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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.

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