterone production by PSA, resulting in a low serum level of the hormone. On the other hand García-Cruz et al [42] observed that low testosterone levels were related to higher prostate-specific antigen and higher tumour burden. A possible explanation for this relationship is that high-grade tumors are more aggressive and may be more androgen-independent than low-grade tumors, thereby continuing to progress despite the relative lack of testosterone [43]. Therefore, low testosterone levels might be an indicator of prostate cancer and not necessarily a cause. Previous studies suggest that low testosterone levels are associated with higher risk of cardiovascular and overall mortality. According to [44] low testosterone level in middle-aged Japanese men was found to be an independent risk factor for cardiovascular disease while [45] reported that lower testosterone levels were also correlated with elevated levels of total cholesterol, LDL-cholesterol and triacylglycerol. However, we did not find any relationship between the lipid parameters and testosterone levels of the prostate cancer subjects in the current study.

Conclusion

In conclusion, our findings indicate that Nigerian men with prostate cancer and BPH have abnormal lipid profile and may have increased risk of cardiovascular diseases. AIP may serve as a veritable tool in predicting the high risk of cardiovascular diseases in prostate cancer patients and to a lesser extent in BPH. Prostate cancer patients have decreased levels of testosterone hormone but this is not correlated with PSA or the atherogenic lipid markers.

Acknowledgements

The authors are grateful to all the staff of University of Nigeria Teaching Hospital Ituku/Ozalla, Enugu, Nigeria and Department of Biochemistry, University of Nigeria Nsukka, for their assistance during the research. We also thank Dr Maduka for his contribution in drafting the manuscript.

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Source of Support: Nil
Conflict of Interest: None