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Original Article

Paraoxonase and arylesterase activity in bladder cancer

Mesane kanserinde paraoksanaz ve arilesteraz aktivitesi

Mehmet Mazhar Utanğaç[1], Ercan Yeni[2], Murat Savaş[3], Adem Altunkol[4], Halil Çiftçi[2], Kemal Gümüş[2], Mehmet Demir[2]

ABSTRACT

Objective: Oxidative stress is the main pathogenetic mechanism in bladder cancer among many other causes. We aimed to investigate whether a potential relationship exists between bladder cancer and the activities of paraoxonase (PON1) and arylesterase (ARE) enzymes.

Material and methods: The study included 56 patients with bladder cancer, and 57 healthy individuals. The relationships between enzyme activity and tumour grade, stage, muscular invasion and tumour size were evaluated. For statistical analysis, One-Sample Kolmogorov-Smirnov, Independent-T, ANOVA and Post-Hoc Bonferroni tests were used.

Results: Serum levels of PON1 and ARE enzymes, and total cholesterol were significantly lower in bladder cancer group. While other lipid parameters were similar in both the patient and the control groups. Levels of ARE were positively correlated with lipid parameters except for HDL cholesterol.

Conclusion: Our results showed that decreased serum PON1 and ARE enzyme activities are related with tumour load and recurrence. Further studies with larger samples are needed to confirm predictive role of enzymatic activities of PON1 and ARE in the diagnosis and prognosis of bladder cancer.

Keywords: Antioxidant; arylesterase; bladder cancer; paraoxonase.

ÖZ

Amaç: Oksidatif stres, mesane kanseri için diğer birçok nedenler arasından ana patogenetik mekanizmadır. Biz mesane tümörü ile paraoksonaz (PON1) ve arilesteraz (ARE) enzim aktiviteleri arasındaki bir ilişki olup olmadığını araştırmayı amaçladık.

Gereç ve yöntemler: Mesane tümörü olan 56 hasta ve 57 sağlıklı birey çalışmaya alındı. Enzim aktivitesi, grade, evre, kas invazyonu ve tümörün büyüklüğü arasındaki ilişki değerlendirildi. One-Sample Kolmogorov Smirnov, Independent-T, Anova and Post Hoc Bonferroni testleri değişkenleri değerlendirmek için kullanıldı.

Bulgular: Her iki enzimin serum düzeyleri hasta grubunda anlamlı olarak düşüktü. Total kolesterol düzeyleri hasta grubunda anlamlı derecede daha düşük ve diğer lipid parametreleri hasta ve kontrol grubu arasında benzer idi. ARE enzim düzeylerinin HDL-kolesterol dışında lipid parametreleri ile pozitif korele olduğu bulundu.

Sonuç: Sonuçlarımız PON1 ve ARE enzim aktivitesindeki düşüşün tümör yükü ve rekürrensi ile ilişkili olduğunu ortaya koymuştur. PON1 and ARE enzim aktivitesinin mesane tümörünün tanısında ve prognozunun tahmininde rolü olduğuna dair daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Antioksidan; arilesteraz; mesane tümörü; paraoksanaz.

[1]Department of Urology, Dicle University School of Medicine, Diyarbakır, Turkey

[2]Department of Urology, Harran University School of Medicine, Şanlıurfa, Turkey

[3]Department of Urology, Ministry of Health, Antalya Training and Research Hospital, Antalya, Turkey

[4]Department of Urology, Ministry of Health, Adana Numune Training and Research Hospital, Adana, Turkey

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Correspondence: Mehmet Mazhar Utanğaç
E-mail: drmazhar21@hotmail.com

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Introduction

Bladder cancer (BC) is the ninth-most common type of cancer in both genders. Approximately 429,000 cases were reported in 2012, and each year, approximately 165,000 deaths worldwide are attributed to BC. The mortality rate is lower than the incidence rate, and for males, the highest incidence is found in West Asia (8.4 in 100,000) and for females, in North Africa (1.6 in 100,000).[1] The most commonly implicated factor in BC etiology is smoking.[2]

Some metabolic and physiologic processes produce reactive oxygen species in the body. Under normal conditions, there is a sensitive balance between formation of free radicals and their elimination by antioxidant enzyme systems. If the balance is disturbed in favor of oxidants, all organ systems are endangered. The organ systems of the body for eliminating waste and toxic materials, including the bladder, may be more sensitive and vulnerable to the effects of oxidants.

The human body has defence systems that prevent the effects of endogenously produced free

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radicals.[3,4] and paraoxonase (PON1)[5-7], and arylesterase (ARE)[8] are among these endogenous antioxidant systems. Paraoxonase is a serum esterase that can hydrolyze the active metabolite of the parathion paraoxon, which is synthesized in the liver. PON1 is located in the serum and the endothelial layer of many tissues, including the liver, kidneys and small intestines.[9] Hydrolyzing toxic organic molecules was the first physiological function of PON1 to be described.[10] The second biological function of PON1 to be defined was its antioxidant activity. PON1 is known to be integrated in the structure of high- density lipoprotein (HDL). PON1 can easily bind HDL lipids. Besides it plays a role in the stabilization of HDL and exerts antioxidant features of HDL.[11] Meanwhile, as have been demonstrated in many studies it protects low-density lipoprotein (LDL) from harmful effects of oxidation.[12] ARE is an esterase enzyme, coded by the same gene, which has similar active centers as PON1.[8]

Total Antioxidant Status (TAS) indicates the overall anti-oxidative status of the serum, while Total Oxidant Status (TOS) denotes oxidative status of the serum.[13] The Oxidative Stress Index (OSI), which is defined as the ratio of between TOS, and TAS values, is applied as a marker of oxidative stress.[14,15] Oxidative stress may play a role in the pathogenesis of human diseases. Genetic alterations causing increased oxidative stress have been shown to be associated with BC.[16,17] Many studies have investigated the relationship between PON1 and ARE enzymes and various diseases that involve oxidative stress in their pathogenesis.

The literature included studies investigating the association of serum enzyme levels of PON1 and ARE with bladder, prostate, colon and rectum, endometrial, gastric, pancreatic, ovarian, esophageal and lung cancers.[18-26] The present study investigated the potential relationship between BC and the activities of serum PON1 and ARE enzymes.

Material and methods

This prospective study was approved by the institution's ethics committee. All patients and all healthy controls gave written informed consent before being recruited in the study. Patients who presented at Urology Department of Harran University Medical School with BC between May 2011 and November 2011 were enrolled in the study. As controls, 57 healthy participants without BC were used. All healthy participants were examined.

The study excluded those taking any cholesterol-lowering drug or having any cancer other than BC. Blood samples were obtained, and lipid parameters, PON1, ARE and other oxidative parameters were studied. Activities of PON1 and ARE were measured using commercially available kits (Rel Assay; Turkey).

Erel[27] described and measured serum TAS levels using an automated method. In the Fenton reaction, a solution of ferrous ion is added to a hydrogen peroxide mixture, resulting in the discharge of potent hydroxyl roots. Then, these hydroxyl roots produce potent brown-coloured dianisidinyl root cations. This analysis determines the anti-oxidative capacity of the sample against the potent free root produced by the hydroxyl root. The analysis has great accuracy, with a coefficient of variation of 3%. Results are defined as millimoles of Trolox per liter. Measurement of the serum TOS rate was accomplished using an automated method defined by Erel.[14] The dianisidine-ferrous ion compound is oxidized by oxidants in the sample, yielding compliant ferric ions. Glycerol was used to improve the oxidation reaction. In a moderately potent acid medium, ferric ions form a colourful complex with xylenol orange. The density of the colour, which can be measured spectrophotometrically, is dependent on the amount of oxidant molecules available in the sample. The analysis is aligned using hydrogen peroxide. Data are defined as micromoles of hydrogen peroxide per liter. The OSI was calculated by dividing the TOS by the TAS.

Statistical analysis

Data were statistically analysed using Statistical Package for the Social Sciences version 11.5 software (SPSS Inc.; Chicago, IL, USA). Parameters were expressed as mean ± SD. The distribution of parameters among groups was investigated using the One-Sample Kolmogorov-Smirnov test. Categorical parameters were evaluated using the Fisher Exact test. The correlations of variables were assessed in each group using Pearson Correlation Analysis. The patient group was further subdivided by tumour grade, presence of muscular invasion, recurrence, number of foci (1, 2-7, and >8) and diameter (<3 cm and >3 cm). Since the distribution of these subdivisions was normal according to the Kolmogorov-Smirnov test, ANOVA tests were performed comparing 2 groups, and 3 groups were compared using independent T-tests. To determine significant differences between groups, the Post-Hoc test with Bonferroni correction was used. The level of statistical significance was set at $p<0.05$.

Results

Demographic data of both groups were comparable as for age, gender distribution and body mass index (BMI) (Table 1). Serum PON1, ARE, total cholesterol, HDL, LDL, very- low- density lipoprotein (VLDL), TG, TAS, TOS and OSI levels were studied in both the patients and control groups. Serum PON1 and ARE activities were 137.63±53.37 U/L and 168.82±37.34 U/L, respectively, in the control group and 103.35±41.44 U/L and 131.83±the 39.94 U/L, respectively, in the patient group. Lower levels of both enzymes in the patient group were statistically significant ($p<0.05$). Serum lipid profiles revealed that the level of total cholesterol was significantly lower in the patient group, while other parameters were comparable in both groups. Tests for serum oxidative stress parameters demonstrated that the patient group had higher TOS, lower TAS levels and higher OSI Index values. These differences between the patient and the control groups were statistically significant (Table 1).

Analyses of the correlation between lipid parameters with enzymatic activities of PON1 and ARE detected a significant positive

correlation between enzymatic activity of PON1 and levels of total cholesterol, HDL and LDL and an insignificant positive correlation between enzymatic activity of PON1 and levels of VLDL and triglycerides. In addition, there was a statistically significant positive correlation between enzymatic activity of ARE, and all lipid parameters except for HDL. Table 2 summarizes the results of correlation analyses.

Table 1. Demographic characteristics and serum PON1, ARE, lipid profile and oxidative stress- associated conditions in the patient and control groups

	Control group (n=57)	Patient group (n=56)	p
Gender (M/F)	46/11	49/7	0.323
Age (years)	57.10±14.50	61.10±11.80	0.119
BMI (kg/m^2)	26.29±3.30	25.81±3.90	0.481
PON1 (U/L)	137.63±53.37	103.35±41.44	0.000
ARE (U/L)	168.82±37.34	131.83±39.94	0.000
Total cholesterol (mg/dL)	195.95±42.50	175.13±46.63	0.015
HDL (mg/dL)	40.07±11.34	38.19±14.46	0.445
LDL (mg/dL)	113.01±32.83	103.98±34.93	0.159
VLDL (mg/dL)	38.91±23.50	31.96±19.30	0.089
Triglyceride (mg/dL)	197.78±117.59	159.83±96.53	0.087
TAS (mmol Trolox equiv/L)	0.99±0.12	0.91±0.17	0.010
TOS (mmol H_2O_2 equiv/L)	17.55±7.79	24.68±6.84	0.000
OSI	1.78±0.76	2.80±0.99	0.000

BMI: Body Mass Index; M: Male; F: Female; PON1: Paraoxonase; ARE: Arylesterase; HDL: High density lipoprotein; LDL: Low- density lipoprotein; VLDL: Very- low-density lipoprotein; TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index

In the patient group, serum PON1 and ARE activities were correlated with tumour grade, muscle invasion, recurrence, number of foci and tumour diameter. Of those parameters, recurrence and/or tumor diameter greater than 3 cm were significantly correlated with lower PON1 activity. Enzyme activities were not significantly affected by the presence of any other parameter (Table 3).

Discussion

Bladder cancer is a common pathology with high mortality and morbidity rates. Many factors, including oncogenes, tumour-suppressor genes, aniline dyes and smoking, have been implicated in BC etiology. Many of these etiologic factors are correlated with oxidative stress. Gecit et al.[26] in 2012 and Badjatia et al.[28] in 2010 reported increased oxidative stress and increased total antioxidant activity in BC patients.

In a healthy organism, oxidant levels and the effects of antioxidant s on them are in balance. Up to a point, increased number of oxidant molecules are neutralized in the body by natural an-

Table 2. Correlation of enzymatic activities of PON1 and ARE with lipid parameters

	PON1		ARE	
	p	r	p	r
Total cholesterol (mg/dL)	0.001	0.321	0.000	0.460
HDL (mg/dL)	0.012	0.237	0.079	0.166
LDL (mg/dL)	0.003	0.274	0.001	0.311
VLDL (mg/dL)	0.189	0.124	0.001	0.307
Triglyceride (mg/dL)	0.188	0.125	0.001	0.307

PON1: Paraoxonase; ARE: Arylesterase; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very- low- density lipoprotein

Table 3. Correlations between tumoral characteristics, and enzymatic activities of PON1 and ARE

		PON1	p	ARE	p
Grade	Low (n=30)	112.87±42.47	0.064	137.68±37.13	0.243
	High (n=26)	92.36±38.11		125.08±42.69	
Muscle invasion	Absent (n=40)	107.38±43.81	0.232	133.89±39.99	0.529
	Present (n=16)	92.33±32.94		126.20±40.66	
Recurrence	Absent (n=26)	116.56±41.52	0.025	125.83±39.08	0.231
	Present (n=30)	91.90±38.46		138.76±40.56	
Number of tumor foci	Single	106.49±39.78	0.942	138.31±38.04	0.859
	2-7 (n=24)	109.26±40.11		126.13±39.58	
	>8 (n=5)	57.50±34.03		126.67±54.65	
Tumor diameter	<3 cm (n=31)	114.33±44.36	0.026	133.79±41.35	0.687
	>3 cm (n=25)	89.73±33.57		129.41±38.83	

PON1: Paraoxonase; ARE: Arylesterase

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tioxidant molecules that are always present to a certain extent. If oxidants are produced at higher levels or if the antioxidant s become ineffective, the equilibrium is disturbed and oxidant molecules destroy the structural elements of the organism, including protein, lipid, carbohydrate, nucleic acid and beneficial enzymes.[28] Increases in free radicals and subsequently in oxidative stress result in accelerated rates of mutation and oncogenic turnover, inducing DNA damage and tumour development.[29]

Since PON1 enzyme has played an antioxidant role in preventing oxidation of LDL, this enzyme has been thought to be associated with many diseases with oxidative stress as part of their pathogenesis. However, the association between serum PON1 activity and cancer has not yet been elucidated, although their levels have been determined to be low in many cancers.[24,30]

To the best of our knowledge, a limited number of studies have investigated the association between BC and the activities of serum PON1 and ARE enzymes. Öztürk et al.[31] investigated the relationship between PON1 gene polymorphism and BC and determined that the genetic polymorphism in the 192nd position differed significantly between healthy subjects and BC patients and that the RR genotype was observed more commonly in bladder tumours.

Aydın et al.[18] investigated the association between BC and the ARE enzyme, finding significantly lower ARE activity in BC patients than in healthy controls. However, there was no significant difference between the two groups regarding PON1 and TAS levels. In contrast, the present study found significantly lower levels of both enzymatic activities of PON1 and ARE in serum in the patient group. Our study is important because, as revealed in our current literature review, it is the first study investigating the correlation between PON1 and BC.

Eroglu et al.[19] found that patients with prostate cancer had significantly lower PON1 levels but without any significant difference between the patients and the controls regarding other oxidative parameters. Enzymatic activity of PON1 has also been investigated in patients with lung, gastric, pancreatic, endometrial, epithelial, ovarian and esophageal cancers, all of which showed significantly lower activity levels for this enzyme.[21-25] All these studies suggest that the antioxidant effects of the PON1 enzyme may protect against cancer.

In the present study, the patient and control groups were similar regarding all demographic characteristics that can affect PON1 and ARE activities, including age, gender, BMI, smoking, diabetes and hypertension. Therefore, these variables, were considered irrelevant in correlation analysis. In addition, the present study investigated the relationship between PON1 enzyme levels and lipid parameters, and demonstrated significant positive correlations between PON1 and levels of total cholesterol, HDL and LDL. These results conform to those of the studies cited in the literature.[22,23,25] Furthermore, the present study investigated serum oxidative stress parameters, and found statistically significantly increased TOS, decreased TAS levels, and increased OSI index in the patient group. As reported in previous studies cited in the literature, these data support the presence of a strong association between oxidative stress and cancer which are commonly present in combination.[32]

The present study further subdivided the patient group by tumor grade, muscular invasion, recurrence, number of tumoral foci and tumor diameter to investigate the relationship between these tumor parameters and enzymatic activities of PON1, and ARE. Results of the present study have indicated that enzyme levels decreased as the severity of each parameter increased. However, these decreases were statistically significant only for recurrent tumors, and tumors larger than 3 cm in diameter. The insignificance of tumor foci, grade, and muscle invasion in correlaation anaalysis may be due to the small sample size of the study.

One potential limitation of this study is the limited number of patients. The findings of this study can be supported by studies with larger number patient groups. Taken together, these finding suggest that measures of enzymatic activities of PON1 and ARE may provide important prognostic data for BC cases.

The present study found disturbances in serum oxidative balance and formation of oxidative stress in BC patients. Oxidative stress is thought to play a role in cancer-development mechanisms mediated by lipid peroxidation. PON1 and associated ARE are known to protect LDL from oxidation, to exhibit antioxidant features and to support the detoxification of carcinogenic, lipid-soluble radicals produced after lipid peroxidation. In addition, the study has demonstrated that decreased serum enzymatic activities of PON1 and ARE are associated with the presence of BC and some of the prognostic features of BC.

This study is one of the first to investigate the correlation between BC, serum enzymatic activities of PON1 and ARE. Results suggest that levels of PON1 and ARE enzyme activity may be important markers for the diagnosis and prognosis of BC and that further investigations on this topic are warranted.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Harran University Department of Scientific Research Coordination (Project Number 1044).

Informed Consent: Written informed consent was obtained from patients who participated in this study.
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