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ORIGINAL ARTICLE

Enhanced HDL-cholesterol-associated anti-oxidant PON-1 activity in prostate cancer patients

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Abstract Increases in the generation of reactive oxygen species and decreases in antioxidant enzyme activities with aging have been reported in the prostate, and are also observed in age-related disorders such as atherosclerosis, Alzheimer's disease, and cataracts. Several studies have demonstrated that proteins are targets for reactive oxidants in cells, and that oxidized proteins accumulate during aging, oxidative stress and in some pathological conditions. However, only a limited number of studies have actually evaluated oxidative damage in relation to HDL-cholesterol-associated antioxidant enzyme activities or have assessed its relationship with prostate cancer. In this study, we examined the effect of HDL-cholesterol-associated antioxidant enzyme activities, paraoxonase1, arylesterase and new oxidative stress parameters (total oxidant status, total antioxidant status [and oxidative stress index]) in newly-diagnosed prostate cancer patients and healthy controls. There were no significant differences in oxidative stress parameters and lipid parameters between prostate cancer patients and controls, however, paraoxonase1 enzyme activity, and non-HDL-cholesterol levels were higher in prostate cancer patients than controls. The results of this study were derived from a small number of subjects, but might represent an important working hypothesis for further research in a larger number of cases to clarify the role of paraoxonase1 overproduction on the prostate and its clinical relevance.

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Introduction

Prostate cancer (PCa) is the most common incidental cancer and the second most common fatal cancer among men, not only in USA but also in some developing countries [1]. Like most cancers, both genetic and environmental factors contribute to the pathogenesis of human PCa. PCa incidence and mortality are known to vary greatly in different geographic regions of the world. PCa mortality is characteristically low in Asia compared to the high risks of mortality in the USA and Western Europe [2]. In a recent study of cancer risks among 44,788 pairs of twins in Sweden, Denmark, and Finland, a statistically significant effect of genotype was observed only for some 42% of PCa cases, indicating that environment and lifestyle (including diet) are likely to play a more dominant role than inheritance in the development of most PCas [3].

How do the environment and lifestyle promote prostatic carcinogenesis? It has been hypothesized that blood lipid levels might be associated with PCa risk. During the past decade, several findings have led to an augmented interest in lipid profiles as predictors of PCa risk [4,5]. It is thought that dietary fat intake might affect PCa risk. Most population-based studies searching lipids and the risk of PCa have focused on triglycerides (TG) and total cholesterol (TC), but very few studies have investigated the functions of HDL-cholesterol in patients with PCa.

A series of epidemiological and laboratory observations suggest that oxidative stress, either from endogenous sources such as inflammation and cellular metabolism, or exogenous sources including ultraviolet light and environmental toxins, contribute to the risk of prostate carcinogenesis [6]. Oxidative stress and free radicals have been associated with the increased risk of various cancers [7,8]. Aerobic organisms, within the course of evolution, have developed complex xenobiotic enzyme systems for protection against environmental genotoxins. The human body has a number of endogenous free-radical scavenging systems, including paraoxonase (PON), which principally conjugate the intermediates to excretable hydrophilic derivatives and bind to HDL-cholesterol, contributing to the detoxification of organophosphorus compounds and carcinogenic lipid-soluble radicals from lipid peroxidation [9,10]. PON1 is a liver-derived glycoprotein that is secreted into the circulation. It is capable of hydrolyzing a diverse array of substrates, including a variety of esters, lactones, and man-made organophosphate compounds. PON1 enzyme activity is affected by a number of factors such as genetic mutations, smoking, stress, and high-fat diets. It has been hypothesized that PON1 polymorphisms might contribute to the increased risks of cancer associated with pollutants and other environmental chemicals [11,12].

Small PCas have been mostly found in men aged 30—40 years old, while diagnoses of clinically-significant PCas are typically found in men aged 60—70 years old [13]. Recent scientific data have shown that basal and salt-stimulated paraoxonase as well as arylesterase (ARE) activities were significantly reduced in elderly compared to young individuals [14]. Actually, the role of PON1 might be underestimated: the enzyme itself may determine the function of HDL-cholesterol. Besides, hyper- and hypolipidemia, and the oxidation of lipoproteins are suggested to be fields in which HDL-cholesterol and HDL-cholesterol-associated proteins affect the course of lifestyle [15].

To the best of our knowledge, there is no study in the literature that has measured the activity of PON 1, ARE and oxidative balance in patients with PCa. The purpose of this study was to identify oxidative stress in PCa patients, and investigate whether the new generation biochemical parameters or those that were previously known are associated with the risk of incidental PCa.

Materials and methods

Study population and clinical examinations

Twenty-three patients with newly-diagnosed PCa (mean age 66.8 $\pm$ 7.9 years) who had presented at the Urology Outpatient Clinic of Antalya Education and Research Hospital were prospectively included in the study. Forty control individuals (mean age 62.3 $\pm$ 10.7 years) were enrolled for comparison. The control group consisted of volunteers with a prostate-specific antigen (PSA) level in the normal range and without any urological medical history. The patients and controls were evaluated by the same urologist. All individuals had a full physical examination and were asked to complete a general questionnaire and gave informed consent before the onset of study. The questions included: the age, social-economic status, origin of ancestors, status of physical activity, smoking, alcohol consumption, and detailed medical history. Blood pressure was measured manually with a sphygmomanometer. Body mass index was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure $>$140 mmHg and diastolic blood pressure $>$90.

Those with a known past history of any major diseases such as cardiac, renal, hepatic or endocrine disease were excluded. None of the participants in the present study were using drug medications including antihypertensive and lipid-lowering agents, vitamins or antioxidant drugs. Smokers and alcohol users were also excluded. The subjects were locals with an average family income, favoring common dietary habits, with a routine daily life. All men were diagnosed with PCa after a pathologic review of transrectal ultrasound-guided prostate needle core biopsies. Indications for biopsy included elevated PSA and an abnormal digital rectal exam. Prostate biopsies were performed utilizing a routine sextant pattern with at least 12 cores being obtained. After the pathology reports were inspected, only patients with Gleason scores of 5—9 were included in the study. According to the pathological reports, Gleason score distributions of the diagnosed carcinomas were as follows:

- 5: 17.3% of patients;
- 6: 47.0 of patients;
- 7: 17.3% of patients;
- 8: 8.6% of patients; and
- 9: 8.6% of patients.

Any patients with a clinical or radiological suspicion of metastatic PCa were excluded. Our aim was to compose as homogenous a population as possible.

This study was performed in accordance with the ethical standards set by the Declaration of Helsinki and was approved by the local ethics committee.

Analytical methods

Blood sample collection

Blood samples were obtained after an overnight fasting state. Serum samples were then separated from the cells by centrifugation at 3000 rpm for 10 minutes. Lipid parameters and serum PSA levels were measured freshly. Remaining serum portions were stored at −80°C and used to analyze PON1, ARE, total oxidant status (TOS) and TAS (total antioxidant status).

Measurement of paraoxonase, arylesterase activities of serum

PON1 and ARE activities were measured using commercially-available kits (Relassay, Turkey). The fully-automated PON1 activity measurement method consists of two different sequential reagents. The first reagent is an appropriate Tris buffer, and it also contains calcium ions, which are a cofactor of PON1 enzyme. A linear increase of the absorbance of *p*-nitrophenol, produced from paraoxon, is followed at kinetic measurement mode. Nonenzymatic hydrolysis of paraoxon was subtracted from the total rate of hydrolysis. The molar absorptivity of *p*-nitrophenol is 18.290 M^{-1} cm^{-1} and one unit of paraoxonase activity is equal to 1 mol of paraoxon hydrolyzed per liter per minute at 37°C [16].

Phenylacetate was used as a substrate to measure the ARE activity. PON1, which is present in the sample, hydrolyses phenylacetate to its products, which are phenol and acetic acid. The produced phenol is colorimetrically measured via oxidative coupling with 4-aminoantipyrine and potassium ferricyanide. Nonenzymatic hydrolysis of phenylacetate was subtracted from the total rate of hydrolysis. The molar absorptivity of colored complex is 4000 M^{-1} cm^{-1} and one unit of arylesterase activity is equal to 1 mmol of phenylacetate hydrolyzed per liter per minute at 37°C [17].

Measurement of the total antioxidant status of serum

The TAS of the serum was measured using a novel automated colorimetric measurement method developed by Erel [18]. In the TAS method, antioxidants in the sample are reduced from dark blue-green colored 2,2′-azino-*bis*(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical to a colorless, reduced ABTS form. The change of absorbance at 660 nm is related to the total antioxidant level of the sample. Using this method, the antioxidative effect of the sample against the potent free radical reactions initiated by the hydroxyl radical produced, is measured. The results are expressed as micromolar trolox equivalent per liter.

Measurement of the total oxidant status of serum

The TOS of the serum was measured using a novel automated colorimetric measurement method developed by Erel [19]. In the TOS method, oxidants present in the sample oxidize the ferrous ion−chelator complex to ferric ion. The ferric ion makes a colored complex with chromogen in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter.

Oxidative stress index

The percentage ratio of TOS level to TAS level was accepted as the oxidative stress index (OSI). For calculation, the resulting unit of TAS was changed to millimoles per liter, and the OSI value was calculated according to the following formula:

OSI (arbitrary unit) = TOS (micromolar hydrogen peroxide equivalent per liter)/TAS (micromolar trolox equivalent per liter).

Routine parameters

The levels of TG, TC, HDL-cholesterol, and LDL-cholesterol were determined by using commercially-available assay kits (Abbott Diagnostics, Illinois, USA) with an autoanalyzer (Architect c16000, Abbott Diagnostics, Illinois, USA). Non-HDL-cholesterol was calculated as total cholesterol minus HDL-cholesterol. Serum PSA levels were determined by using commercially-available assay kits (Beckmann Access, Krefeld, Germany) with an autoanalyzer (DXI 800, Beckmann Coulter, Krefeld, Germany).

Statistical analysis

Statistical analyses were carried out using the MedCalc statistical software (MedCalc, Mariakerke, Belgium). The results were expressed as mean ± standard deviation. The significance of the differences between groups was determined by the Student unpaired *t* test and the Mann−Whitney *U*-test. The Pearson correlation coefficient was used to test the strength of any associations between different variables. Values of $p < 0.05$ were accepted as significant.

Results

The clinical data from patients and age-matched controls are summarized in Table 1. The means of the body mass index of the groups did not differ significantly. Nearly all of the cancer patients reported unintentional weight loss, so the finding was thought to be due to the cancer itself rather than lifestyle. When the groups were compared according to lipid parameters, non-HDL-cholesterol was higher in PCa patients compared to the controls. Of interest, TC, TG, and LDL-cholesterol levels did not differ significantly, suggesting the superiority of clinical use of non-HDL-cholesterol as a parameter. The PSA levels of PCa patients were higher than controls, as expected (Table 1).

In oxidant/antioxidant parameters, the only statistically-significant parameter was PON1 enzyme activity, which was higher in PCa patients compared to controls ($p < 0.01$). ARE enzyme activity, TAS, and TOS did not show any significant difference. A striking finding was the *p* value of ARE enzyme activity ($p = 0.94$), demonstrating very close enzyme activity in both groups (Table 2).

Table 1 Clinical data from patients and age-matched controls. The groups' body mass index means did not differ significantly. Non-HDL-cholesterol was higher in prostate cancer patients compared to the controls. The prostate-specific antigen levels of prostate cancer patients were higher than controls, as expected.

Parameter (mean ± SD)/(median) (interquartile range)	Prostate cancer (n = 23)	Control (n = 40)	p-value
Age, mean ± SD	66.8 ± 7.9	62.3 ± 10.7	0.08
Body mass index (kg/m^2), mean ± SD	26.6 ± 4.3	26.7 ± 2.9	0.91
Family history of prostate cancer (n)	8 (34.7%)	—	0.92
Total cholesterol (mg/dL)	208.4 ± 33.8	197.0 ± 43.2	0.28
Triglyceride (mg/dL)	148.9 ± 74.6	165.9 ± 76.3	0.40
HDL-cholesterol (mg/dL)	45.5 ± 11.4	41.7 ± 9.9	0.17
LDL-cholesterol (mg/dL)	130.4 ± 27.9	124.0 ± 36.7	0.48
Non-HDL-cholesterol (mg/dL)	162.9 ± 31.5	155.3 ± 41.5	<0.01
Prostate-specific antigen (ng/mL)	7.78 (6.5—21.2)	1.41 (1.1—2.1)	<0.0001

Statistical analysis showed a positive Pearson correlation between PON1, ARE, TAS and TOS in the PCa group. A negative correlation between HDL-cholesterol and TOS, HDL-cholesterol and OSI was found (Fig. 1).

Discussion

The results of this study suggest that PON1 levels may influence the risk of PCa. Frehman et al. reported that PON1 deficiency in mice was associated with decreased macrophage scavenger receptor class B member 1 (SR-BI) expression, decreased cellular HDL-cholesterol binding, and consequently the loss of HDL-cholesterol-mediated cytoprotection against apoptosis [20]. Sekine et al. have reported that HDL-cholesterol leads to increased proliferation and migration of PCa cells [21]. In theory, PON1 activity may influence carcinogenesis not only by limiting exposure to toxic organophosphate metabolites, but also by influencing the putative effects of pesticides on immune function and oxidative stress. PON1 can also hydrolyze *N*-acyl-homoserine lactones, which are quorum-sensing signals of pathogenic bacteria [22]. PON1 variants are under investigation because their activity may limit the damage caused by bacterial endotoxins, prevent lipid oxidation, and possibly decrease the risk of inflammation-related diseases such as atherosclerosis and cancer [23—25].

PON1 Arg^{192}Gln and Met^{55}Leu variants have been associated with substrate-dependent effects on activity. Recently-discovered −108T and −162A promoter variants have been shown to be associated with increased activity [26]. This is a gene encoding the human serum paraoxonase enzyme consistently implicated in lipid metabolism and in the elimination of carcinogenic lipid-soluble radicals. Moreover, PON1 genotypes significantly affect the susceptibility of LDL- and HDL-cholesterol to lipid peroxidation [27].

Measurement of TAS and TOS are valuable, as they provide information about the "totals" of oxidants and antioxidants not yet recognized or not easily measured. However, they present unrefined, vague results for the same reason, making it crucial to further examine particular enzyme activities. Accordingly, we measured PON1 and ARE activities, two enzymes particularly important in antioxidative defense. We did not find any significant differences in TAS and TOS. Worryingly, PON1 enzyme activity was significantly increased in PCa patients, while ARE enzyme activity was similar in both groups, in spite of the significant difference expected. The discrepancy clearly underscores the fact that PON1 is a multi-facetted enzyme with functional sites specialized for distinctly separate activities [28].

Kok et al. reported serum TC, HDL-cholesterol, LDL-cholesterol and TG as potential risk factors for PCa using multivariable Cox proportional hazard regression models. Higher TC and higher LDL-cholesterol were significantly associated with an increased risk of PCa (hazard ratios [HR] and 95% confidence interval [CI] per mmol l^{-1} were 1.39 (95% CI 1.03—1.88) and 1.42 (95% CI 1.00—2.02), respectively) [29]. A recent study showed that HDL-cholesterol increased serine 727 phosphorylation of Stat3, S1P, and that rHDL-S1P, also induced the phosphorylation [30]. However, the exact roles of different cholesterol fractions on PCa aggressiveness should be further evaluated.

The number of subjects was a major limitation of this study. However, the selected patients were free from any diseases requiring medication, and from smoking and alcohol consumption, that might have been confounding

Table 2 The comparison of various parameters in prostate cancer patients and controls, showing that PON1 was the only parameter differing between groups. PON1 was higher in prostate cancer patients.

Parameter (mean ± SD)/(median) (interquartile range)	Prostate cancer (n = 23)	Control (n = 40)	p-value
PON1 (U/L)	103.8 ± 64.7	76.5 ± 46.5	<0.01
Arylesterase (kU/L)	136.7 ± 59.9	135.5 ± 65.7	0.9419
Total antioxidant status (nmol Troloks/L)	1.31 ± 0.42	1.35 ± 0.29	0.4639
Total oxidant status (μmol H_2O_2 Equiv./L)	4.02 (3.4—5.4)	4.76 (3.9—6.1)	0.1929
Oxidative stress index	372 (338—453)	353 (294—424)	0.2962

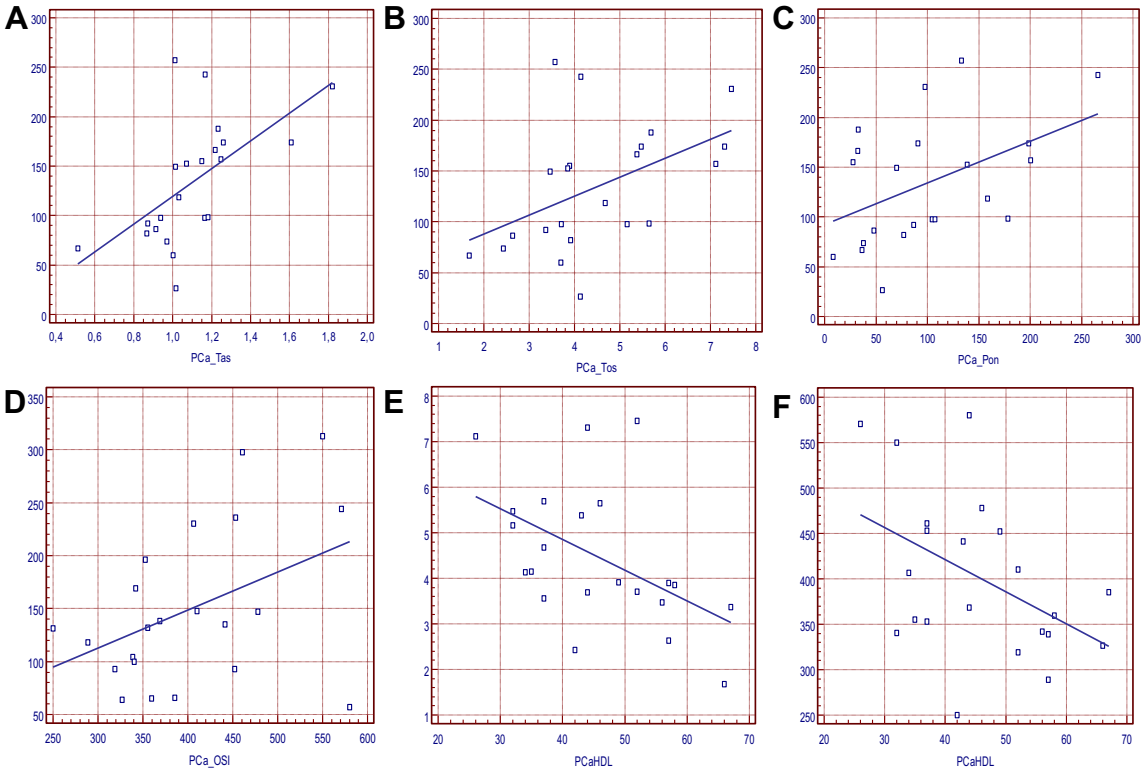

Figure 1. Graphics of significant correlations in prostate cancer patients. (A) Arylesterase (ARE) and total antioxidant status ($r = 0.58$, $p = 0.004$); B) ARE and total oxidant status ($r = 0.45$, $p = 0.03$); C) ARE and paraoxonase ($r = 0.45$, $p = 0.03$); D) triglycerides and oxidative stress index ($r = 0.42$, $p = 0.04$); E) total oxidant status and HDL-cholesterol ($r = -0.49$, $p = 0.01$); F) oxidative stress index and HDL-cholesterol ($r = -0.48$, $p = 0.01$).

factors. We should appreciate the difficulty of composing groups of patients and controls in the relevant age group fulfilling the aforementioned criteria. After all, we strongly believe in the specificity of our findings. This study should therefore be recognized as having an impact on new ones with larger groups of patients.

There are great deals of data in the literature indicating that oxidative stress is involved in the pathomechanism of many diseases, including cancer. Lipid parameters, and particularly HDL-cholesterol, have been the ultimate focus of studies so far. However, our recent understanding of the "functionality of HDL-cholesterol" has made the measurements of the quality of HDL-cholesterol the primary target instead of traditional measurements of the quantity of HDL-cholesterol [31]. Unsurprisingly, an exuberant welcome awaits the therapeutics aiming to decrease or avoid oxidative damage in the human body. PON1 is the most promising actor in this area of research. Against such a background of aberrant optimism, rare studies like ours present clues that PON1-targeted medications bare unwanted consequences, such as promoting carcinogenesis. Oxidative stress and antioxidative therapies should be handled with extra care in cancer, due to the potential diversities in patient behavior.

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