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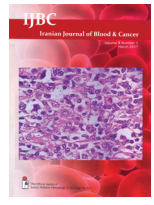

ORIGINAL ARTICLE

Paraoxonase and Arylesterase Activities in Patients with Cancer

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ABSTRACT

Background: Cancer has the highest disease-related mortality rate in Iran. Reduced activity of paraoxonase reported in patients with cancer may be due to a reduction in its antioxidant properties and a subsequent increased risk of developing cancer. We aimed to assess antioxidant and oxidative status in patients with cancer through measuring the activity of PON1 as an antioxidant enzyme and determining MDA as a marker of oxidative stress.
Methods: This case-control study was conducted on 50 patients with colon, lung, blood or breast cancer and 50 age- and sex-matched healthy controls matching during 2014-2015. Paraoxonase-1 and arylesterase activities were measured with paraoxon and phenylacetate substrates and their malondialdehyde levels and serum lipid profile were determined through spectrophotometry.
Results: Serum paraoxonase activity was lower in patients with cancer (28.52±2.77 IU/L) compared with the healthy subjects (96.57±1.49 IU/L; P<0.0001). Similarly, serum arylesterase activity was lower in patients with cancer (49.27±2.90) than the controls (66.91±2.47; P<0.0001). MDA levels were higher in patients with cancer (1.3166±0.0876) than the healthy controls (0.9008±0.0452). The Mann-Whitney U-Test showed significant differences between the two groups in terms of their triglyceride levels (P<0.05). Although serum HDL levels were higher in the control group compared with the cases, the difference was not statistically significant (P>0.05). Serum VLDL, LDL and total cholesterol levels differed significantly between the two groups (P<0.05).
Conclusion: The results obtained showed a reduction in paraoxonase activity and an increased lipid oxidation in the patients with cancer and thereby reduced the antioxidant power of paraoxonase and weakened the body's antioxidant system.

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Introduction

In many countries, cancer is the second cause of mortality.[1,2] in Iran, it is the third leading cause of death after cardiovascular diseases and accidents.[3] The etiology of cancer remains unknown and different factors have been proposed to cause it. Some studies propose genetic factors as the fundamental causes of cancer,[4,5] and other have proposed environmental factors,[6,7] nutrition,[8,9] and infections, smoking and alcohol.[10-12] Nevertheless, the most fundamental cause of cancer is known to be oxidative stress, which is inevitable for aerobic organisms,[13] and can be a major mediator in the damage of cell structures such as proteins, membranes, lipids and the DNA,[14] as an excessive reactive oxygen species (ROS). Increased oxidative stress and oxygen free radicals increase the risk of developing different types of cancer.[15] Low antioxidant levels that increase free radical activities significantly increase the risk of cancer.[16] Reactive oxygen metabolites play a major role in the pathogenesis of gastric and intestinal mucosal

inflammation and cancer.[17] Lipid peroxidation is a known indicator of free radical activity[16] and malondialdehyde (MDA) is one of the final products of lipid peroxidation with a higher rate in patients with cancer.[18-21] The antioxidant system is a set of enzymes and antioxidants that act against free radicals and oxidants; paraoxonase 1 (PON1) appears to be one of these antioxidant enzymes. Some in-vitro studies have proposed paraoxonase as a strong oxidation inhibitor that causes H2O2 hydrolysis.[22] Moreover, PON1 prevents LDL oxidation by removing the oxidized phospholipids.[23]

Paraoxonase 1 is synthesized in the liver and binds to HDL (an active site) in the blood and improves the antioxidant properties of HDL.[24] This enzyme has several different catalytic activities, including paraoxonase, arylesterase, diazoxonase and lactonase activities.[25-27] PON1 is the best and most known PON and is able to destroy lipid peroxides before their accumulation on LDL.[28] The physiological substrates of the enzyme are still unknown, but paraoxonase and arylesterase activities are both performed on single PON1 and paraoxon and phenylacetate are their synthetic substrates, respectively.[17] Oxidizers may be produced or restored in the body through the oxidation metabolic pathways or due to the consumption of oxidized fats. Given that this enzyme binds to HDL, its activity levels were measured along with the lipid profile. Changes in size significantly affect the shape of the binding and the stability of PON1 and reduce its antioxidant capacity.[29] The oxidation of low-density lipoproteins (LDL) in the artery walls is responsible for the initiation and progression of atherosclerosis. High-density lipoproteins (HDL) prevent atherosclerosis and can reduce LDL oxidation. HDLs have a variety of functions that help its protective effect against atherosclerosis, including antioxidant, anti-fibrinolytic and anti-inflammatory properties, and also inhibit matrix metalloproteinase and help keep the endothelial plaques normal and intensify endothelial restoration. As LDLs and their oxidized species are associated with the failure of various tissues followed by different diseases such as cerebral, cardiac, hepatic and renal diseases, diabetes and cancer, most recent studies has been dedicated to the antioxidant properties of paraoxonase.[30] Different studies have also confirmed the role and significance of PON1 in the pathogenesis of different diseases such as diabetes, chronic renal failure, obesity, and the metabolic syndrome, cardiovascular diseases, Alzheimer's disease, HIV infection, chronic hepatic disorder and cancer.[31,32] As a result, paraoxonase 1 is likely to reduce the risk of cancer through its antioxidant properties. Given the limited number of studies on the role of PON1 in cancer, we aimed to assess antioxidant and oxidative status in patients with cancer through measuring the activity of PON1 as an antioxidant enzyme and determining MDA as a marker of oxidative stress.

Materials and Methods

The present case-control study was conducted on 50 patients from Khuzestan province with colon, lung, blood, or breast cancer admitted to the Adult Hematology Division of Shafa Hospital in Ahvaz, Iran, during 2014-2015. The patients were diagnosed with these cancers through blood tests and histopathological findings.

A total of 50 age- and sex- matched healthy individuals were selected as the control group. The controls lacked underlying diseases, diabetes, kidney or liver failure and blood diseases and were selected from the healthy subjects referring to the hospital's medical laboratory. Fasting venous blood samples were obtained and after being transferred to the laboratory, their serum was centrifuged at 3000 rpm for 15 minutes and immediately frozen at -80 °C for the tests.

Paraoxonase Activity Measurement

Paraoxonase activity was measured by adding 20 µl of the serums (dilution 1:10) to 180 µl of paraoxon (1.2 mmol paraoxon in 1 M Tris-Hcl and 1 M NaCl buffer containing 1 M CaCl2 and PH=8.5) at 37 °C and with a wavelength of 405 nm.[33] Paraoxonase activity was expressed in $nmolmin^{-1}ml^{-1}$ in serum.

Arylesterase Activity Measurement

Arylesterase activity was measured with phenyl acetate (Fluka) according to the method proposed by Gan and colleagues using the synthetic substrate of paraoxonase 1. Phenyl acetate was purchased from the Merck Group in Germany along with some other necessary substances. The substrate solution was prepared fresh every day and stored in a closed container and shaken intensely before each use. 10 µl of the serum was then added to the reaction mixture containing 2 mmol of phenyl acetate and 2 mmol of CaCl2 in 100 mmol of Tris-HCl buffer (pH=8). The substrate hydrolysis rate was measured using a spectrophotometer at 37 °C and with a wavelength of 270 nm with UV 1250 (made by Shimadzu in Japan). The enzyme activity was calculated with an extinction coefficient of 1310 $M^{-1}cm^{-1}$ mol/liter and the results were reported in mol/min/ml of serum.[34]

Oxidative Status Measurement

Serum levels of MDA were measured as a marker of lipid peroxidation using Yagi's method, [35] and based on their reaction with thiobarbituric acid and a measurement of the solution absorption and its mixture with n-butanol by mixing 125 µl of its serum with 5.1 ml of phosphoric acid in a test tube and by adding 0.5 ml of thiobarbituric after stirring. The tube containing the mixture was then placed in boiling water for 45 minutes. After cooling, 1 ml of n-butanol was added and centrifuged for 10 minutes; the mixture's pink supernatant was then separated and its absorption was measured at a wavelength of 532 nm and the standard curve solution of MDA formed from tetraethoxypropane was thus obtained.[35]

Lipid Profile Measurement

Triglycerides (TG), Total Cholesterol (CH) and High-Density Lipoproteins (HDL) were measured with standard biochemical methods using commercial laboratory kits (made by Pars Azmoon Co., Tehran, Iran) and also with enzymatic methods using autoanalyzer BT3000; LDL

levels were calculated using Friedewald's formula or through electrophoresis.[36]

Friedwald's Formula

LDL=Total cholesterol-[HDL+TG/K], where k=5.

Very low-density lipoprotein cholesterol, VLDL-C

The samples' VLDL-C was calculated using the following equation:

VLDL-C (mg/dl)=TG (mg/dl)/5

Data Analysis

Data analysis was done using SPSS software, version 22. The quantitative variables were expressed as mean ± standard deviation and the qualitative variables as a percentage. The t-test was used to compare the groups and assess their differences. Pearson's correlation coefficient was used to assess the dependence between the variables. Non-parametric tests were used for the non-normally-distributed variables. The level of statistical significance was set at P≤0.05.

Results

Of the 50 patients examined, 14 (28%) were women and 36 (72%) were men with a mean±SD age of 54.22±13.99 years (range: 25-88 years). Of the total of 50 healthy subjects examined, 17 (34%) were women and 33 (66%) were men with a mean±SD age of 42.22±11.96 years (range: 25 to 70 years) (table 1).

Table 2 presents a comparison of the paraoxonase and arylesterase activities, the MDA levels and the lipid profile. These results suggest a significant reduction in paraoxonase and arylesterase activities in the patients and a significant increase in serum levels of MDA and triglyceride in the group of patients compared to the control group. An inverse correlation was therefore observed between paraoxonase and arylesterase activities and MDA levels (r=-0.457, P≤0.0001 and r=-0.303, P<0.002, respectively) and a direct correlation was also observed between paraoxonase activity and HDL cholesterol levels (r=0.213, P=0.039).

Discussion

Few studies have been conducted to measure PON1 activity in patients with cancer. The present study is one of the few in which paraoxonase, MDA and arylesterase levels are simultaneously measured in patients with blood, colon, lung, or breast cancer. Oxidative stress damages the biological membranes, the intracellular organelles and macromolecules such as proteins and DNA, and can lead to the production of active compounds such as aldehydes, ketones, and hydroxy acids. These radicals are produced in the body as a result of oxidation and restoring reactions within the body or else as a result of environmental factors outside the body. An imbalance in the formation and removal of these radicals, including reactive oxygen species (ROS), can cause genetic damage, interfere with cellular signals and cause neurodegenerative diseases, aging and metastasis. Cardiovascular diseases such as atherosclerosis and coronary artery disease are their long-term pathological presentation.[37] Oxidant-antioxidant balance appears to be important in the initiation and progression of cancer.[38] This study therefore measured PON1 in patients with cancer relying on the enzyme's antioxidant properties and found the enzyme's activity to be significantly lower in patients with cancer compared with the controls. Previous studies have reported similar findings. For example, Akçay and colleagues examined patients with gastric cancer and found PON1 activity to be significantly lower in them compared to in the controls.[23] Baskül[19] also obtained similar results. In line with the present findings, another study examined

Table 1: Mean age and BMI of the case and control group

Variables	Patients group		Control group	
	Men	Women	Men	Women
Sex	36	14	33	17
Age (year)	12.718±55.72	50.35±16.735	46.909±11.601	33.11±6.009
(kg/m2) *BMI	28.84±0.257	28.35±0.201	26.306±0.208	26.55±0.325

*BMI, body mass index

Table 2: Comparison of Paraoxonase, Arilesterase enzymes activity, Lipid peroxidation and lipid profile in two groups of the study (individuals suffering from cancer and healthy ones)

Variable	Patients group	Control group	P value
Paraoxonase)U/L)	28.52 ±2.77**	96.57±1.49	0.000
Aril Esteraz)U/L)	2.9**±49.27	66.91±2.47	0.000
MDA(nmol/L)	1.316±0.087 **	0.9008±0.0452	0.000
HDL-C (mg/dl)	48.91±2.72	53.98±1.56	0.281
Triglyceride (mg/dl)	137.17±12.92 *	105.12±5.0	0.02
LDL-C (mg/dl)	58.28±2.59 **	88.96±2.63	0.000
Cholesterol)mg/dl)	139.93±5.09 **	168.1±3.29	0.000
VLDL-C (mg/dl)	27.11±16.56*	21.02±7.085	0.02

TG: Triglycerides; LDL: Low-density lipoprotein; CHO: Cholesterol; HDL: High-density lipoprotein; VLDL: Very low density lipoprotein; PON Serum paraoxonase ARE: Arylesterase; MDA: Malondialdehyde; Results have been stated as±standard deviation average (values are mean±SD). *Significant difference with control group approximate to 0.05; **Significant difference with control group approximate to 0.0001

patients with esophageal and gastric malignancies and found a significant reduction in arylesterase and paraoxonase in them.[17] Another study observed a significant reduction in PON1 in patients with lung cancer.[15] Oxidative stress is also one of the main risk factors for cancer[35] that sometimes occurs in the body due to disrupted mitochondrial function or inadequate defense mechanisms.[36,37] The present study used MDA as a measure of serum lipid peroxidation. Low antioxidant enzyme activities reduce the antioxidant capacity and increase lipid peroxidation and its metabolic product, MDA, while increased antioxidant enzyme activities inhibit lipid peroxidation and thus reduce MDA production.[39] As expected, MDA levels were significantly higher in cancer patients compared to in the healthy controls, suggesting an increased lipid peroxidation in these patients. Previous studies also confirm this finding.[19,21,39,40] One of the main capabilities of HDL is that it functions as a depository of antioxidant enzymes that can reduce ample levels of oxidized phospholipids from the blood. Paraoxonase is one of the main blood plasma antioxidants that limit the accumulation of oxidized phospholipids in plasma lipoproteins.[41] Although some other HDL-binding proteins, such as apolipoprotein A1, lecithin cholesterol acyl transferase and platelet-activating factor acetyltransferase, also have antioxidant properties, the antioxidant activity of PON1 appears to be the most significant.[42]

Measuring the lipid profile yielded the following results: Triglyceride and VLDL levels increased significantly in the group of patients compared to in the controls; however, HDL cholesterol levels were lower in the patients than in the controls, although the difference was not statistically significant. A significant reduction was also observed in LDL and total cholesterol levels in the patients compared to in the controls. Similar results were reported in the study by Akçay et al.[23] Previous studies have compared PON1 and lipid peroxidation (MDA) levels in patients with gastric cancer and hepatitis and have found a significant inverse relationship between them.[19,43] In another study, PON1, ARE and MDA levels were measured in those exposed to ionizing radiation and a significant inverse relationship was observed, although not between ARE and MDA.[44] A negative correlation appears to exist between PON activity and MDA levels due to the extensive oxidative damage to PON. The binding of PON to HDL confirms the dependence of this enzyme on lipids. The hydrophobic environment of HDL is necessary to paraoxonase activity. Phospholipids, especially those with long fatty acid chains, stabilize PON and are essential to its binding on lipoprotein surfaces.[45] The mechanism of reduced PON1 activity in cancer is not yet identified. The reduced paraoxonase activity in the group of cancer patients compared to in the healthy controls could be due to several factors, including enzyme inactivation. In this process, PON1 free sulfhydryl group reacts with specific oxidized lipids and ultimately becomes inactive.[46] The attack of free radicals (ROS) on the enzyme may be responsible for its inactivation. Moreover, the reduction in paraoxonase activity may be caused by the increased oxidative stress in the patients.[47] The present study found no significant reductions in HDL levels in the group of patients compared to in the control group. Previous studies have shown that changes in HDL structure can lead to the non-binding of PON1 to HDL, thereby reducing serum PON1 levels. Another mechanism associated with the reduction of PON1 activity could be due to the suppression of the enzyme due to genetic defects[46] or perhaps due to the down regulation of its transcription in the liver. Another reason for the reduction in paraoxonase may be the disrupted liver structure and function. Since the liver is the largest and most important organelle in the body and since colon, lung and breast cancer commonly metastasize to the liver, patients with cancer tend to also develop liver damage. Since PON1 is produced in the liver, an impaired liver function can reduce the production of PON1 or cause the production of impaired HDL.[48]

Overall, paraoxonase has been shown to become inactive after the hydrolysis of lipid peroxides in patients with high levels of lipid peroxidation.[47] Moreover, paraoxonase is an HDL-dependent enzyme and any changes in the metabolism and structure of HDL can reduce paraoxonase activity.[48] Moreover, since PON1 is reduced as an antioxidant enzyme in the body, the oxidant-antioxidant balance is impaired and oxidative stress thus increases. The oxidant, inflammatory and angiogenic environments then lead to carcinogenesis and enable the progression of cancer.[23] As PON1 is an antioxidant factor, using factors that increase its activity may help with the treatment of cancer. Overall, the present study shows that paraoxonase levels reduce in patients with cancer and consequently increase oxidative stress and lipid peroxidation. This finding suggests the positive effects of antioxidants on cancer. Nevertheless, the high levels of MDA and the reduced PON1 activity suggest an impaired oxidant-antioxidant balance in patients with cancer, suggesting oxidant-antioxidant balance to have a major role in the pathogenesis of cancer.

One of the limitations of the present study is that it did not assess the many different elements involved in oxidant-antioxidant balance, thereby making the generalization of the results to the entirety of oxidant-antioxidant balance irrespective of the other factors at play a matter that should be pursued with extreme caution; the following measures are therefore recommended: To better understand the antioxidant properties of paraoxonase in patients with cancer, antioxidant factors such as vitamins, including vitamin E and C, and antioxidant enzymes such as catalase, glutathione and peroxidase are recommended to be studied along with paraoxonase. Dietary antioxidants are also recommended to be administered to patients with cancer either in combination or separately and their effects to be assessed on PON1.

Conclusion

In patients with cancer, reduced paraoxonase activity accompanied by reduced arylesterase activity indicates weak antioxidant activities in the body. Increased MDA levels as a marker of lipid peroxidation suggest the lower oxidative status potentially caused by oxidant-antioxidant imbalance (including reduced antioxidant power, more

oxidized substances or both). These findings demonstrate oxidative stress or its aggravation in patients with cancer.

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