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Oxidised low-density lipoprotein, a possible distinguishing lipid profile biomolecule between prostate cancer and benign prostatic hyperplasia

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Abstract

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) share common conditions such as lower urinary tract symptoms (LUTS) and dyslipidaemia. Whether an extensive lipid profile analysis could discriminate between BPH and PCa was the objective. Thirty-six (36) BPH and twenty (20) PCa outpatients of a urology clinic plus forty (40) controls without LUTS, but normal PSA, were recruited. Body mass index (BMI), lipid profile (total cholesterol [CHOL], triglycerides [TG], high-density lipoprotein [HDL], very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL] and Castelli's risk index I [CR I] [TC/HDL]), oxidised LDL, apolipoprotein E, ceramide and PSA were determined. Mean ages for BPH, PCa and control were 69 ± 13, 67 ± 10 and 53 ± 7 years respectively. Most parameters apart from BMI and HDL were significantly different compared to the control group. oxLDL for BPH versus control, PCa versus control and BPH versus PCa was significant ($p < 0.001$, $p = 0.02$ and $p < 0.001$ respectively). Ceramide showed significant group differences. Between BPH and PCa, total cholesterol, LDL and Apo E were significantly different ($p = 0.00$, $p = 0.01$ and $p = 0.03$ respectively). Apo E could potentially be a discriminating biomarker. Receiver operating characteristic curves for TPSA, Apo E and oxLDL demonstrated sensitivity of 69.44 and specificity of 88.24 for oxLDL, hence more discriminatory.

KEYWORDS

Apo E, benign prostatic hyperplasia, lipid profile, prostate cancer

1 | INTRODUCTION

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are disorders that apparently have similar clinical presentations. One common characteristic feature is lower urinary tract symptoms (LUTS) that reduces the quality of life of patients suffering from this condition. Various detection techniques have been employed in an attempt to make a clear distinction between the two conditions. Digital rectal examination (DRE) and prostate-specific antigen (PSA) have limitations and do not distinguish PCa from BPH. Histological examination of biopsies appears to be the widely used approach to distinguish BPH from PCa.

A re-consideration of some of the aetiological factors may help shed light on the need to re-examine some old and new biomarkers. Metabolic syndrome (MetS) is a common feature of the two conditions (Gacci et al., 2017; Ngai, Yuen, Ng, Cheng, & Chu, 2017). The role of lipids in the pathogenesis of BPH and PCa is also an established fact. Lipids such as cholesterol, oxidised low-density

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lipoprotein (oxLDL) and apolipoprotein E (Apo E) among others are involved in the cholesterol, high-density lipoprotein (HDL) and LDL pathway. Furthermore, some studies have associated the development of BPH and PCa to increase in cholesterol (Freeman & Solomon, 2011; Pelton, Freeman, & Solomon, 2012).

Metabolic syndrome itself is made up of various factors such as visceral adiposity, dyslipidaemia, endothelial dysfunction and insulin resistance (Kaur, 2014). These metabolic abnormalities may then promote the development of BPH and LUTS (Ngai et al., 2017). Furthermore, accumulation and faster synthesis of cholesterol in prostate cells compared to the liver have been demonstrated (Krycer & Brown, 2013).

Cholesterol is needed for cell proliferation particularly in the cell cycle progression phase (Pelton et al., 2012), while sphingolipids are known for their function as structural components of the cell membrane and its integrity (Milhas, Clarke, & Hannun, 2010). Sphingomyelins are a class of sphingolipids that are involved in intracellular signalling. The actions of these signalling molecules have also been shown to be involved in stress response, cell proliferation, survival, cell cycle arrest and autophagy (Hannun & Obeid, 2008). Ceramide, one of such sphingolipids, serves as a secondary messenger and is mostly produced from the hydrolysis of sphingomyelins by the action of sphingomyelinases (Woodcock, 2006). Furthermore, it serves as a tumour suppressor molecule. However, no study has been done to compare ceramide levels in BPH and PCa patients.

Sphingomyelinase-dependent conversion of sphingomyelin to ceramides is regarded as a preliminary signal for Apo E-mediated tissue remodelling of the damaged vasculature and in nerve injury (Morita et al., 2005). It has been shown that oxLDL increased ceramide and lactosylceramide expression leading to ceramide-rich membrane microdomains, whereas loading with enzymatically LDL (eLDL) induced sphingomyelin-/cholesterol-rich membrane microdomains (Grandl et al., 2006). Ceramide salvage pathway transcripts undergo upregulation by oxLDL (Wallner et al., 2016). The formation of cholesterol-/ceramide-rich microdomains during oxLDL loading leads to a higher cell surface binding of Apo E in contrast to the uniform affinity of Apo A-I which could contribute to impaired lipid efflux and enhancement of inflammatory processes.

Apolipoprotein E is important in cholesterol and triglyceride (TG) metabolism by serving as a receptor-binding ligand and as an intermediate in the removal of chylomicrons and VLDL cholesterol from the blood (Slattery et al., 2005). Cancer cells may depend on Apo E for cell survival in Apo E-expressing tumours (Chen et al., 2005).

Circulating lipids and apolipoproteins have been assessed for their association with the risk of cancer incidence. Apo A-I and Apo B have shown no such association with cancer incidence (Borgquist et al., 2016). A lipid signalling molecule such as Apo E constitutes majority of all cholesterol-transporting molecules in the body and has at least four known pleomorphic forms which are: E-I, E-II, E-III and E-IV (Donma & Donma, 1989). Intracellular Apo E goes through certain pathways which result in the formation of aggregates of growth signalling molecules, which increase cell survival and cell proliferation (Ifere, Desmond, Demark-Wahnefried, & Nagy, 2013). A detailed analysis of lipid profiles, using apolipoproteins, has not yet been conducted in BPH and PCa patients. The aim of the study therefore was to determine whether Apo E and other lipid profile biomarker could provide differentiation between BPH and PCa.

2 | METHODS

2.1 | Ethics

Ethics clearance was obtained from the Ethics and Protocol Review Committee of the School of Biomedical and Allied Health Sciences of the College of Health Sciences, University of Ghana. Permission was also obtained from the Korle-Bu Teaching Hospital and the Ghana Police Hospital Urology Departments. Informed consent was also obtained from participants selected for the study. Participants indicated consent by signing the consent form. The study complied with the Helsinki Declaration of 1964, with revision in October 2008.

2.2 | Experimental design

The participants in the study were 40 controls who were apparently healthy workers recruited from Korle-Bu Teaching Hospital, 20 patients who had PCa and 36 patients with BPH. However, clinical information was retrieved for only 15 out of the 36 patients with BPH and 15 out of the 20 PCa cases. The 15 BPH cases whose records were retrieved were on treatment (tamsulosin/finasteride). Fourteen (14) out of the 20 PCa cases were also on treatment (mainly chemo- [Zoladex] followed by radiotherapy). Both BPH and PCa were histologically established from prostate biopsies. Of the PCa patients, none had metastasis.

2.2.1 | Anthropometric parameters

Participants wearing light clothing and no shoes stood barefooted, knees and heels together. This was done such that the Frankfurt plane was parallel to the floor. Height was measured to the nearest 0.1 cm using a Seca stadiometer, and weight was obtained to the nearest 0.1 kg using Seca 770 scale. Body mass index was calculated using the standard equation (kilograms per metre squared). Anthropometric measurements were taken twice, and mean values were used for analyses.

2.2.2 | Lipid profile

Fasting blood samples were used for all the biochemical assays.

The VITROS cholesterol (CHOL) slide method was performed using the VITROS triglyceride, total cholesterol, high-density lipoprotein (HDL) CHOL, slides and calibrator kits on a VITROS Chemistry System. Low-density lipoprotein (LDL) was calculated using the Friedewald equation.

Apolipoprotein E, oxidised LDL and ceramide were determined by ELISA techniques. In brief, ELISA kits purchased from Sunlong

TABLE 1 Socio-demographic, anthropometric and clinical parameter analyses of the three groups of participants of the study

	BPH (*N* = 36)	PCA (*N* = 20)	CONTROL (*N* = 40)	
Parameter/units	Mean ± *SD*	Mean ± *SD*	Mean ± *SD*	*p*-value
AGE, years	69 ± 13	67 ± 10	53 ± 7	<0.001*
BMI, mmol/L	22.5 ± 3.4	24.4 ± 6.0	24.0 ± 3.8	0.474
CHOL, mmol/L	3.7 ± 0.5	4.7 ± 0.9	4.4 ± 1.0	0.004*
TG, mmol/L	1.1 ± 0.2	1.2 ± 0.3	1.7 ± 0.7	0.001*
HDL, mmol/L	1.2 ± 0.3	1.3 ± 0.4	1.1 ± 0.4	0.176
LDL, mmol/L	2.1 ± 0.4	2.8 ± 0.9	2.5 ± 0.8	0.041*
VLDL, mmol/L	0.5 ± 0.1	0.5 ± 0.2	0.8 ± 0.3	0.001*
CRI	3.4 ± 0.7	3.9 ± 1.1	4.5 ± 1.8	0.036*
oxLDL, mg/dl	0.92 ± 0.37	0.56 ± 0.16	0.58 ± 0.17	<0.001*
APO E, mg/L	31.55 ± 7.65	40.01 ± 15.4	30.95 ± 13.9	0.050*
TPSA, ng/ml	5.47 ± 2.79	0.85 ± 0.46	1.19 ± 0.58	<0.001*
Ceramide (pg/ml)	6.46 ± 1.25	7.90 ± 1.30	5.48 ± 0.64	<0.001*

Abbreviations: APO E, apolipoprotein E; BMI, body mass index; CHOL, cholesterol; CRI I, Castelli's risk index I; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *N*, sample size; oxLDL, oxidised low-density lipoprotein; TG, triglyceride; TPSA, total prostate surface antigen; VLDL, very-low-density lipoprotein.
**p*-value ≤0.05 was considered significant.

Biotech Co. Ltd. were used according to the manufacturer's instructions.

Total PSA was performed using Human PSA ELISA kits purchased from HUMAN Laboratory Diagnostics Reagents. The ELISA plate was coated with highly specific monoclonal anti-PSA antibodies, and the sandwich assay was performed according to the manufacturer's instructions.

2.3 | Statistical analysis

Statistical data were analysed using SPSS version 22. The mean ± standard deviation was calculated, after which analysis was done using one-way ANOVA to determine the statistical differences. A p-value of ≤0.05 was considered statistically significant. Post hoc analysis was used to determine the source of the statistical significance between the three groups. The relationship between serum Apo E, oxLDL, Lipid profile, PSA levels, age and BMI in PCa, BPH and control groups was determined using the Pearson's coefficient. Receiver operating characteristics for oxLDL, Apo E and TPSA were performed to determine sensitivity and specificity of individual and combined parameters.

3 | RESULTS

Age was significantly different between the prostate groups and the control (BPH = 69 ± 13; PCa = 67 ± 10; Contr = 53 ± 7 years). Age was not statistically different between the BPH and PCa groups. Body mass index was not significantly different in all three groups.

From "Table 1," most of the lipid profile parameters were significantly different with the exception of HDL. Post hoc analysis, however, revealed that cholesterol was significantly different between the two prostate groups. Cholesterol was 3.7 ± 0.5 mmol/L in the BPH group and 4.7 ± 0.9 mmol/L in the PCa group ($p = 0.00$). Triglyceride, however, was not distinctly different in BPH and PCa but significantly different in the control group ($p = 0.01$ and $p = 0.02$ respectively). Low-density lipoprotein level in the BPH group was 2.1 ± 0.4 mmol/L, while that of the PCa was 2.8 ± 0.9 mmol/L. Low-density lipoprotein level of the BPH group was slightly lower than the control group (2.5 ± 0.8 mmol/L). Significant differences were observed between the BPH and PCa groups ($p = 0.01$). Very-low-density lipoprotein differences were seen between the prostate groups and the control group only (Table 1).

Oxidised LDL was significantly different between the prostate groups and the control group. Additionally, very strong significant differences existed between the BPH (0.92 ± 0.37 mg/dl) and PCa (0.56 ± 0.16 ng/ml) groups ($p < 0.001$). CR I for BPH was 3.4 ± 0.7, and that of PCa was 3.9 ± 1.1. Both were lower than the control group (4.5 ± 1.8). However, differences between the control group and PCa were not significant. BPH CR I and the control group CR I were significantly different ($p = 0.01$). More importantly, BPH CR I and PCa CR I were highly different ($p < 0.001$; Table 1).

Apo E did not show any difference between the control and BPH groups (Table 1). However, significant differences were seen between PCa/control Apo E ($p = 0.02$) and PCa/BPH Apo E ($p = 0.03$; Table 2). The three analytes that were distinctly different between BPH and PCa groups were cholesterol, LDL and Apo E (Tables 1 and 2).

TABLE 2 Post hoc analysis of biochemical and other parameters of the control, BPH and prostate cancer groups (PCa)

	BPH	PCA
AGE		
Control	<0.001	<0.001*
BPH	–	0.67
BMI		
Control	0.34	0.75
BPH	–	0.24
CHOL		
Control	0.13	0.26
BPH	–	**0.00***
TG		
Control	0.01	0.02*
BPH	–	0.29
HDL		
Control	0.56	0.65
BPH	–	0.29
LDL		
Control	0.14	0.18
BPH	–	**0.01***
VLDL		
Control	0.01	0.02*
BPH	–	0.63
CRI		
Control	0.01	0.16
BPH	–	<0.001*
oxLDL		
Control	<0.001	0.02*
BPH	–	<0.001*
APO E		
Control	0.85	0.02*
BPH	–	**0.03***
TPSA		
Control	<0.001	0.60
BPH		<0.001*
Ceramide		
Control	0.002	<0.001*
BPH		<0.001*

Not of any significant.
Abbreviations: APO E, apolipoprotein E; BMI, body mass index; CHOL, cholesterol; CRI I, Castellis risk index I; HDL, high-density lipoprotein; LDL, low-density lipoprotein; oxLDL', oxidised low-density lipoprotein; TG, triglyceride; TPSA, total prostate surface antigen; VLDL, very-low-density lipoprotein.
*p-value ≤0.05 was considered significant.

One set of correlation that runs through all three groups is TG/VLDL from 96%–100% positive correlation with p = 0.00; HDL/CR I showed 80%–83.7% negative correlation (p = 0.00) in the three groups (Tables 3–5). Of the three discriminatory analytes between BPH and PCa (cholesterol, LDL and Apo E), cholesterol and LDL maintained a strong positive correlation in the order control > PCa > BPH (r = 0.891, r = 0.842, r = 0.803, respectively); p-values were 0.00 throughout (Tables 6–8) respectively. Apo E showed fair negative correlations for HDL (p = 0.03, r = −0.472), positive correlation for VLDL (p = 0.03, r = 0.472) and a modest positive correlation for CR I (p = 0.00, r = 0.558; Table 6). Apo E correlations occurred in the control group only. Although Apo E was seen as a discriminatory marker, it did not correlate with any of the lipid profile analytes in the PCa and BPH groups (Tables 7 and 8).

Receiver operating characteristic (ROC) curve for Apo E between BPH and PCa gave AUC of 0.523 (95% CI 0.381–0.662). Sensitivity was 47.22 and specificity 70.57. AUC was not significant (Figure 1). However, between BPH and PCa, AUC for oxLDL was 0.766 (95% CI 0.630–0.872; p = 0.001). Sensitivity and specificity were 69.44 and 88.24 respectively (Figure 2). For the Impact of TPSA on BPH and PCa, sensitivity of TPSA was 91.67 and specificity 47.06; AUC was not significant (Figure 3). Pairwise comparison of ROC for TPSA and Apo E (Figure 4), and TPSA and oxLDL (Figure 5) did not demonstrate significant AUC values. In the pairwise comparison of ROC for Apo E and oxLDL, the difference between the two AUCs was almost significant (p = 0.052; Figure 6).

4 | DISCUSSION

Lipid profile has been of importance in many disease conditions. It has been largely used for assessing dyslipidaemia, metabolic syndrome and cardiovascular diseases among others. Its role in BPH and PCa is herein being examined.

The study participants had normal BMI except for the PCa group that was slightly overweight. In a recent large case–control study involving 789 cases and 1,008 controls of African American and European men, high BMI was associated with a decreased risk to PCa development in African American men. However, high BMI participants of European American origin had a tendency of demonstrating risk to PCa development (Pichardo, Smith, Dorsey, Loffredo, & Ambs, 2018). On the contrary, Bagheri et al. examining dietary patterns and the risk of PCa demonstrated that BMI was not associated with PCa risk among Iranian men, but an unhealthy dietary pattern was (Bagheri et al., 2018).

Estimates of cancer incidence retrieved from GLOBOCAN and the Brazilian National Cancer Institute in 2012 suggest that among the 926 new PCa cases, PCa was attributable to high BMI. Furthermore, most of the cases came from rich communities (de Rezende et al., 2018). In another study, BMI values of 35 kg/m^2 and above showed an increased risk of aggressive PCa, but did not demonstrate an association between BMI and overall risk of PCa development (Bonn, Barnett, Thornquist, Goodman, & Neuhouser, 2018). Recently, it has been suggested that higher weight and BMI in early middle-aged men have an increased risk for PCa and death. However, the investigators of that study were quick to add that BMI and weight did not impact significantly on PSA levels (Assel et al., 2018).

TABLE 3 Correlation table of control subjects

Correlations	BMI	CHOL	TG	HDL	LDL	VLDL	CRI	oxLDL	APO E	TPSA
AGE										
r	0.15	−0.17	−0.20	0.17	−0.24	−0.21	−0.23	−0.29	−0.35	−0.24
p	0.46	0.40	0.33	0.40	0.23	0.34	0.27	0.23	0.10	0.30
BMI										
r	1.00	−0.38	−0.02	0.02	−0.32	−0.01	−0.24	−0.32	−0.04	0.484*
p		0.05	0.91	0.92	0.11	0.97	0.23	0.19	0.85	0.03
CHOL										
r		1.00	0.12	0.05	0.891**	0.13	0.432*	0.15	0.29	−0.22
p			0.57	0.83	0.00	0.53	0.03	0.54	0.16	0.35
TG										
r			1.00	−0.715**	0.04	1.000**	0.750**	0.25	0.39	−0.04
p				0.00	0.85	0.00	0.00	0.31	0.06	0.87
HDL										
r				1.00	−0.06	−0.711**	−0.800*	−0.486*	−0.440*	−0.19
p					0.78	0.00	0.00	0.03	0.03	0.43
LDL										
r					1.00	0.05	0.434*	0.30	0.39	−0.09
p						0.81	0.03	0.21	0.06	0.70
VLDL										
r						1.00	0.756**	0.25	0.472*	−0.04
p							0.00	0.31	0.03	0.88
CRI										
r							1.00	0.43	0.558**	−0.01
p								0.07	0.00	0.96
oxLDL										
r								1.00	0.30	−0.26
p									0.21	0.38
APO E										
r									1.00	0.09
p										0.72

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

It has been suggested that obesity may suppress tumour-associated PSA, thereby leading to a bias in diagnosis using PSA (Chow et al., 2018). Some studies conducted in Nigeria showed no correlation between anthropometrics and PCa or PSA (Ugwumba, Okoh, Echetabu, Udeh, & Nnabugwu, 2017). Similar findings asserted that overweight and obesity were common among healthy Nigerian men, but was not associated with serum total PSA levels, PCa or BPH development (Ikuerowo, Omisanjo, Bioku, Ajala, & Esho, 2012). Others found BPH volume to correlate with age but not anthropometrics, and therefore, anthropometrics was not a risk factor in developing BPH (Badmus et al., 2013). Yet, others have suggested that waist-to-hip ratio (WHR) may be a significant predictor of elevated PSA (after adjusting for age and enlarged prostate) (Ukoli et al., 2008). Further to the aforementioned body of evidence on PCa, BPH and anthropometry, our study also did not demonstrate BMI differences between patients with PCa and BPH and the control group.

Age was significantly different between PCa and BPH groups on the one hand and the control group on the other hand. However, between the PCa and BPH groups, age was not significantly different. One study among Ghanaians that stratified data of lipid profile by age seems to suggest peak values in TC and TG for men between 45 and 49 years. Thereafter, lipid profile values seem to decline significantly although that study did not capture the 65–69 age group represented in our study (Agongo et al., 2018). However, based on the aforementioned, the closeness of the ages of the PCa (67 ± 10 years)

TABLE 4 Correlation table for PCa subjects

	BMI	CHOL	TG	HDL	LDL	VLDL	CRI	oxLDL	APO E	TPSA
AGE										
r	−0.13	−0.38	−0.15	−0.16	−0.36	−0.26	−0.04	0.10	−0.30	0.31
p	0.59	0.09	0.54	0.49	0.12	0.31	0.87	0.75	0.30	0.36
BMI										
r	1.00	−0.13	0.27	0.02	−0.20	0.35	−0.15	−0.19	−0.33	−0.51
p		0.58	0.29	0.94	0.41	0.16	0.53	0.54	0.25	0.11
CHOL										
r		1.00	0.32	0.37	0.842**	0.29	0.10	−0.16	−0.18	−0.06
p			0.19	0.11	0.00	0.26	0.67	0.62	0.54	0.86
TG										
r			1.00	−0.02	0.24	1.000**	0.15	−0.16	−0.15	−0.26
p				0.93	0.34	0.00	0.55	0.64	0.61	0.44
HDL										
r				1.00	0.08	−0.10	−0.837**	0.08	0.03	−0.27
p					0.74	0.71	0.00	0.81	0.91	0.42
LDL										
r					1.00	0.17	0.27	0.02	−0.09	0.13
p						0.52	0.25	0.95	0.75	0.71
VLDL										
r						1.00	0.22	−0.17	−0.22	−0.25
p							0.40	0.62	0.46	0.45
CRI										
r							1.00	−0.02	0.02	0.28
p								0.94	0.95	0.41
oxLDL										
r								1.00	0.25	0.57
p									0.46	0.14
APO E										
r									1.00	−0.28
p										0.47
TPSA										
r										
p										

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

and BPH (69 ± 13 years) groups in this study may not impact significantly on differences in their lipid levels.

Alterations in fatty acids and sphingomyelin in human BPH and PCa have been suggested. Enzymatic activities appear to be responsible for these alterations in sphingomyelin levels between BPH and PCa tissues. Arachidonic acid level was significantly reduced in PCa tissues compared to BPH tissues (Narayan & Dahiya, 1991). In this study, ceramide, a sphingomyelin, was significantly higher in BPH and PCa groups compared to the controls, but was not a distinguishing marker between the two conditions compared to cholesterol and LDL. In another study, patients with PCa had lower total cholesterol and HDL values and higher TG/HDL than those with BPH and controls (Grosman et al., 2010). BPH patients in this study were on finasteride or dutasteride therapy as the normal clinical line of treatment. These have been reported to increase total cholesterol levels with long-term use but decrease HDL cholesterol (Doulabi, Kavoussi, Isapour, Hashemian, & Taheriniya, 2013). In a study of 460 men, half were treated with dutasteride (Avodart) and the other with tamsulosin (Flomax). After 36- to 42-month follow-up, dutasteride was associated with LDL increases while tamsulosin showed both LDL and HDL increases but in a smaller proportion (Traish, Haider, Doros, & Haider, 2017). In this study however, cholesterol was lower in the BPH group than the PCa and control groups. Perhaps some of the patients may have

TABLE 5 Correlation table of BPH subjects

Correlations	BMI	CHOL	TG	HDL	LDL	VLDL	CRI	oxLDL	APO E	TPSA
AGE										
r	−0.39	−0.29	−0.30	−0.11	−0.21	−0.23	−0.14	−0.38	0.09	−0.71
p	0.15	0.29	0.27	0.71	0.46	0.40	0.61	0.32	0.79	0.07
BMI										
r	1.00	0.45	0.26	−0.04	0.518*	0.34	0.32	0.09	−0.14	−0.12
p		0.09	0.35	0.89	0.05	0.21	0.25	0.82	0.67	0.80
CHOL										
r		1.00	0.679**	0.43	0.803**	0.741**	0.10	−0.15	−0.05	0.70
p			0.01	0.11	0.00	0.00	0.71	0.70	0.87	0.08
TG										
r			1.00	0.16	0.46	0.961**	0.28	−0.41	−0.21	0.21
p				0.57	0.08	0.00	0.32	0.28	0.51	0.66
HDL										
r				1.00	−0.05	0.07	−0.837**	0.16	0.26	0.05
p					0.86	0.80	0.00	0.69	0.41	0.92
LDL										
r					1.00	0.564*	0.50	0.08	0.13	0.70
p						0.03	0.06	0.83	0.69	0.08
VLDL										
r						1.00	0.38	−0.54	−0.34	0.13
p							0.16	0.13	0.29	0.77
CRI										
r							1.00	−0.17	−0.31	0.37
p								0.66	0.32	0.41
oxLDL										
r								1.00	−0.06	−0.07
p									0.78	0.84
APO E										
r									1.00	−0.20
p										0.50

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

been on cholesterol-lowering drugs as some of them suffered from hypertension.

In a study to determine the association of metabolic indices, lipid profile and androgen levels in patients with PCa, cholesterol, TG and LDL were significantly higher in the PCa group compared to the BPH group (Tewari et al., 2014). Similar significant difference was observed in this study. One possible explanation for this phenomenon with PCa patients is the use of medication such as cholesterol-lowering drugs which leads to a 50% lower mortality rate among PCa patients (Platz et al., 2006). Using red bone marrow, it was demonstrated that cancer cells migrate towards adipocytes (Clarke & Brown, 2007). Furthermore, it has been postulated that PCa cells may have a higher uptake of lipids as its energy source for development and progression (Clarke, Hart, & Brown, 2009). Lipid accumulation and lipid composition programming have been associated with lipogenesis, phospholipid remodelling and lipid uptake.

Another medication that could have created confounding factors is Zoladex. Zoladex is a chemotherapeutic drug used to reduce the PSA level (to <4.0 ng/ml) before the commencement of radiation therapy. PCa patients in this study were administered Zoladex. Its use is known to increase HDL sub-fraction three levels in patients suffering from endometriosis (Crook et al., 1989). However, its effect on HDL levels of PCa patients remains unknown. Nonetheless, HDL levels in this study remained relatively unchanged in all groups.

Apo E is mainly synthesised in the liver and is associated not only with VLDL particles but also with the protein portion of many plasma

TABLE 6 A summary of very strong, strong and moderate correlations found in the control group

Group	Analyte	r-value	p-value
Control	TG/VLDL	1.000	0.00
	TG/HDL	−0.715	0.00
	CHOL/LDL	0.891	**0.00**
	VLDL/HDL	−0.711	0.00
	TG/CRI I	0.750	0.00
	HDL/CRI I	−0.800	0.00
	VLDL/CRI I	0.756	0.00
	CHOL/CRI I	0.432	0.03
	LDL/CRI I	0.434	0.03
	HDL/oxLDL	−0.486	0.03
	CRI I/oxLDL	0.43	0.07
	HDL/APO E	−0.440	0.03
	VLDL/APO E	0.472	0.03
	CRI I/APO E	0.558	0.00
	BMI/TPSA	0.484	0.03

Not of any significant.

TABLE 7 A summary of very strong, strong and moderate correlations found in the BPH group

Group	Analyte	r-value	p-value
BPH	TG/VLDL	0.961	0.00
	CHOL/TG	0.679	0.01
	CHOL/LDL	0.803	**0.00**
	CHOL/VLDL	0.741	0.00
	HDL/CRI I	−0.837	0.00
	AGE/TPSA	−0.71	0.07
	CHOL/TPSA	0.70	0.08
	LDL/TPSA	0.70	0.08
	BMI/CHOL	0.45	0.09
	CHOL/HDL	0.43	0.11
	BMI/LDL	0.518	0.05
	TG/LDL	0.46	0.08
	LDL/VLDL	0.564	0.03
	LDL/CRI I	0.50	0.06
	TG/oxLDL	−0.41	0.28
	VLDL/oxLDL	−0.54	0.13

Not of any significant.

TABLE 8 A summary of very strong, strong and moderate correlations found in the PCa group

Group	Analyte	r-value	p-value
Prostate cancer	TG/VLDL	1.000	<0.001
	CHOL/LDL	0.842	0.00
	HDL/CRI I	−0.837	0.00
	BMI/TPSA	−0.51	0.11
	oxLDL/TPSA	0.57	0.14

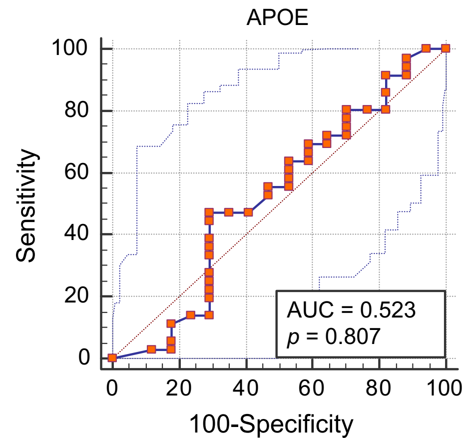

FIGURE 1 Impact of Apo E on BPH and PCa. The blue dashed line represents the theoretical perfect performance of an ideal marker. The red diagonal line is the theoretical performance of an ideal marker equivalent to the identity line. The prominent curve is the actual performance of the result. For receiver operating characteristic (ROC) curve for Apo E between BPH and PCa, AUC = 0.523 (95% CI 0.381–0.662). Sensitivity was 47.22 and specificity 70.57. The Youden index (*J*) was 0.1781. AUC was not significant. Thus, from a diagnostic perspective Apo E represents low accuracy

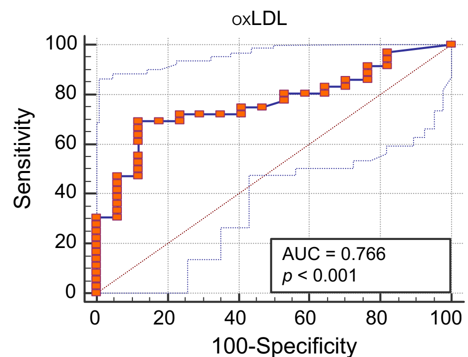

FIGURE 2 Impact of oxLDL on BPH and PCa. The blue dashed line represents the theoretical perfect performance of an ideal marker. The red diagonal line is the theoretical performance of an ideal marker equivalent to the identity line. The red dotted line is the actual performance of the result. Receiver operating characteristic (ROC) curve for oxLDL between BPH and PCa. AUC = 0.766 (95% CI 0.630–0.872). Sensitivity was 69.44 and specificity 88.24. The Youden index (*J*) was 0.5768. AUC was significant $p = 0.001$. Thus, from a diagnostic perspective oxLDL represents good accuracy

lipoproteins such as chylomicrons, IDL and HDL. However, only a small fraction is found in LDL. A major function of Apo E is related to the clearance of Apo B-containing remnants. Furthermore, it plays an important role in HDL metabolism and reverse cholesterol transport, whereby excess cholesterol is removed from peripheral tissues and into liver. Some studies seem to suggest an association of various polymorphisms of Apo E with PCa and BPH. In one study, higher values of LDL and HDL were found with PCa compared to BPH patients

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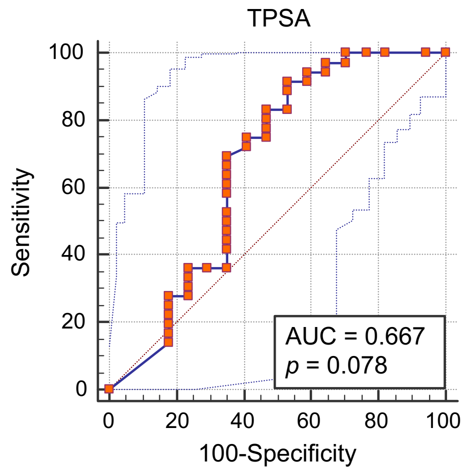

FIGURE 3 Impact of TPSA on BPH and PCa. The blue dashed line represents the theoretical perfect performance of an ideal marker. The red diagonal line is the theoretical performance of an ideal marker equivalent to the identity line. The red dotted line is the actual performance of the result. The receiver operating characteristic (ROC) curve for TPSA between BPH and PCa, AUC = 0.667 (95% CI 0.524–0.790). Sensitivity was 91.67 and specificity 47.06. The Youden index (*J*) was 0.3873. AUC was not significant. Thus, from a diagnostic perspective TPSA represents poor accuracy

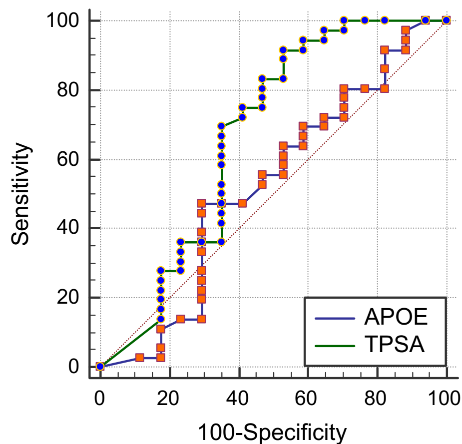

FIGURE 4 Pairwise comparison of ROCs of TPSA and Apo E: the ROC curve crosses each other at the lower sensitivity and specificity. From the baseline (the identity line), each biomarker shows the overall ability of predicting the disease condition. However, TPSA AUC of 0.667 (CI 0,524–0.790) has a better diagnostic capability compared to Apo E AUC 0.523 (CI 0.381–0.662), using 67.92% positive cases and 36.08% negative cases (control)

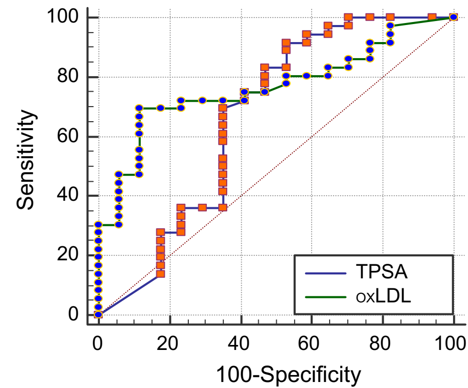

FIGURE 5 Pairwise comparison of ROC of TPSA and oxLDL. From the baseline (the identity line), each biomarker shows the overall ability of predicting the disease condition. However, oxLDL AUC of 0.0.766 (CI 0,630–0.872) has a better diagnostic capability compared to TPSA AUC of 0.667 (CI 0,524–0.790), using 67.92% positive cases and 32.08% negative cases. Pairwise CI −0,132 to 0.331; the difference between the two AUCs was not significant (*p* = 0.398)

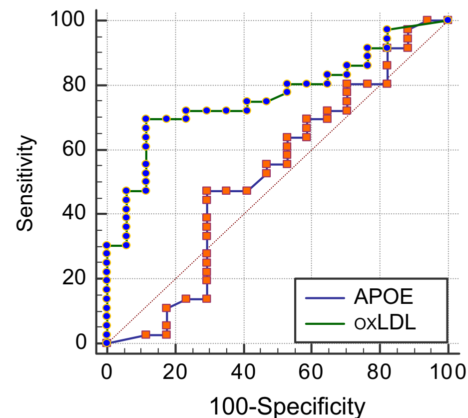

FIGURE 6 Pairwise comparison of ROC of Apo E and oxLDL. The ROC curve appears to display the same pattern. From the baseline (the identity line), each biomarker shows the overall ability of predicting the disease condition. However, oxLDL of 0.766 (CI 0.630–0.832) has a better diagnostic capability compared to Apo E AUC 0.523 (CI 0.381–0.662), using 67.92% positive cases and 32.08% negative cases. Pairwise CI −0.00225 to 0.489; the difference between the two AUCs was almost significant (*p* = 0.052)

but no significant difference was observed with TG. Furthermore, for PCa patients, HDL and LDL were higher in the E3 and E4 allele groups compared with BPH patients (Niemi et al., 2000).

From a diagnostic perspective, ROCs for Apo E demonstrated low sensitivity (47.22%) but high specificity (70.57%; Figure 1). However, TPSA demonstrated high sensitivity (91.67%) and low specificity (47.06%). AUC for both markers in relation to PCa and BPH was not significant. From a diagnostic perspective, the two markers had low diagnostic accuracy to discriminate between PCa and BPH. However, oxLDL AUC was 0.766 (95% CI 0.630–0.872), with 69.44% sensitivity and 88.24% specificity (Figure 2). TPSA and Apo E, TPSA and oxLDL, and Apo E and oxLDL (Figures 4–6) did not show significant differences after pairwise comparison of their ROCs. Thus, from a diagnostic point of view, oxLDL represents good accuracy. Not many studies have been done on oxLDL and BPH. oxLDL through a similar mechanism involving signal transduction is hypothesised to stimulate abnormal cell growth of the prostate leading to BPH (Nandeesha, 2008). oxLDL receptor expression influences multiple signalling

pathways. Additionally, it is associated with the activation of proteins involved in proliferation (including β-catenin, cMyc, NF-κB, STAT1 and STAT3) and apoptosis (including p27 and caspase-3). A combination of high serum oxLDL and its receptor expression is suggestive of lymph node and advanced-stage PCa (Wan et al., 2015).

In nude mice experiments, lectin-like oxidised LDL receptor-1 (LOX-1), which is activated by oxLDL, potentiated tumorigenicity of PCa cells and its expression. The researchers concluded that oxLDL and LOX-1 could possibly explain why obese people have an accelerated tumour expression in PCa (González-Chavarría et al., 2018). Further to this, the relationships between prostate size and the degree of chronic inflammation induced by local arteriosclerosis were examined and the pathogenesis of this association was attributed to LOX-1, inducing infiltration of macrophages in prostatic arteries (Haga et al., 2019).

Several other biomarkers have been proposed with the view of discriminating between BPH and PCa as well as predicting PCa staging. PCA3 protein found in urine is as a result of the overexpression of PCA3 gene found in PCa tissue (Bussemakers et al., 1999). PCA3 is totally absent in normal tissues and tumours from other organs and therefore serves as a useful biomarker demonstrating good sensitivity and specificity using ROC and logistic regression analysis (Filella et al., 2013). [−2] proPSA is one of the seven isoforms of PSA. The malignant prostate epithelium is where it originates, especially in the periphery zone where most cancers develop (Mikolajczyk et al., 2001). This therefore is a marker for the early detection of PCa. (Guazzoni et al., 2012) and has been incorporated into the prostate health index (PHI) by a mathematical equation [PHI = (p2PSA/fPSA) × (square root of PSA)]. PHI and %p2PSA may be a potential tool in detecting PCa and also providing Gleason score differentiation (Vukovic, Djordjevic, Bojanic, Babic, & Soldatovic, 2017).

The four-kallikrein panel is a combination of total PSA, fPSA, iPSA and human kallikrein 2. Kallikrein 2 is a glycoprotein with high homology to PSA and the test panel is a combination of patient age, history and DRE, all formed into an algorithm before biopsy. The panel calculates the patient's risk for high-grade PCa (Filella & Foj, 2015). For several microarray biomarkers of PCa, only a few have been tested in large studies and found appropriate. miR-16, miR-148a and miR-195 in plasma were found to be significantly related to a Gleason score ≥ 8, and therefore, miRNAs may differentiate between intermediate- and high-risk Gleason scores (Al-Qatati et al., 2017).

From the aforementioned, it is obvious that the first laboratory/clinical objective will be to have a highly specific and sensitive marker that will differentiate PCa from BPH. Additionally, PCa differentiation and grading will reduce biopsies and produce better patient management outcome. It is hereby concluded that the potential of oxLDL as a discriminatory marker between PCa and BPH could be further explored.

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CONFLICT OF INTEREST

None of the authors declare competing financial interest.

AUTHORS CONTRIBUTION

GAA conceptualised the project and wrote the paper. EO-B and EE collected and analysed samples. BA performed the statistical analysis. BYA assisted with sample collection and proofreading of manuscript; RO collected samples. All authors edited the manuscript.

DATA ACCESSIBILITY

Data are available upon request.

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