Araştırma Makalesi / Research Article

Investigation of dysfunctional HDL using myeloperoxidase / paraoxonase ratio in lymphoma

Lenfomada miyeloperoksidaz/paraoksonaz oranı kullanılarak disfonksiyonel HDL'nin araştırılması

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Abstract

Background: The aim of this study is to investigate the myeloperoxidase/paraoxonase ratio which indicates dysfunction of high-density lipoprotein in various types of lymphoma characterized by abnormal lipid metabolism, oxidative stress, and inflammation.
Methods: Thirty lymphoma patients and 30 healthy subjects were enrolled in this study. Serum myeloperoxidase, paraoxonase, arylesterase, lipid hydroperoxide and routine biochemistry tests levels were measured on an automated analyzer. The diagnosis of lymphoma patients was made according to the histological examination of the biopsy material.
Results: Compared with healthy control group; the albumin, arylesterase, high-density lipoprotein, thiol, and Hemoglobin levels were significantly lower while myeloperoxidase / paraoxonase, myeloperoxidase/arylesterase, and lipid hydroperoxide levels were significantly higher, in patients with lymphoma. Also, lipid hydroperoxide level was significantly correlated with myeloperoxidase / paraoxonase and myeloperoxidase / arylesterase (r= 0.330, p=0.046; r= 0.588, p< 0.001, respectively).
Conclusions: We think that dysfunctional high-density lipoprotein is an important factor in the inflammatory process, atherosclerosis, oxidative stress, and impaired lipid metabolism that can be observed in patients with lymphoma. We believe that in the future the myeloperoxidase/paraoxonase ratio can be used as a treatment criterion to prevent diseases that cause dysfunctional high-density lipoprotein.

Keywords: Arylesterase; Dysfunctional high-density lipoprotein; Lipid hydroperoxide; Myeloperoxidase/paraoxonase ratio; Paraoxonase

Öz.

Amaç: Bu çalışmanın amacı, anormal lipid metabolizması, oksidatif stres ve inflamasyon ile karakterize çeşitli lenfoma tiplerinde disfonksiyonel HDL'yi gösteren miyeloperoksidaz / paraoksonaz oranını araştırmaktır.
Materyal ve Metod: Çalışmaya 30 lenfoma hastası ve 30 sağlıklı birey alındı. Otomatik analizörde serum myeloperoksidaz, paraoksonaz, arilesteraz, lipid hidroperoksit parametrelerinin ve rutin biyokimya testlerinin düzeyleri ölçüldü. Lenfoma hastalarının tanısı biyopsi materyalinin histolojik incelemesine göre konuldu.
Bulgular: Sağlıklı kontrol grubu ile karşılaştırıldığında; albumin, arilesteraz, HDL, tiyol ve Hemoglobin seviyeleri anlamlı derecede düşükken, myeloperoksidaz / paraoksonaz oranı, myeloperoksidaz / arilesteraz oranı ve lipid hidroperoksit seviyeleri, lenfomalı hastalarda anlamlı olarak daha yüksekti. Ayrıca lipid hidroperoksit düzeyi, miyeloperoksidaz / paraoksonaz oranı ve miyeloperoksidaz / paraoksonaz oranı ile anlamlı şekilde ilişkiliydi (sırasıyla r= 0.330, p=0.046; r= 0.588, p< 0.001)
Sonuç: Biz disfonksiyonel HDL'nin, lenfoma hastalarında gözlenen inflamatuar süreç, ateroskleroz, oksidatif stres ve bozulmuş lipid metabolizmasında önemli bir faktör olduğunu düşünüyoruz. Gelecekte myeloperoxidase/paraoxonase oranının, disfonksiyonel HDL'ye sebep olan hastalıkları önlemek için bir tedavi kriteri olarak kullanılabileceğine inanıyoruz.

Anahtar kelimeler: Arilesteraz; Disfonksiyonel HDL; Lipid hidroperoksit; Miyeloperoksidaz/paraoksonaz oranı; Paraoksonaz

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Geliş tarihi / Received: 19/06/2019

Kabul tarihi / Accepted: 07/08/2019

DOI: 10.35440/hutfd.579011

Introduction

Lymphoma is a kind of cancer which originates from lymphocyte cells. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are the two main types of lymphoma. Hodgkin lymphoma is an infrequent B-cell malignant neoplasm. Classical and nodular lymphocyte predominant types are the two main types of Hodgkin lymphoma (1). Non-Hodgkin lymphomas that infiltrate both lymphoid and hematopoietic tissues are malignant neoplasms. They are also able to extend to other organs. There is an association between etiology of non-Hodgkin lymphoma and various genetic and infectious diseases. Different subtypes of non-Hodgkin lymphoma's biological behavior and clinical outcome are highly variable. Diffuse large B-cell lymphoma, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, T-cell lymphoma are the most common non-Hodgkin lymphoma subtypes (2).

Many neoplastic hematologic diseases have been associated with oxidative stress. When reactive oxygen species (ROS) dominates the antioxidant defense mechanism, a biological damage which is known as oxidative stress occurs (3,4). In several lymphoma studies, it's shown that there is an increase in plasma reactive oxygen species and a decrease in antioxidant levels (5).

In addition, lymphoma patients generally present with abnormal lipid metabolism. In these patients there is generally a dysfunction of high-density lipoprotein (HDL). It has also been reported that HDL is an independent prognostic factor in some types of malignant lymphomas (6,7).

The structural and functional properties of HDL cholesterol are impaired by undergoing oxidative modifications by the effect of oxidative stress. These modifications cause the change of biological activities of paraoxonase, lecithin cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) enzymes. Thus, HDL, which normally has anti-inflammatory and anti-atherogenic properties turns into proinflammatory and atherogenic status (8,9). HDL cholesterol inhibits lymphoma cell proliferation. Because of this feature of HDL, new treatment approaches have been developed by synthesizing HDL-like nanoparticles. But, there is not enough information about the function of HDL in lymphoma patient (7,10). Paraoxonase (PON) is known to be integrated into the structure of HDL and HDL fractions have over 85% of paraoxonase and arylesterase (ARE) activity. PON plays a role in the stabilization of HDL, it can easily bind HDL lipids and exerts antioxidant features of HDL (11,12). Also, it protects low-density lipoprotein (LDL) from the destructive effects of oxidation (13). ARE is an esterase enzyme, coded by the same gene, which has similar active centers as PON. The ARE and PON enzymes can detoxify organophosphates. The most important substrate of PON enzyme is paraoxon. Paraoxon hydrolysis activity varies widely among individuals. Part of this variability is caused by the polymorphism of PON gene. However, ARE activity borne by the same protein is not affected by polymorphism and can be considered as an index of actual protein concentrations, independent of PON variability (14-17). It has been reported that increased HDL particle size may lead to its dysfunction (18).

Some evidence revealed that the small and dense subgroups of HDL (HDL_3) possess a higher capacity to protect LDL against oxidation than the larger and light HDL subgroups (HDL_2). Given the importance of relationships between HDL size and function, it seems that myeloperoxidase (MPO) and PON are the important determinants of HDL function (19).

The HDL isolated from patients with high MPO/PON ratio exhibited attenuated anti-inflammatory properties and impairment of cholesterol efflux capacity. Also, It has been shown that the MPO/PON ratio significantly affects and alters the function of HDL and there is a direct correlation between this ratio and the function of HDL (20).

Our first aim in this study is to determine and interpret the MPO/PON ratio, which is a valuable marker for the altered function of modified HDL in lymphoma patients. Our other aim is to determine a new alternative biomarker (MPO/ARE) to MPO/PON ratio using an ARE activity of PON. To our knowledge, this is the first study in the literature on this subject.

Materials and Methods

Thirty lymphoma patients and 30 healthy subjects were enrolled in this study. Patients and healthy control groups were matched in terms of body mass index (BMI), age, and gender. The diagnosis of lymphoma patients was made according to the histological examination of the biopsy material. This study includes classical Hodgkin's lymphoma, Nodular lymphocyte-predominant Hodgkin's lymphoma, and those groups which are, the most common non-Hodgkin's lymphoma subtypes: diffuse large B-cell, mantle cell, marginal zone, and follicular lymphoma (Table 1).

Blood samples were taken from all of the subjects through antecubital vein following overnight fasting. After centrifuging these samples at 1500xg for 10 minutes, the sera were taken apart and placed in eppendorf tubes to preserve at -80°C until the day of study. The local ethics committee approved this study.

Assays

Serum MPO, PON, ARE (Rel Assay, Turkey), lipid hydroperoxide (LOOH), thiol and routine biochemistry tests such as HDL, albumin, uric acid, and lactate dehydrogenase (LDH) levels were measured on an automated analyzer (Roche, Cobas C 501, Mannheim, Germany). Hemoglobin (HGB), white blood cell (WBC), platelet (PLT) and mean platelet volume (MPV) levels were measured on an automatic analyzer (Sysmex XE-2100, USA) by using K2 EDTA samples.

The modification of the o-dianisidine method which is based on kinetic measurement at 460 nm with the rate of the yellowish orange product formation from the oxidation of o-dianisidine with MPO activity in the presence of hydrogen peroxide is used for measuring serum MPO activity. One unit of MPO was described as; degrading 1 µmol of H_2O_2 min^{-1} at 25°C. For calculating a molar extinction coefficient of 1.13×10^4 M^{-1} cm^{-1} of oxidized o-dianisidine was used. MPO activity was defined as units per liter serum (21).

For measuring PON activity, we measured the rate of paraoxon hydrolysis by monitoring the increase of absorbance at 412 nm. For calculation the amount of generated p-nitrophenol, we used the molar absorptivity coefficient at the pH of 8.5, which was 18290 M^{-1} cm^{-1}. PON activity was defined as U/L serum (22).

For measuring ARE activity, phenylacetate was used as a substrate. Molar absorptivity coefficient of the phenol produced was 1310 M^{-1} cm^{-1}. We calculate the enzymatic activity from this coefficient. One unit of ARE activity was defined as 1 µmol phenol generated/min under the above conditions and expressed as kU/L serum (23).

Serum level of LOOH was measured with an automated method by using xylenol orange. The method is based on the oxidation of Fe^{+2} to Fe^{+3} by lipid hydroperoxides, under acidic conditions (24).

Serum thiol concentration was measured by Ellman's method. According to this method, thiols interact with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and form a highly colored anion with maximum peak at 412 nm (Molar absorptivity coefficient = 13600 M^{-1} cm^{-1}). The concentration of sulfhydryl groups was defined in µmol/L (25).

Routine biochemical and hematological tests were measured using standard laboratory methods with the company's own kits.

Statistical Analysis

Visual (histograms and probability plots) and statistical methods (Shapiro–Wilk test) were used to determine whether the data were normally distributed. Descriptive analyses were showed using mean and standard deviation (mean ± SD) for the normally distributed variables. As the data were normally distributed, independent sample t-tests were performed to compare the parameters between groups. Correlation analyses were done using Pearson's correlation. An overall 5% type 1 error was accepted to infer statistical significance. Statistical analyses were performed using the SPSS software version 20 (SPSS Inc. Chicago, IL, USA). Figures were created by using GraphPad Prism (Version 6.0; GraphPad Software Inc., La Jolla California USA).

Table 1. Demographic and clinical characteristics of the lymphoma patients and the control group

Variables	Healthy group (*n*=30)	Lymphoma (*n*=30)	*p* value
Age	51.24±13.40	50.04±18.10	0.665
Gender (male/female)	15/15	16/14	0.785
BMI	24.7±2.7	24.6±2.2	0.812
BM involvement (n/%)	8/26.6		
HL (n/%)	6/20		
HL-NLP (n/%)	1/3.3		
DLBCL (n/%)	11/36.6		
FL (n/%)	5/16.6		
MCL (n/%)	1/3.3		
MZL (n/%)	6/20		
MPO/PON	0.32±0.23	0.51±0.42	0.025*
MPO/ARE	0.43±0.32	0.73±0.51	0.017*
MPO/HDL	2.81±1.67	3.68±2.89	0.193
MPO (U/L)	119.75±58.90	113.51±58.95	0.708
ARE (kU/L)	278.29±117.43	192.81±84.92	0.004*
HDL (mg/dL)	47.89±12.72	39.69±15.72	0.049*
PON (U/L)	393.57±294.67	287.10±191.80	0.132
Albumin (g/dL)	5.20±1.03	4.25±1.08	0.002*
LOOH (µmol/L)	4.25±1.40	7.05±3.98	0.003*
Thiol (µmol/L)	287.98±49.10	229.81±56.61	<0.001*
LDH (U/L)	179.57±23.39	320.37±25.29	<0.001*
HGB (g/dL)	14.12±1.13	12.21±2.62	<0.001*
WBC X $10^3/mm^3$	7.0±1.7	9.0±7.4	0.046*
PLT X $10^3/mm^3$	260.0±67.0	258.3±139.8	0.933
MPV (fl)	9.26±1.33	8.57±1.39	0.006*
Uric acid (mg/dL)	4.94±1.07	5.36±2.38	0.214

**Indicates a significant statistical difference with p< 0.05; All values were given as mean ± SD*

ARE: Arylesterase; BM: Bone marrow; BMI: Body mass index; DLBCL: Diffuse Large B-cell Lymphoma; FL: follicular Lymphoma; HDL: High density lipoprotein; HGB: Hemoglobin; HL: Hodgkin lymphoma; HL-NLP: Nodular lymphocyte-predominant Hodgkin lymphoma; LDH: Lactate dehydrogenase; LOOH: Lipid hydroperoxide; MCL: Mantle Cell Lymphoma; MPO: Myeloperoxidase; MPV: Mean platelet volume; MZL: Marginal Zone Lymphoma; PLT: Platelet; PON: Paraoxonase; WBC: White blood cell

Results

There were 30 patients with lymphoma (14 females 16 males; age 50.04±18.10 years) and 30 healthy individuals as the control group (15 females 15 males; age 51.24±13.40 years). The most common lymphoma subtypes, Hodgkin lymphoma (20.0 %), Nodular lymphocyte-predominant Hodgkin lymphoma (3.3 %), diffuse large B-cell lymphoma (36.6 %), follicular lymphoma (16.6 %), mantle cell lymphoma (3.3 %), and marginal zone lymphoma (20 %) were included in the study. Bone marrow involvement is present in 26.6 % of the patients. The distribution of age, gender, and BMI (kg m^{-2}) were not different between the groups (p>0.05) (Table 1).

Compared with healthy control group; the albumin, ARE, HDL, thiol, HGB and MPV levels were significantly lower (p= 0.002; p= 0.004; p= 0.049; p< 0.001; p= 0.002; p< 0.001; p= 0.006 respectively) while MPO/PON, MPO/ARE, LOOH, LDH and WBC levels were significantly higher (p= 0.025; p= 0.017; p= 0.003; p< 0.001; p= 0.046 respectively), in patients with lymphoma (Table 1).

As shown in Table 2 and Figure 1, the significant correlations were found between the MPO/PON level of patients with lymphoma and their LOOH, albumin, and ARE levels (r= 0.330, p= 0.046; r= - 0.358, p= 0.010; r= - 0.530, p< 0.001, respectively). Besides this, the statistically significant correlations were found between the MPO/ARE level of lymphoma patients and their LOOH, albumin, and thiol levels (r= 0.588, p< 0.001; r= - 0.362, p= 0.012; r= - 0.306, p= 0.034, respectively). Also, the relationship between MPO/PON and MPO/ARE levels (r= 0.631, p< 0.001) and the relationship between LOOH and thiol levels (r= - 0.309, p< 0.033) were also striking (Table 2 and Figure 1).

Table 2. Correlation between variables

Variables		PON	ARE	Thiol	MPO	HDL	LOOH	MPO/HDL	MPO/ARE	MPO/PON
Albumin	*r*	0.402	0.494	0.788	-0.024	0.632	-0.133	-0.447	-0.362	-0.358
	p	0.003*	<0.001*	<0.001*	0.865	<0.001*	0.368	0.001*	0.012*	0.010*

PON	*r*		0.607	0.264	-0.125	0.178	-0.122	-0.003	-0.252	-0.640
	p		<0.001*	0.049*	0.381	0.222	0.407	0.983	0.084	<0.001*

ARE	*r*			0.270	-0.031	0.328	-0.185	-0.160	-0.557	-0.530
	p			0.047*	0.831	0.021*	0.208	0.273	<0.001*	<0.001*

Thiol	*r*				-0.001	0.470	-0.309	-0.377	-0.306	-0.195
	p				0.993	<0.001*	0.033*	0.008*	0.034*	0.171

MPO	*r*					-0.066	-0.106	0.516	0.682	0.425
	p					0.650	0.482	<0.001*	<0.001*	0.002*

HDL	*r*						-0.268	-0.691	-0.158	-0.171
	p						0.072	<0.001*	0.294	0.241

LOOH	*r*							0.311	0.588	0.330
	p							0.051	<0.001*	0.046*

MPO/HDL	*r*								0.380	0.265
	p								0.009*	0.066

MPO/ARE	*r*									0.631
	p									<0.001*

**Indicates a significant statistical difference with p< 0.05*

Discussion

Recently, it has been shown that the MPO/PON ratio is an index reflecting the function of HDL. To date, studies of the MPO/PON ratio have only been investigated in relation to cardiovascular diseases, such as researching the function of HDL and the assessment of Coronary artery disease risk. But, conditions such as inflammation, oxidative stress, and dyslipidemia which may cause the dysfunction of HDL are also related to many diseases besides cardiovascular diseases (3,4,6,7,20,26,27). To our knowledge, this is the first study in the literature to evaluate MPO/PON ratio in lymphoma patients.

HDL is a lipoprotein which has anti-oxidative, anti-inflammatory, and anti-apoptotic effects. In addition, HDL ameliorates endothelial dysfunction and removes excess cholesterol from macrophages. Recent studies have shown that HDL has complete dysfunction and in some cases loss of function in terms of anti-inflammatory activity, vasodilator function, anti-apoptotic activity, anti-oxidative activity and cholesterol efflux capacity (28-35).

A recent study has shown that MPO, PON, and HDL form a functional complex and MPO and PON enzymes partially inhibit each other's activities (36). While MPO causes oxidative modifications in the lipid and protein components of HDL, contrarily PON strongly protects HDL against the oxidative stress (37,38). So it seems acceptable that the MPO/PON ratio represents the function of HDL. In studies, a higher MPO/PON ratio was observed in patients with acute coronary symptoms than in the healthy control group. It has been found that the anti-inflammatory properties and cholesterol efflux capacity of HDL isolated from these patients are impaired. Also, in studies with HDL_2 and HDL_3, which are HDL's different sized and functional subfractions, it was found that particle size and MPO/PON ratio were inversely proportional. Thus, these extensive experimental studies have shown that the MPO/PON ratio is an important indicator for determining the dysfunctional HDL (19,20).

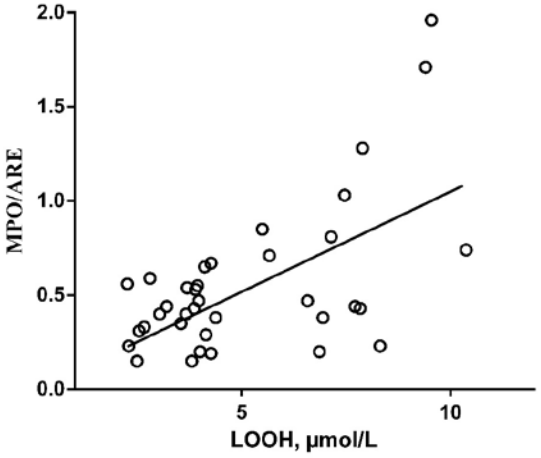

Figure 1. The relationship between the LOOH level and MPO/ARE ratio.

In the common subgroups of lymphoma involving in our study, routine hematological and biochemical parameters, antioxidant and oxidant parameters, and HDL-associated PON and ARE enzymes were investigated. Levels of antioxidant parameters such as thiol, ARE, PON, and albumin decreased in lymphoma patients while levels of oxidant parameters such as MPO and LOOH increased. Also, as expected, there were negative correlations between oxidant and antioxidant parameters. So, the lymphoma patients are under the influence of oxidative stress. Although uric acid is an important antioxidant parameter, it was found to be high in the lymphoma patients as expected due to the increase of purines generated as a result of nucleoprotein degradation. In addition to these parameters, routine hematological and biochemical parameters were also investigated.

Lipid hydroperoxide is the first product of oxidized lipids and indicates the oxidation of lipids in the serum (24) . HDL, which is more sensitive to oxidation than other lipoproteins, is the main carrier of lipid hydroperoxides and plays an important role in LOOH metabolism (39). Lipid hydroperoxides are the factors that can make HDL dysfunction. Lipid hydroperoxides can affect antioxidant, anti-inflammatory and cholesterol receptor activities of HDL (40) . MPO/PON ratio showing HDL dysfunction and LOOH level were significantly higher in lymphoma patients compared to healthy controls. Furthermore, there was a significant correlation between LOOH and MPO/PON ratio. These results we obtained, clearly show that the function of HDL is impaired in lymphoma patients. In light of the foregoing, we think that dysfunctional HDL is an important factor in the inflammatory process, atherosclerosis, oxidative stress, and impaired lipid metabolism that can be observed in patients with lymphoma.

Due to the low number of lymphoma subgroups, it is predicted that reliable statistics can not be made. Therefore, HL, non-HL and non-HL subgroups were not compared with each other.

The paraoxonase-1 enzyme which is on the surface of HDL, exhibits three different catalytic activities. (1) It hydrolyses organophosphates and pesticides with PON activity, (2) it hydrolyzes non-phosphorous arylesters with ARE activity, (3) it hydrolyzes lactones, with lactonase activity. These hydrolases are well known to be the main factors responsible for the antioxidant and anti-inflammatory properties of HDL (41). Therefore, in our study, MPO/ARE ratio was also investigated besides MPO/PON ratio in lymphoma patients. Compared with the control group, the MPO/ARE ratio in lymphoma patients was significantly increased. In addition, the MPO/HDL ratio was also examined but no change was observed.

Lipid hydroperoxides are known to cause HDL dysfunction (40). When the correlation between the LOOH level and MPO/ARE and the correlation between the LOOH level and MPO/PON investigated separately, it was observed that the correlation level of MPO/ARE parameter was higher than MPO/PON. Furthermore, when compared with the control group, it was found that the level of significance of MPO/ARE ratio in lymphoma patients was higher than the ratio of MPO/PON. These results suggest that MPO/ARE ratio may be a better predictor of dysfunctional HDL than MPO/PON ratio. However, extensive experimental work is needed for this.

To date, research on the MPO/PON ratio has only been investigated in cardiovascular events. We believe that this study could also lead to the investigation of dysfunctional HDL through MPO/PON ratio in diseases related to inflammatory, dyslipidemic and oxidative stress besides cardiovascular diseases.

Consequently, we think that dysfunctional HDL is an important factor in the inflammatory process, atherosclerosis, oxidative stress, and impaired lipid metabolism that can be observed in

patients with lymphoma. We believe that, in the future the MPO/PON ratio can be used as a treatment criterion to prevent diseases that cause dysfunctional HDL. Furthermore, with advanced and extensive experimental studies, we claim that the MPO/ARE ratio can be an alternative test to the MPO/PON ratio.

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