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Original Article

Lipid associated antioxidants: arylesterase and paraoxonase-1 in benign prostatic hyperplasia treatment-naïve patients

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ABSTRACT

Background: Oxidative stress and antioxidants have been implicated in many diseases including prostate cancer and benign prostatic hyperplasia (BPH). Lipid peroxidation contributes to oxidative stress. However, new and emerging antioxidants such as paraoxonase 1 (PON1) and arylesterase (ARE) associated with lipoprotein peroxidation have not been examined in BPH patients. PON1 and ARE, a high-density lipoprotein (HDL) cholesterol-bound enzyme system of antioxidants, protect low-density lipoprotein (LDL) cholesterol and HDL from oxidation by hydrolysis. The study primarily determined paraoxonase (PON1) and ARE activities in BPH treatment-naïve patients.

Materials and methods: Sixty newly diagnosed patients (treatment-naïve) alongside 30 apparently healthy controls were recruited. Blood examinations included lipid profile (total cholesterol, triglycerides, LDL, HDL), glutathione peroxidase, PON1, ARE, and prostate specific antigen (PSA).
Prostate volume and International Prostate Symptoms Score (IPSS) were determined.

Results: PSA was significantly different between patient and control groups ($P < 0.0001$). Total cholesterol, triglycerides, and LDL were significantly higher in the patient group ($P = 0.002$, $P < 0.001$, $P = 0.003$, respectively). Glutathione peroxidase was very low in the patient group compared to the control group (5.65 ± 2.30 ng/mL and 17.43 ± 10.98 ng/mL, respectively). Although PON1 was higher in the patient group (50.22 ± 19.68/61.30 ± 29.55 ng/mL; $P > 0.05$), ARE was significantly lower in the patient group (61.31 ± 21.76/49.30 ± 19.82 ng/mL; $P = 0.0098$). No correlation was established between antioxidants and the lipid profile except for the LDL and PON1 patient group ($r = 0.1486$, $P = 0.0374$). Similarly, a weak correlation was also established between PSA and LDL in the patient group ($r = -0.275$, $P = 0.033$). PON1/HDL ratio was not significantly different. However, the ARE/HDL ratio was significantly lower in the patient group ($P < 0.0001$).

Conclusion: These results signify the presence of a higher lipoprotein peroxidation activity and lower lipid-associated antioxidant activity in the patient group. The ARE/HDL ratio is a better indicator of the HDL associated antioxidant than the PON1/HDL ratio or the individual antioxidants (PON1 and ARE) as reported by others.

1. Introduction

Benign prostatic hyperplasia (BPH) is a prevalent and chronic progressive disease of ageing men and carries a distressingly high poor quality of life (QoL) because of its irritating and obstructive symptoms. It is a noncancerous enlargement of the prostate as a result of hyperproliferation of stromal, glandular, and mesenchymal cells[1] and the imbalance in prostatic stroma-epithelium interaction.[2] Although it is rarely fatal, it affects the QoL of the aged. This condition accounts for 80% of prostate disorders worldwide. Much focus on its management in the past has been on androgens as a risk factor for BPH development. The conversion of testosterone to estradiol is achieved by aromatase. Aromatase is a CYP450 enzyme which is found in increased amounts in obesity.[3]

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This will potentially increase the estrogen/androgen ratio, which may ultimately lead to BPH development. However, the role of lipids in BPH pathogenesis is beginning to gain attention.[4]

ω-6-Fas, which is largely found in animals, is a risk factor associated with BPH.[5] The link between insulin-resistance, obesity, and BPH is also prompting interest in the role of lipids in the etiology of BPH. It has been suggested that low-density lipoprotein (LDL) cholesterol is a risk factor for BPH development in diabetic men.[6] Other population-based studies have demonstrated no relationship between serum lipid levels and BPH.[7]

Although the etiology of BPH is not well understood, it has been hypothesized that BPH is an immune-mediated inflammatory disease and inflammation may directly contribute to the prostate growth.[8] Other factors such as genetic,[9] hormonal,[10] environmental (diet),[11] metabolic syndrome[12], and oxidative stress have been implicated.[13]

Oxidative stress occurs when there is an imbalance between the production and detoxification of reactive oxygen species (ROS) causing tissue damage which is further aggravated under hypoxia.[14] In the case of inflammation, the production of ROS is elevated and can exhaust the antioxidative protection system[15] leading to depletion of the antioxidant defense system. Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), paraoxonase 1 (PON1), and arylesterase (ARE) are important enzyme antioxidants responsible for detoxifying ROS.

PON1 and ARE are a high-density lipoprotein (HDL)-bound enzyme system of antioxidants which protect LDL and HDL from oxidation by hydrolysis, thereby preventing atherosclerosis.[16] The name PON1 was derived from the observation of the detoxification of paraoxone, a xenobiotic toxicant.[17] The detoxification of lipid peroxides by PON1 is possibly through its ARE activity and this is also described as a calcium-dependent esterase/lactonase. The role of these lipids and their associated antioxidants is being examined. The aim of this study was to determine paraoxonase (PON1) and ARE activities, lipid profile, and oxidative damage in BPH treatment-naïve patients.

2. Material and methods

2.1. Study design

Ethics approval was obtained from the Ethics and Protocol Review Committee of the School of Biomedical and Allied Health Sciences with Ethics number SAHS-ET/SAHS/PSM/ML/09/AA/26A/2012-2013. Furthermore, approval was sought from the Police Hospital administration. Informed consent was also sought from all participants whose information and samples were used. The study complied with the Helsinki Declaration of 1964, with revision in October 2008.

The study was a prospective study involving 60 BPH treatment-naïve patients and 30 apparently healthy controls. Patients were recruited from the Urology Department of the Ghana Police Hospital which serves Police Officers and their families, other security personnel, and civilians. Patients were examined by the urologist and histologically diagnosed as having BPH. Controls were screened using the prostate specific antigen (PSA) test. Digital Rectal Examination (DRE) and urodynamic studies were not performed as it is not the routine. The International Prostate Symptoms Score (IPSS) was also used to determine the QoL. Controls were screened using the PSA test only.

2.2. IPSS determination

The IPSS is structured on the answers to seven questions concerning urinary symptoms and one question concerning QoL. Each question concerning symptoms in passing urine allowed the patient to choose one out of six answers which represents increasing severity of a particular symptom. The answers were assigned points from 0 to 5, with 5 signifying worsening symptoms. The total score therefore ranged from 0 to 35 (asymptomatic to very symptomatic). The symptoms were graded as follows: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. The eighth question dealt with the patient's perceived QoL and was scored 0–6, which were graded as: delighted, pleased, mostly satisfied, mixed—about equally satisfied and dissatisfied, mostly dissatisfied, unhappy, and terrible in the increasing order of severity, indicating poor QoL.

2.3. Histological diagnosis of BPH

Standard surgical procedures for taking biopsies were employed. Prostate biopsies were immediately fixed in 10% buffered formaldehyde solution. Tissues were histologically processed using standard protocols. Three micrometer sectioned slides of prostate were hematoxylin and eosin stained and evaluated microscopically by competent pathologists for histological changes using an Olympus BX 51TF (Olympus Corporation; Tokyo, Japan) light microscope and reported accordingly as requested by the urologist. Patients proven positive histologically and willing to be part of the study were recruited.

2.4. Blood sample collection

Blood samples were obtained following an overnight fasting state. Venous blood samples (3 mL) were collected from the antecubital vein of each individual participant into a gel separator tube. Samples were centrifuged at 3,000 rpm for 5 minutes, separated and stored at −20°C until ready for use.

2.5. Biochemical analysis of antioxidants

Serum levels of SOD, GSH-Px, PON1, and ARE were determined for all samples and controls using enzyme linked immunosorbent assay (ELISA) kits (specific for each enzyme) obtained from Sun-Long Biotech Co., Ltd, Zhejiang, China. PSA was determined using an Accu-Bind ELISA kit obtained from Monobind Inc. (North Pointe, Lake Forest, CA, USA). The Vitros Chemical Analyser (version 5.1 FS, Raritan, New Jersey, USA) and reagents were used for the lipid profile determination.

2.5.1. Measurement of PSA

The tests were performed using human PSA kits (Wiesbaden, Germany) according to the manufacturer's instructions. Serum samples were added alongside standards to the streptavidin-coated wells. Biotinylated highly specific monoclonal PSA antibody was then added. After mixing, the resultant reaction between the serum antigen and antibodies formed a soluble sandwich complex immobilized on the surface of the well. After incubation, decantation, and washing, tetramethylbenzidine/hydrogen peroxide (substrate) was added to react with the complex after which the reaction was stopped with 1N HCl solution. The final chromogen was read at 450 nm using the Multiskan MS microplate reader (Bradenton, FL, USA). The enzyme activity was directly proportional to the serum antigen concentration. By utilizing reference standards, a curve was generated from which the antigen concentrations of the samples were determined.

2.5.2. Measurement of antioxidants (SOD, GSH-Px, PON1, and ARE)

The tests were performed according to the manufacturer's instructions. Serum samples were added alongside standards to an antibody precoated well specific for SOD, GSH-Px, PON1 or ARE.

The procedure was the same as the above described for PSA determination.

2.5.3. Lipid profile analysis

Total cholesterol, triglyceride, HDL, and LDL were analyzed using the Vitros system auto-analyzer (version 5.1 FS, Raritan, New Jersey, USA). The Vitros system analyzer uses a multilayered analytical element coated on a polyester support (spreading layer, reagent layer, and support layer) on which the reactions occur to form a colored dye. The intensity of the dye formed was proportional to the analyte concentration present in the sample.

2.6. Statistical data analysis

All the data for the biochemical analysis were processed using GraphPad Prism version 6.01 (La Jolla, California, USA) for statistical analysis. Means and standard deviations were determined under the XY data analysis option and the column data analysis option was used to establish the significance of the biochemical analytes. Student *t* test was used for unpaired data. Pearson's correlation test within the column analysis option was used to establish a relationship between the antioxidants and lipids level. Multivariate analysis was performed to determine the association between PSA and prostate volume against all other parameters. A P value < 0.05 was considered significant.

3. Results

The control group's age was 51.90 ± 10.11 years versus 65.84 ± 10.40 years for the patient group ($P < 0.0001$), and PSA was 1.51 ± 0.60 ng/mL versus 12.66 ± 7.06 ng/mL for the patient group ($P < 0.0001$). GSH-Px in the control and patient groups was 17.43 ± 10.98 ng/mL and 5.65 ± 2.30 ng/mL, respectively ($P < 0.0001$) (Table 1). PON1, an HDL associated antioxidant, was significantly different for the control and patient groups; 61.31 ± 21.76 ng/mL versus 49.30 ± 19.82 ng/mL ($P < 0.0098$). However, HDL was not significantly different between the patient and control groups. The rest of the lipid profile parameters (total cholesterol, triglycerides, and LDL) showed significant differences between control and patient groups ($P < 0.0022$; $P < 0.001$; $P < 0.0033$, respectively) (Table 2). There was no correlation between the individual antioxidants and the lipid profile parameters (Tables 2–5) except for LDL and PON1 (Table 6). Similarly, PSA did not correlate with any of the antioxidants (Table 7). However, PSA correlated negatively with LDL in the patient group ($r = -0.2758$, $P = 0.030$) (Table 8). Antioxidants associated with HDL showed a significant difference for the ARE/HDL ratio between control and patient group (122.00 ± 66.03 vs. 58.79 ± 35.10) ($P < 0.0001$) (Table 9). There was no correlation between ARE/HDL, PON1/HDL, and prostate volume as well as IPSS (Table 10). Mean prostate volume was 102.5 ± 48.6 cm^3 for the BPH group, while IPSS was significantly different between the control and BPH group ($P < 0.0001$) (Table 11). Multivariate analysis did not show any association except for a negative correlation between PSA and LDL in the patient group ($P = 0.0300$, $r = -0.2758$) (Table 12). Further analysis between prostate volume and other analytes did not show any association.

Table 1
Table showing mean age, prostate specific antigen (PSA) and antioxidant levels of patient and control groups.

Parameter	Mean ± SD Control	Mean ± SD Patient	*P*
Age (yr)	51.90 ± 10.11	65.84 ± 10.40	< 0.0001*
PSA (ng/mL)	1.51 ± 0.60	12.66 ± 7.06	< 0.0001*
SOD (pg/mL)	675.10 ± 262.40	597.60 ± 258.50	0.1836
GSH-Px (ng/mL)	17.43 ± 10.98	5.65 ± 2.30	< 0.0001*
ARE (ng/mL)	61.31 ± 21.76	49.30 ± 19.82	0.0098*
PON1 (ng/mL)	50.22 ± 19.68	61.30 ± 29.55	0.0660

*Significant p-value.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase; SD, standard deviation.

Table 2
Table showing lipid profile of patient and control groups.

Parameter	Mean ± SD Control	Mean ± SD Patient	*P*
TC (mmol/L)	3.71 ± 1.38	4.92 ± 1.44	0.0022*
TG (mmol/L)	0.96 ± 0.51	1.48 ± 0.56	< 0.001*
HDL (mmol/L)	0.68 ± 0.37	0.61 ± 0.26	0.3265
LDL (mmol/L)	2.59 ± 1.50	3.61 ± 1.50	0.0033*

*Significant p-value.
HDL, high-density lipoprotein; LDL, low-density lipooprotein; SD, standard deviation;TC, total cholesterol; TG, triglycerides.

Table 3
A correlation between total cholesterol (TC) and the individual antioxidants.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	0.2740	−0.1076	0.1429	0.4064
GSH-Px (ng/mL)	0.0535	−0.0166	0.7788	0.8983
ARE (ng/mL)	0.1152	−0.0631	0.5444	0.6261
PON1 (ng/mL)	0.1824	0.1970	0.3346	0.1249

R is the statistical language for correlation co-efficient.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase.

Table 4
A correlation between triglycerides (TG) and the individual antioxidants.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	0.2202	−0.0737	0.2424	0.5692
GSH-Px (ng/mL)	−0.0985	−0.0759	0.6045	0.5576
ARE (ng/mL)	0.0441	−0.0793	0.8172	0.5399
PON1 (ng/mL)	−0.0724	0.0553	0.7037	0.6695

R is the statistical language for correlation co-efficient.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase.

Table 5
A correlation between high density lipoproteins (HDL) and the individual antioxidant.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	−0.2661	0.2721	0.1552	0.2735
GSH-Px (ng/mL)	0.0034	−0.0624	0.7608	0.0958
ARE (ng/mL)	−0.1963	0.0008	0.2985	0.7947
PON1 (ng/mL)	0.1856	−0.3643	0.3261	0.2650

R is the statistical language for correlation co-efficient.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase.

Table 6
A correlation between low density lipoproteins (LDL) and the individual antioxidant.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	0.2626	0.0318	0.1610	0.2385
GSH-Px (ng/mL)	0.0813	0.2315	0.6694	0.7561
ARE (ng/mL)	0.1500	−0.0711	0.4288	0.5712
PON1 (ng/mL)	0.1686	0.1486	0.3733	0.0374*

R is the statistical language for correlation co-efficient.
*Significant p-value.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase.

Table 7
A correlation between prostate specific antigen (PSA) and the individual antioxidant.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	0.0646	0.0471	0.7345	0.7162
GSH-Px (ng/mL)	−0.0637	−0.1093	0.7380	0.3978
ARE (ng/mL)	0.0987	0.0247	0.6039	0.8492
PON1 (ng/mL)	0.3534	−0.1109	0.0554	0.3909

R is the statistical language for correlation co-efficient.
ARE, arylesterase; GSH-Px, glutathione peroxidase; PON1, paraoxonase 1; SOD, superoxide dismutase.

Table 8
A correlation between prostate specific antigen (PSA) and the individual lipids.

Parameter	R Control	R Patient	*P* Control	*P* Patient
TC (mmol/L)	0.3101	−0.1418	0.0954	0.2717
TG (mmol/L)	−0.0804	0.1926	0.6728	0.1338
HDL (mmol/L)	−0.1570	0.2249	0.4073	0.0788
LDL (mmol/L)	0.3496	−0.2758	0.0583	0.0300*

R is the statistical language for correlation co-efficient.
*Significant p-value.
HDL, high-density lipoprotein; LDL, low-density lipooprotein; TC, total cholesterol; TG, triglycerides.

Table 9
Ratio between HDL related antioxidants (ARE, PON1) and HDL.

Parameter	Mean ± SD Control	Mean ± SD Patient	*P*
ARE/HDL	122.00 ± 66.03	58.79 ± 35.10	< 0.0001*
PON1/HDL	73.85 ± 42.54	100.49 ± 69.77	0.2886

*Significant p-value.
ARE, arylesterase; HDL, high-density lipoprotein; PON1, paraoxonase 1.

Table 10
Correlation between ARE/HDL, PON1/HDL ratios and prostate volume and IPSS.

Parameter	R Control	R Patient	*P* Control	*P* Patient
ARE/HDL vs. IPSS	−0.1256	−0.3455	0.6085	0.1474
PON1/HDL vs. IPSS	−0.0913	0.1712	0.7099	0.4833
ARE/HDL vs. Prostate volume	–	0.2627	–	0.2773
PON1/HDL vs. Prostate volume	–	−0.1950	–	0.4238

R is the statistical language for correlation co-efficient.
ARE, arylesterase; HDL, high-density lipoprotein; IPSS, International Prostate Symptoms Score; PON1, paraoxonase 1.

Table 11
Clinical parameters of patients and control.

Parameter	Mean ± SD Control	Mean ± SD Patient	*P*
IPSS	4.17 ± 2.21	15.10 ± 8.74	< 0.0001*
Prostate volume (mL)	–	102.5 ± 48.6	–

*Significant p-value.
IPSS, International Prostate Symptoms Score.

Table 12
Relationship between prostate specific antigen (PSA) and the individual analytes.

Parameter	R Control	R Patient	*P* Control	*P* Patient
SOD (pg/mL)	0.0646	0.0471	0.7345	0.7162
GSH-Px (ng/mL)	−0.0637	−0.1093	0.7380	0.3978
ARE (ng/mL)	0.0987	0.0246	0.6039	0.8492
PON1 (ng/mL)	0.3534	−0.1109	0.0554	0.3909
TC (mmol/l)	0.3101	−0.1418	0.0954	0.2717
TG (mmol/l)	−0.0804	0.1926	0.6728	0.1338
HDL (mmol/l)	−0.1570	0.2249	0.4073	0.0788
LDL (mmol/l)	0.3496	−0.2758	0.0583	0.0300*
ARE/HDL	0.1195	−0.1472	0.5293	0.2535
PON1/HDL	0.3410	−0.1764	0.0652	0.1703
Prostate vol (mL)	–	0.2897	–	0.2290
IPSS	−0.2921	−0.1338	0.2249	0.5849

R is the statistical language for correlation co-efficient.
*Significant p-value.
ARE, arylesterase; GSH-Px, glutathione peroxidase; HDL, high-density lipoprotein; IPSS, International Prostate Symptoms Score; LDL, low-density lipooprotein; PON1, paraoxonase 1; SOD, superoxide dismutase; TC, total cholesterol; TG, triglycerides.

4. Discussion

A total of 60 BPH patients and 30 controls were recruited in this study with a mean of 65.84 ± 10.40 years and 51.90 ± 10.11 years for patients and controls, respectively. There was a significant difference between the QoL of the BPH group and the controls. It was observed that the PSA was significantly lower in the controls, and GSH-Px and ARE levels were significantly higher in the control group than in the patient group with $P < 0.0001$, $P < 0.0001$, and $P = 0.0098$, respectively.

A key indicator of the presence of oxidative stress is the reduction in antioxidants. Under the two broad spectrums of enzyme and vitamin antioxidants, it is envisaged that while genetic factors such as polymorphisms can affect enzyme antioxidants, environmental factors affect the level of vitamin antioxidants; hence, the different presentations of antioxidant effects in BPH according to different people groups. Although SOD levels were lower in the controls than patients, the change was rather insignificant. Similar insignificant SOD changes in BPH patients have been reported by others.[18] On the contrary, a study conducted to investigate the oxidative stress indicators in patients with prostate disorders reported significant lower GSH-Px and SOD levels in patients.[19] The role of antioxidants in BPH development does not appear to be clear due to conflicting observations from other studies.

In this study, antioxidants associated with lipids such as GSH-Px and PON1 and their effect on the lipid profile in BPH patients and controls were studied. GSH-Px is part of the enzymes in the redox cycle responsible for the reduction of hydrogen peroxide and lipid hydroperoxides that are generated as a result of membrane lipid peroxidation,[20] which has a cascading effect in increasing ROS. GSH-Px reduction has also been demonstrated in the erythrocytes and plasma of BPH patients.[21,22] Furthermore reduced GSH-Px has been associated with a concomitant increase in lipid peroxidation.[21] The role of lipids in the etiology of BPH is beginning to gain momentum. Lipids have always served as a good platform for the promotion of lipid peroxidation, oxidative stress, and oxidative damage. Oxidative stress has been implicated in over 100 diseases, including BPH. However, the exact mechanism of oxidative stress in the disease development remains unknown. Furthermore, whether oxidative stress leads to the disease development, or BPH results in the development of oxidative stress, is a matter of conjecture.

An endogenous free radical system noted for savaging is PON1. It is involved in lipid hydroperoxide and organophosphate detoxification.[23,24] PON1is known as a free-radical scavenging enzyme associated with circulating serum HDL. PON1 catalyzes the hydrolysis of multiple compounds such as arylesters, lactones, and hydroperoxides. In addition to hydroperoxide hydrolysis, PON1 is involved in the hydrolysis of arylesters and lactones. Due to the association of PON1 with lipid peroxidation, most studies have focused on PON1 as an antiinflammatory marker because of its paraoxonase activity which is not the totality of its physiological activity.[25] PON1 activities have not been previously examined in BPH patients; however, they were found to be significantly higher in prostate cancer (PCa) patients.[26] Our study shows that PON1 activity may influence the risk of BPH. PON1 was higher in BPH and almost significant. In the case of PCa, it has been reported that HDL

cholesterol leads to increased proliferation and migration into PCa cells. This mechanism may also exist in BPH. The HDL biomolecule is said to carry PON1 for the purpose of protection against oxidation.[16] However, a number of studies have indicated that ARE activity is a better reflection of the overall function of the HDL enzyme antioxidant system.[25,27,28]

Inflammation and oxidative stress are commonly associated with BPH, and ARE activity is reduced in many clinical conditions involving oxidative stress and inflammation. Additionally, this antioxidant savaging enzyme activity reduces with age.[29] ARE antioxidant was significantly lower in the patient group of this study ($P < 0.003$). Furthermore, ARE relates better to the antioxidant activity of PON1 and is accountable for oxidized lipids detoxification.

Apolipoprotein A-1, which is a major lipoprotein associated with HDL, is also said to stabilize the activity of ARE.[28] In agreement with previous studies, the lipoprotein was also significantly lower in the BPH group.[30] Finally, genetic polymorphisms do not affect the activity of ARE compared to PON1.[27]

The PON1/HDL activity ratio has been suggested to be a better abnormal parameter in end stage renal disease for assessing the enzyme activity than PON1activity alone.[31] In a study by de la Iglesia et al[32], ARE/HDL ratio was significantly different from the patient group following an energy restricted diet than ARE levels alone. In this study, the ARE/HDL ratio was significantly different between the groups but not with the PON1/HDL ratio. To the best of our knowledge, the effect of BPH on ARE and ARE/HDL is being shown for the first time.

A mild negative correlation was observed between PSA and LDL. This is contrary to the study of Telli et al[33] where no such correlation was observed. However, a positive correlation has been observed between PSA and LDL in noncolored people but not colored people.[34,35] This mild inverse association in this study is difficult to explain and will require further studies.

The limitations of this study include the lack of more clinical parameters. For example, DRE and urodynamic studies are not routinely carried out and in this study these was not done. Furthermore, the sample size was small and a larger sample size would have increased the power of the study.

In conclusion, the study demonstrates the significant reduction of GSH-Px in BPH patients and more importantly the role of lipid peroxidation and the involvement of ARE, an antioxidant scavenger. This process suggests the involvement of oxidative stress in BPH. Whether oxidative stress is a causative factor or a resultant factor in BPH which could be taken advantage of in the course of treatment, is yet to be investigated.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Kirby RS, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P. *Textbook of benign prostatic hyperplasia*. 2nd ed. UK: Taylor and Francis; 2005:19–20.
2. Hetzl AC, Favaro WJ, Billis A, Ferreira U, Valéria HA, Cagnon. Prostatic diseases in the senescence: structural and proliferative features. Aging Male 2013;2:124–32.
3. Subbaramaiah K, Howe LR, Bhardwaj P, Du B, Gravaghi C, Yantiss RK, et al. Obesity is associated with inflammation and elevated aromatase expression in the mouse mammary gland. Cancer Prev Res (Phila) 2011;4:329–46.
4. Escobar EL, Gomes-Marcondes MC, Carvalho HF. Dietary fatty acid quality affects AR and PPARgamma levels and prostate growth. Prostate 2009;69:548–58.
5. Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. Am J Clin Nutr 2002;75:689–97.
6. Parsons JK, Bergstrom J, Barrett-Connor E. Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men. BJU Int 2008;101:313–8.
7. Lekili M, Müezzinoğlu T, Uyanik BS, Büyüksu C. Serum lipid levels in benign prostatic hyperplasia. World J Urol 2006;24:210–3.
8. Bostancia Y, Kazzazia A, Momtahenb S, Lazea J, Djavana B. Correlation between benign prostatic hyperplasia and inflammation. Curr Opin Urol 2013;23:5–10.
9. Sanda MG, Beaty TH, Stutzman RE, Childs B, Walsh PC. Genetic susceptibility of benign prostatic hyperplasia. J Urol 1994;152:115–9.
10. Marker PC, Donjacour AA, Dahiya R, Cunha GR. Hormonal, cellular, and molecular control of prostatic development. Dev Biol 2003;253:165–74.
11. Bravi F, Bosetti C, Dal Maso L, Talamini R, Montella M, Negri E, et al. Food groups and risk of benign prostatic hyperplasia. Adult Urol 2006;67:73–9.
12. Giorgio IR, Cimino S, Morgia G. Benign prostatic hyperplasia and metabolic syndrome: the expanding evidences of a new disease of aging male. Aging Male 2015;18:133–4.
13. Udensi KU, Tchounwou PB. Oxidative stress in prostate hyperplasia and carcinogenesis. J Exp Clin Can Res 2016;35:139.
14. Ren H, Xiaona Li, Cheng G, Li N, Hou Z, Suo J, et al. The effects of ROS in prostatic stromal cells under hypoxic environment. Aging Male 2015;18:84–8.
15. Kullisaar T, Türk S, Punab M, Mändar R. Oxidative stress-cause or consequence of male genital tract disorders? Prostate 2012;72:977–83.
16. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998;101:1581–90.
17. Costa LG, Vitalone A, Cole TB, Furlong CE. Modulation of paraoxonase (PON1) activity. Biochem Pharmacol 2005;69:541–50.
18. Szewczyk-Golec K, Tyloch J, Czuczejko J. Antioxidant defense system in prostate adenocarcinoma and benign prostate hyperplasia of elderly patients. Neoplasma 2015;62:119–23.
19. Duru R, Njoku O, Maduka I. Oxidative stress indicators in patients with prostate disorders in Enugu, South-East Nigeria. Biomed Res Int 2014, 313015.
20. Flohé L. Glutathione peroxidase. Basic Life Sci 1988;49:663–8.
21. Aydin A, Arsova-Sarafinovska Z, Sayal A, Eken A, Erdem O, Erten K, et al. Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. Clin Biochem 2006;39:176–9.
22. Zachara BA, Szewczyk-Golec K, Tyloch J, Wolski Z, Szylberg T, Stepien S, et al. Blood and tissue selenium concentrations and glutathione peroxidase activities in patients with prostate cancer and benign prostate hyperplasia. Neoplasma 2005;52:248–54.
23. Davies HG, Richter RJ, Keifer M, Broom CA, Sowalla J, Furlong CE. The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin. Nat Genet 1996;14:334–6.
24. Marchesani M, Hakkarainen A, Tuomainen T-P, Kaikkonen J, Pukkala E, Uimari P, et al. New paraoxonase 1 polymorphism I102V and the risk of prostate cancer in Finnish men. J Natl Cancer Inst 2003;95:812–8.
25. Rosenblat M, Gaidukov L, Khersonsky O, Vaya J, Oren R, Tawfik DS, et al. The catalytic histidine dyad of high density lipoprotein-associated serum paraoxonase-1 (PON1) is essential for PON1-mediated inhibition of low density lipoprotein oxidation and stimulation of macrophage cholesterol efflux. J Biol Chem 2006;281:7657–65.
26. Eroglu M, Yilmaz N, Yalcinkaya S, Ay N, Aydin O, Sezer C. Enhanced HDL-cholesterol-associated anti-oxidant PON-1 activity in prostate cancer patients. Kaohsiung J Med Sci 2013;29:368–73.
27. Eckerson H, Wyte C, La Du B. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126–38.
28. Sorenson RC, Bisgaier CL, Aviram M, Hsu C, Billecke S, La Du BN. Human serum paraoxonase/arylesterase's retained hydrophobic N-terminal leader sequence associates with HDLs by binding phospholipids : apolipoprotein A-I stabilizes activity. Arterioscler Thromb Vasc Biol 1999;19:2214–25.
29. Mehdi MM, Rizvi SI. Human plasma paraoxonase 1 (PON1) arylesterase activity during aging: correlation with susceptibility of LDL oxidation. Arch Med Res 2012;43, 438– 43.
30. Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1:157–62.
31. Mahrooz A, Zargari M, Sedighi O, Shaygani H, Gohari G. Increased oxidized-LDL levels and arylesterase activity/HDL ratio in ESRD patients treated with hemodialysis. Clin Invest Med 2012;35:E144–51.
32. de la Iglesia R, Mansego ML, Sánchez-Muniz FJ, Zulet MA, Martinez JA. Arylesterase activity is associated with antioxidant intake and paraoxonase-1 (pon1) gene methylation in metabolic syndrome patients following an energy restricted diet. EXCLI J 2014;13:416–26.
33. Zapata D, Howard LE, Allott EH, Hamilton RJ, Goldberg K, Freedland SJ. Is PSA related to serum cholesterol and does the relationship differ between black and white men? Prostate 2015;75:1877–85.
34. Sidaway P. Cholesterol level correlates with PSA level in white but not black men. Nat Rev Urol 2015;12:594.
35. Telli O, Demirbas A, Kabar M, Karagoz MA, Sarici H, Resorlu B. Does metabolic syndrome or its components correlate with lower urinary tract symptoms in benign prostatic hyperplasia patients? Nephrourol Mon 2015;7:e27253.