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THE PHENOTYPE DISTRIBUTION OF PARAOXONASE-1 IN PATIENTS WITH MULTIPLE MYELOMA, BLADDER, AND COLORECTAL CANCER

FENOTIPSKA DISTRIBUCIJA PARAOKSONAZE-1 KOD PACIJENATA SA MULTIPLIM MIJELOMOM, KANCEROM BEŠIKE I KOLOREKTALNIM KANCEROM

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Summary

Background: Human serum paraoxonase-1 (PON1) shows wide variation among different ethnic groups around the world. The aim of the present study was to determine the phenotype distribution and enzymatic activity of PON1 and ARE (arylesterase) in colorectal cancer (CRC), bladder cancer (BC) and multiple myeloma (MM) patients compared to healthy subjects.
Methods: A total of 160 subjects (40 CRC patients, 40 BC patients, 40 MM patients and 40 healthy controls) were admitted to the study. The phenotype distribution of PON1 was determined by using the dual substrate (paraoxon and phenylacetate) method.
Results: PON 1 and ARE activities were significantly lower in the cancer patients compared to the control group. The following phenotype distributions were assessed in the cancer and control groups: MM: 52.5% (QQ), 40% (QR), 7.5% (RR); CRC: 52.5% (QQ), 40% (QR), 7.5% (RR); BC: 55% (QQ), 35% (QR), 10% (RR); and controls: 40% (QQ), 57.5% (QR), 2.5% (RR).
Conclusions: We found that MM, CRC and BC patients were associated with lower PON1, ARE and stPON1 enzyme activities compared to the healthy subjects. However, PON1 phenotypes were similar between the cancer groups and control group.

Keywords: paraoxonase, arylesterase, oxidative stress, phenotype

Kratak sadržaj

Uvod: Humana serumska paraoksonaza-1 (PON-1) ispoljava velike varijacije među različitim etničkim grupama širom sveta. Cilj ove studije bio je da se odrede fenotipska distribucija i enzimska aktivnost PON1 i ARE (arilesteraze) kod pacijenata sa kolorektalnim kancerom (KRK), kancerom bešike (KB) i multiplim mijelomom (MM) u poređenju sa zdravim ispitanicima.
Metode: Studijom je obuhvaćeno ukupno 160 ispitanika (40 pacijenata sa KRK, 40 sa KB, 40 sa MM i 40 zdravih osoba). Fenotipska distribucija PON1 određena je metodom dvostrukog supstrata (paraokson i fenilacetat).
Rezultati: Aktivnosti PON1 i ARE bile su značajno niže kod obolelih od kancera u poređenju sa kontrolnom grupom. U grupama obolelih od kancera i kontrolnoj grupi utvrđene su sledeće fenotipske distribucije: MM: 52,5% (QQ), 40% (QR), 7,5% (RR); KRK: 52,5% (QQ), 40% (QR), 7,5% (RR); KB: 55% (QQ), 35% (QR), 10% (RR); i u kontrolnoj grupi: 40% (QQ), 57,5% (QR), 2,5% (RR).
Zaključak: Otkrili smo vezu između pacijenata sa MM, KRK i KB i nižih enzimskih aktivnosti PON1, ARE i stPON1 nego kod zdravih ispitanika. Međutim, fenotipi PON1 bili su slični u grupama sa kancerom i kontrolnoj grupi.

Ključne reči: paraoksonaza, arilesteraza, oksidativni stres, fenotip

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Introduction

Human serum paraoxonase (PON1) and arylesterase (ARE) are lipophilic antioxidant enzymes. Serum PON1 binds to high density lipoprotein (HDL) and contributes to the elimination of organophosphorus compounds and free radicals. PON1 is one of the endogenous free-radical scavenging systems in the human organism (1, 2). Serum PON1 and ARE have been demonstrated to function as a single enzyme (3). Human serum PON1 indicates neither age-related change in activity nor gender differences (4). However, cigarette smoking, acute phase proteins, pregnancy and diet affect serum PON1 activities (5–7). Reduced PON1 enzyme activities have been shown in several groups of patients with hypercholesterolemia, diabetes mellitus, and cardiovascular disease, in which the patients are under increased oxidative stress (8, 9).

PON1, PON2 and PON3 are members of a family of proteins. The genes encoding these enzymes are located on the long arm of chromosome 7q21.3. PON1 is widely distributed among tissues such as the liver, kidney, intestine and blood plasma. There is a 10 to 40-fold inter-individual variability in serum PON1 activity, when paraoxon is used as the substrate (10). One source of the variability is the polymorphism of the PON1 gene. Molecular and epidemiologic studies have shown that there are two significant common functional genetic polymorphisms in the coding region of the gene at positions 55 and 192 of the PON1 gene. Substitution of glutamine (Q genotype) at position 192 in exon 6 of the PON1 gene by arginine (R genotype) is the first polymorphism. Likewise, substitution of leucine (L genotype) at position 55 in exon 3 by methionine (M genotype) is the second polymorphism (11, 12). Studies emerged that polymorphisms of the PON1 gene may affect PON1 activity. The PON1 activity of the PON1 192 R allele carriers was reported to be higher than that of the Q carriers (13, 14). Accordingly, human paraoxonase has three phenotypes: RR with high paraoxonase activity, QR with intermediate activity, and QQ with low activity (6). Epidemiologic studies have shown associations between these polymorphisms and different types of cancer, such as lung (15), breast (16), brain (17), and ovarian (18) cancers.

The aim of the present study was to determine the phenotype distribution and enzymatic activity of PON1-ARE in colorectal cancer (CRC), bladder cancer (BC) and multiple myeloma (MM) patients and healthy subjects.

Materials and Methods

Subjects

A total of 160 people (40 CRC patients, 40 BC patients, 40 MM patients and 40 healthy subjects as the control group), all Caucasian in origin, were admitted to the study. Any subject, whether in the cancer or control group, who had pathologies that could cause secondary lipid disorders, cardiovascular diseases, diabetes mellitus, chronic infection and inflammation, alcohol abuse or who used antilipidemic and antioxidant drugs, was excluded from the study. We had a questionnaire that included questions on demographics, diet, and other lifestyle factors. In light of this questionnaire, we included patients with similar diet and lifestyle.

CRC patients

Forty newly diagnosed – receiving no treatment CRC patients (18 females, 22 males; mean age: 56.9±13.7 years) admitted to the Outpatient Clinic of Surgery were prospectively included in the study. Final diagnosis of each patient was confirmed by the microscopic evaluation of colonoscopic biopsy samples, followed by total excision of tumors. The following pathologic findings were assessed: Grade 1 adenocarcinoma in 6 patients, grade 2 adenocarcinoma in 27 patients, grade 3 adenocarcinoma in 7 patients.

BC patients

Forty newly diagnosed – receiving no treatment BC patients (15 females and 25 males; mean age: 68.4±10.8 years) who had presented to the Urology Outpatient Clinic were prospectively included in the study. All subjects were diagnosed to have BC (urothelial carcinoma) after pathologic review of transurethral resection (TUR) biopsies of the bladder. The final pathology reports of BC patients were evaluated, and subjects were divided into groups according to the tumor grades (high/low grade) and presence of muscularis propria invasion (present/absent). Twenty-five patients were low grade, 15 patients were high grade and in 10 patients the tumor showed muscularis propria invasion.

MM patients

Forty MM patients (18 females and 22 males; mean age: 67.5±8.4 years) were prospectively included into the study. The patients were in various stages of disease and in different phases of treatment and response. The following paraproteins were assessed using gel electrophoresis: IgG kappa in 21 patients, IgG lambda in 4 patients, IgA kappa in 6 patients, IgA lambda in 2 patients, IgM kappa in 5 patients and IgM lambda in 2 patients.

Control group

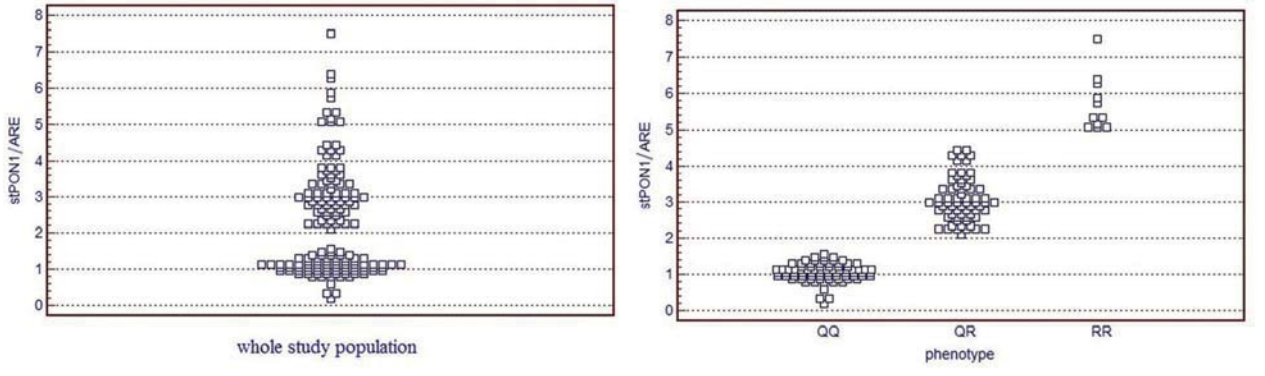
Forty healthy control subjects of corresponding gender and age (19 females and 21 males; mean age: 66.4±6.7 years) were also enrolled for comparison.

Analytical Methods

Measurement of paraoxonase and arylesterase enzyme activities in serum. PON1 and ARE enzyme activities were measured by using commercially available kits (Relassay®, Turkey). A fully automated PON1 activity measurement method consists of two different sequential reagents; the first reagent is an appropriate Tris buffer and it also contains a calcium ion, which is a cofactor of the PON1 enzyme. Linear increase in the absorbance of p-nitrophenol, produced from paraoxon, was followed by kinetic measurements. Non-enzymatic 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 mmol of paraoxon hydrolyzed per liter per minute at 37 °C (19). Phenylacetate was used as a substrate to measure the ARE activity. PON1, present in the sample, hydrolyzes 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. Non-enzymatic hydrolysis of phenylacetate was subtracted from the total rate of hydrolysis. The molar absorptivity of the 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 (20).

Paraoxonase phenotype distribution. The genetic polymorphism Q/R in codon 192 is responsible for three isotypes: QQ (low activity), QR (intermediate activity), and RR (high activity). The phenotype distribution of PON1 was determined using the dual substrate method. The ratio of paraoxon hydrolysis in the presence of 1 moL/L NaCl (salt stimulated paraoxonase: stPON) to phenylacetate hydrolysis was used to assign individuals to one of the phenotypes (19). The ratio provided by dividing salt-stimulated paraoxonase by the arylesterase enzyme activity demonstrated a trimodal PON1 frequency distribution in the whole study population (*Figure 1*). Accordingly, the cut-off values for assigning a participant to a phenotype were <2.0 for QQ, 2.0 to 5.0 for QR and >5.0 for RR. Allele-Q and allele-R were in excellent agreement with the Hardy-Weinberg equilibrium (*Figure 1*).

Routine parameters. The levels of triglycerides (TG), total cholesterol (TC), HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) were determined by using commercially available assay kits (Abbott) with an autoanalyzer (Architect ®c16000, Abbott Diagnostics).



Hardy-Weinberg equilibrium for the whole study population				
Observed number of individuals with each phenotype*	Observed allele frequencies	Expected genotype frequency	Expected number in population	Observed-Expected population
Phenotype-QQ=80 (50%)	Allele (p)=0.7156	p^2=0.512	81.9	–1.9
Phenotype-QR=69 (43%)	Allele (q)=0.2843	2pq=0.406	65.1	3.9
Phenotype-RR=11 (7%)		q^2=0.08	12.9	–1.9
Whole study population=160	Hardy-Weinberg equilibrium:	$p^2+2pq+q^2=1$		x^2=0.1 NS

*Based on stPON1/ARE (dual substrate method); the cut-off values for assigning a participant to a phenotype were <2.0 for QQ, 2.0 to 5.0 for QR and >5.0 for RR. NS: Non-significant

Figure 1 Paraoxonase phenotype distribution in the whole study population.

Statistical analysis

Statistical analyses were carried out using statistical software (version 11.5.1.0, MedCalc, Mariakerke, Belgium). In normally distributed groups the results were presented with mean and SD. The significance of the differences between groups was determined by Student's unpaired t-test for normal distributions, and by the Mann-Whitney U-test in abnormal distribution. The significance of association between variables was evaluated by using Chi-square. P value of 0.05 was accepted as the significance level.

Results

CRC patients were significantly younger than the three other age matched groups ($p<0.001$). LDL-C was significantly higher in the BC patients ($p<0.001$). PON1, ARE and stPON1 activities were significantly lower in cancer patients compared to the healthy subjects ($p<0.001$ for PON1, ARE activities and $p=0.001$ for stPON1). Demographic and laboratory findings obtained from cancer patients and controls are summarized in *Table I*.

The phenotype distribution of PON1 was determined by using the dual substrate method. The resulting ratio was used to assign a phenotype to each par-

Table I Laboratory findings and demographic characteristics of cancer patients and healthy controls.

Parameter	MM (n=40)	CRC (n=40)	BC (n=40)	Control (n=40)	p
Age, M±SD, year	67.5± 8.4	56.9±13.7	68.4±10.8	66.4±6.7	<0.001
Male	22 (%55)	22 (%55)	25 (%62.5)	21 (%52.5)	
Female	18 (%45)	18 (%45)	15 (%37.5)	19 (%47.5)	0.47
Smoker	10 (%25)	14 (%35)	7 (%17.5)	10 (%25)	0.58
BMI, kg/m^2	26.2±3.6	25.74±2.54	25.9±4.8	25.1±4.2	0.65
TC, mmol/L	3.9±1.4	3.7±0.5	4.15±1.0	4.2±0.6	0.06
HDL-C, mmol/L	0.87±0.3	0.91±0.2	0.93±0.1	1.0±0.2	0.08
LDL-C, mmol/L	2.41±1.1	2.6±0.3	3.2±0.4	2.5±0.6	<0.001
TG, mmol/L	1.17±97	1.06±0.9	1.54±0.8	1.6±1	0.79
PON1, (U/L)	139.8±88	128.2±63	146.6±28	231.8±96	<0.001
ARE, (kU/L)	188.6±98	150.6±49	162.6±20	231±53	<0.001
stPON1, (U/L)	347±238	323±195	364±269	541±300	0.001
stPON1/ARE	2.2±1.6	2.3±1.5	2.2±1.4	2.2±1.1	0.74

TC: Total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, TG: triglyceride, BMI: body mass index, PON1: paraoxonase-1, ARE: arylesterase, stPON1: salt stimulated paraoxonase-1.

Table II The phenotype distribution of cancer patients and healthy controls.

Parameters (n)	**MM (n=40)**	**CRC (n=40)**	**BC (n=40)**	**Control (n=40)**	**p**
QQ (80)	21 (52.5%)	21 (52.5%)	22 (55%)	16 (40%)	0.47
QR (69)	16 (40%)	16 (40%)	14 (35%)	23 (57.5%)	
RR (11)	3 (7.5%)	3 (7.5%)	4 (10%)	1 (2.5%)	

There were no significant differences in the PON1 phenotype distribution when cancer patients and control group were compared (Chi-square test).

Table III PON1 phenotype and lipid parameters in whole study population.

Parameter	TC	TG	HDL-C	LDL-C
QQ (80)	83.5	82.6	32.6	81.5
QR (69)	81.3	78.2	36.1	80.8
RR (11)	73.3	79.0	47.1	70.6
p	**0.5**	**0.8**	**0.06**	**0.7**

HDL-C levels were higher in RR phenotype, but it did not show a significant difference. (Kruskal-Wallis test and avarage rank for all parameters)

ticipant: QQ, QR and RR. The following phenotype distributions were found in the cancer and control groups: MM: 52.5% (QQ), 40% (QR), 7.5% (RR); CRC: 52.5% (QQ), 40% (QR), 7.5% (RR); BC: 55% (QQ), 35% (QR), 10% (RR), and control: 40% (QQ), 57.5% (QR), 2.5% (RR). QQ (low activity) phenotypic distribution was more common in cancer groups than controls, but it did not show a significant difference. The following phenotype distributions were found in the study population (n=160): QQ in 80 (50%) subjects, QR in 69 (43%) subjects and RR in 11 (7%) subjects. The phenotype distribution and its relation with cancer groups are shown in *Table II*.

When lipid parameters were compared between the phenotype groups, HDL-C levels were higher in the RR phenotype, but it did not show a significant difference (*Table III*). TC, LDL-C and TG levels did not differ significantly between the phenotype groups.

Discussion

All cells in the human body sustain a condition of homeostasis between the oxidant and antioxidant species. Oxidant–antioxidant balance is very important for normal metabolism, signal transduction and regulation of cellular functions. When an increase in the oxidants and a decrease in the antioxidant defense system cannot be prevented, the oxidative/antioxidative balance eventually shifts toward the oxidative status. Proteins, lipids and DNA are significant targets for oxidative attack, and modification of these molecules can increase the risk of somatic mutations and neoplastic transformation. In fact, the development of cancers and their progression have already been linked to DNA mutations and damage, genome instability, and cell proliferation caused by oxidative stress (21, 22).

The human body has a number of endogenous free-radical scavenging systems. HDL-associated PON1 and ARE are among the enzymes involved in such systems. These enzymes contribute to the detoxification of organophosphorus compounds and carcinogenic lipid-soluble radicals from lipid peroxidation (1–3). Studies have revealed that PON1 expression is alleviated in human lung cancer (23), pancreatic (24), and gastric cancer (25). Accordingly, in our study, we found PON1 and ARE activities to be significantly lower in the MM, CRC and BC patients compared to the healthy subjects. We detected that salt stimulated PON1 was significantly decreased in all cancer patients. The reason for this might be an increase in intracellular oxidants that leads to a parallel decrease in antioxidants, finally disrupting the structure of enzymes, in this case PON1 and ARE. Cachexia and malnutrition in cancer patients are important problems due to a variety of mechanisms. In the later stages of disease, malnutrition and inflammation suppress protein synthesis (26). Likewise, PON1 and ARE activities may decrease due to suppressed protein synthesis, cachexia and malnutrition, as the host response to the tumor.

PON1 shows wide variation among different ethnic groups all around the world. One source of the variability is the polymorphism of the PON1 gene (19). The low-activity phenotype has been shown subsequently to represent homozygosity for the PON1 192 Q allozyme. The high–PON1 activity phenotype represents a combination of the heterozygotes and the homozygotes for the PON1 192 R allele (27, 28). The PON1 activity phenotyping method, based on the ratio of the stimulated PON1 activity and the ARE activity, could determine the low-activity homozygotes (QQ), intermediate activity heterozygotes (QR), and high-activity homozygotes (RR) regardless of the genotype (29). However, the phenotyping ratio process, mentioned above, provided a direct quantitative measure of the functional effects of the classic or variant forms of the PON1 with several substrates. This information, referred to as the »PON1 enzyme activity status«, supplies more data than the genotype for the relationship with disease sensitivity (30).

In our study, the distribution of paraoxonase activity was trimodal and suggested low (Type QQ), high (Type RR) and intermediate (Type QR) activity. PON1 phenotypes are similar between cancer patients and the control group. However, QQ (low activity) phenotypic distribution was more common in cancer patients than controls, but it did not show a significant difference. PON1 phenotype distributions were assessed in the whole study population (n=160) as: QQ in 50% subjects, QR in 43% subjects and RR in 7% subjects.

In summary, we found no significant differences in the phenotype frequencies of PON1 between the cancer patients and control subjects. We found that MM, CRC and BC patients were associated with PON1-ARE and stPON enzyme activities lower than in the healthy subjects. Accordingly, there was no predisposition of the phenotype of PON1 in the cancer patients. The reason for the decrease in the activity of PON1 and ARE may be impaired oxidant/antioxidant balance or other factors. The major limitation of our study was the small number of participants, and the lack of markers of oxidative stress like TBARS, to judge the exact state of oxidative status in the subjects. Further work is required in large case–control studies to determine the PON1 function (PON1 activity, phenotype and genotype) in diseases; thus, we will be able to understand the impact of PON1 function in the etiology, pathophysiology and prognosis of diseases.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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