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Antioxidant-oxidant status in patients with hydatid cyst

[Hidatik kist hastalarında antioksidan-,oksidan durum]

Sevtap Bakır[1],
Ali Çeliksöz[2],
V. Kenan Çelik[1],
İsmail Sari[1],
Hüseyin Aydın[1]

Departments of [1]Biochemistry and [2]Parasitology, School of Medicine, Cumhuriyet University, Sivas, Turkey

Yazışma Adresi
[Correspondence Address]

İsmail Sari, MSc

Faculty of Medicine, Department of Biochemistry, Cumhuriyet University, 58140, Sivas, Turkey,
Tel: +90-346-219-1010
Fax: +90-346-219-1103
E-mail: smlsr@hotmail.com

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ABSTRACT

Objectives: To determine whether oxidative stress plays a role in the pathogenesis of hydatid cyst by examining levels of total antioxidant status, total oxidant status, oxidative stress index, and activities of the enzymes paraoxonase and arylesterase in patients with hydatid cyst.

Methods: Thirty patients with hydatid cyst whom were positive for indirect hemagglutination and *Echinococcus granulosus* IgG ELISA tests were included in the patient group. Thirty-five healthy subjects that were negative for hydatid cyst by indirect hemagglutination and *Echinococcus granulosus* IgG ELISA tests, and did not have any parasites on stool inspection constituted the control group. Total antioxidant status, total oxidant status levels and paraoxonase, arylesterase activities were determined using commercial kits on an autoanalyzer. Oxidative stress index was calculated from a percent ratio of total peroxide level to the total antioxidant status level.

Results: Serum total antioxidant status, total oxidant status and oxidative stress index levels of patients with hydatid cyst were significantly increased compared to the control group ($p < 0.05$). Paraoxonase, and arylesterase activities of patients with hydatid cyst were significantly lower than the control group ($p < 0.05$).

Conclusion: Oxidative stress is increased in patients with hydatid cyst resulting in decreased paraoxonase and arylesterase activities. Increased oxidative stress might lead to increased tissue necrosis and inflammation. Therefore administration of an antioxidant therapy in addition to the routine treatment should be considered in this group of patients. It should also be noted that anti-atherosclerotic effect is reduced for a prolonged time secondary to decreased paraoxonase activity in cases of delayed diagnosis of hydatid cyst.

Key Words: Hydatid cyst, oxidative stress, paraoxonase 1, arylesterase.

Conflict of interest: The authors report no conflicts of interest.

ÖZET

Amaç: Bu çalışmada, kist hidatik hastalarında total antioksidan durum, total oksidan durum, oksidatif stres indeks düzeyleri, paraoksonaz ve arilesteraz enzim aktiviteleri inclenerek, oksidatif stresin bu hastalığın patogenezinde bir role sahip olup olmadığının belirlenmesi amaçlanmıştır.

Yöntem ve gereçler: İndirekt Hemaglütinasyon Testi ve *Echinococcus granulosus* IgG ELISA testi pozitif olan 30 kist hidatik hastası hasta grubumuzu oluşturmuştur. İndirekt Hemaglütinasyon ve *Echinococcus granulosus* IgG ELISA testi negatif olan ve gaita incelemesinde herhangi bir parazit bulunmayan sağlıklı 35 birey ise kontrol grubunu oluşturmuştur. Total antioksidan durum, total oksidan durum düzeyleri ve paraoksonaz, arilesteraz aktivitleri ticari kitler kullanılarak, otoanalizörde belirlendi. Oksidatif stres indeksi total peroksit düzeyinin yüzde oranının total antioksidan durum düzeyine bölünmesiyle hesaplandı.

Bulgular: Serum total antioksidan durum, total oksidan durum düzeyleri ve oksidatif stres indeks düzeyleri hidatik kist hastalarında kontrole göre anlamlı olarak daha yüksek tespit edildi ($p < 0.05$). Paraoksonaz ve arilesteraz aktiviteleri hidatik kist hastalarında kontrole göre anlamlı olarak daha düşüktü ($p < 0.05$).

Sonuç: Kist hidatik hastalarında oksidatif stres artmakta ve buna bağlı olarak paraoksonaz ve arilesteraz aktiviteleri azalmaktadır. Bu durum doku nekrozu ve inflamasyonun artmasına neden olabilir. Bu nedenle bu hastalarda normal tedaviye ek olarak antioksidan tedavinin de uygulanması düşünülebilir. Ayrıca, tanısı geç konan kist hidatik hastalarında paraoksonazın azalan aktivitesi sonucu antiaterosklerotik etkisinin uzun süre düşük olabileceğinin dikkate alınması yarar sağlayabilir.

Anahtar Kelimeler: Hidatik kist, oksidatif stres, paraoksonaz 1, arilesteraz.

Çıkar çatışması: Yazarların çıkar çatışması bulunmamaktadır.

Introduction

Hydatid cyst is a zoonosis caused by the larval form of *Echinococcus granulosus*. The definitive host is dog although the metacestode form of *E. granulosus* is also found in the small intestine of various carnivores. Eggs of *E. granulosus* are excreted in dog feces and lead to infection in natural intermediate hosts including sheep, goats, cattle, and incidentally in humans. This parasite might dwell particularly in liver, but also in almost all organs including lungs, kidneys, spleen, brain, bones, and heart. Pain in the right upper quadrant is the most common complaint. Nonspecific signs including fatigue, fever, dyspepsia and nausea might also be seen. Complicated hydatid cysts might present with fever plus jaundice and even anaphylactic reaction [1-3]. Several case series on great number of patients have demonstrated that intraperitoneal rupture has occurred in 1.7%-8.6%of the cases with hydatid cyst. The risk of rupture increases with the size of the cyst and the pressure it is exposed to. Rupture into the intraperitoneal space might also occur spontaneously or as result of a secondary trauma. The rates of anaphylaxis and sudden death have been reported as 25%in these cases [4, 5].

Atom or molecules that have one or more uncouples electrons in their outer orbit are termed free radicals. This uncoupled electrons put the molecule in a very unstable status. These compounds have a reactive structure to react with other molecules in order to couple the electron in the outer orbit. Formation of free radicals might occur during the natural course of normal metabolic events or following exposure to various extrinsic factors [6, 7]. Several defense mechanisms have been developed in the body to prevent the formation of reactive oxygen radicals and delay or prevent the damage caused by these radicals. These mechanisms are known as antioxidant defense mechanisms. Antioxidants are grouped into two categories including endogenous and exogenous originated mechanisms. Antioxidants might have an enzyme or non-enzyme structures [8]. Paraoxonase 1 (PON1, EC.3.1.8.1) and arylesterase (EC.3.1.1.2) are two recently determined antioxidant enzymes [9, 10]. Human serum PON1 enzyme is an ester hydrolase synthesized in the liver. It is found in the endothelium of several organ tissues including liver, kidney, small intestine and in serum [11]. PON1, protects LDL cholesterol from the oxidation induced by copper ion and free radicals. The PON1 enzyme found in HDL cholesterol degrades the active lipids found in minimally modified LDL and has protective effects against the formation of inflammatory response in the cells of the arterial wall [12, 13]. Additionally, PON1 has arylesterase activity without polymorphism. The activity of arylesterase has been reported to be a marker of original protein concentration independently of the alterations in PON1 activity [10, 14].

Levels of total oxidants and antioxidants are at balance in a healthy organism. The balance is disrupted in favor of the oxidants when the amount of exogenous and endogenous oxidants produced during normal physiological events or secondary to exposure to harmful environmental agents exceed a certain level or when antioxidants are inadequate, resulting in several pathological events including atherosclerosis, respiratory distress syndrome and sepsis [15].

Host immune systems protect the organism from parasites via cellular mechanism. Cytotoxic agents, reactive oxygen and nitrogen intermediate products secreted by activated phagocytes play roles in this mechanism [16, 17]. Cells specialized in phagocytosis such as neutrophils kill the phagocytosed body by a series of reactions called respiratory burst. Hence, respiratory burst has a central role in the host immunity as well as inflammatory tissue injury [18]. NADPH oxidase found on cellular membrane of leukocytes and myeloperoxidase (MPO) that is a lysosomal enzyme found in the primary (azurophilic) granules of neutrophil and monocytes play critical roles. The activities of NADPH oxidase and MPO increase the oxidant stress in inflammation [19, 20]. Therefore, the balance between oxidant and antioxidants might be disrupted in favor of oxidants in prolonged exposure to infection with *E. granulosus* that increase oxidant stress. This process results in oxidative stress that has been suggested to have a role in the complications of several diseases including sepsis, atherosclerosis and diabetes.

Our objective was to determine whether oxidative stress resulting from infection with larval forms of *E. granulosus* plays a role in the pathophysiology and inflammation of hydatid cyst disease. Therefore, we determined the levels of anti-oxidative PON1 and arylesterase enzyme activities, total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) in patients with hydatid cyst and control subjects.

Material and methods

Study population

The study protocol and the procedures were approved by Human Ethics Committee of Cumhuriyet University School of Medicine (Protocol No: 23/05/2011-137) and were in accordance with the Helsinki Declaration. Serum samples used in the study were obtained from several clinics where they had been pre-diagnosed with hydatid cyst (*E.* granulosus) by radiological and other imaging modalities, and diagnosed with hydatid cyst (*E. granulosus*) by examination of cyst samples following surgical procedure. The Hydatidose Fumouze (Echinococcosis Fumouze) Kit was used in the indirect hemagglutination tests (sensitivity 93%and specificity 94.9%) and RIDASCREEN *Echinococcus* IgG kit of the r-biopharm company was used in the EIA Ig tests (sensitivity 100%and specificity 100%) in patients with a pre-diagnosis of hydatid cyst. In the etiological examination of patients in terms of hydatid

cyst, we knew that they did not receive any treatment prior to the establishment of a diagnosis and did not receive chemotherapy for any other diseases. Routine biochemical, hematological and microbiological examinations performed before the establishment of a diagnosis of hydatid cyst (*E. granulosus*) were normal. The participants in both patient and control groups were examined for the intestinal parasites and cyst hydatid using manual Indirect Hemaglutination Technique (IHA) and *Echinococcus* IgG Antibody ELISA Test Kit. 30 patients and 35 control individuals were included in the study. The control group consisted of volunteers from the Cumhuriyet University staff. None of them were smokers, had any known pathologies and taking steroids or medications such as iron for anemia at the time of sampling.

Blood collection

Venous blood samples were collected in tubes after an 8-h fasting state and immediately stored at 4° C. All samples were separated from the cells and fibrins by centrifugation at 1610xg for 10 min and stored in several aliquots at -80°C until assayed.

TAS, TOS levels and PON1, arylesterase activities were determined by using commercial kits (Rel Assay Diagnostic) on an autoanalyzer (Beckman Coulter Synchron LX–20) at the Biochemistry Laboratory, Research and Training Hospital, Faculty of Medicine, Cumhuriyet University.

PON1 and arylesterase activities determination

PON1 activity was measured using paraoxon as a substrate and the rate of hydrolysis of paraoxon was continuously monitored at 405 nm and 37°C [21]. Paraoxonase activity is expressed as U/L of serum.

Phenylacetate was used as the substrate to measure arylesterase activity. The rate of hydrolysis of phenylacetate was continuously monitored at 270 nm and 37°C [22]. One unit of arylesterase activity was defined as 1 μmol of phenol generated per min and is expressed as U/L of serum.

Measurement of the total antioxidant status

The TAS levels of the sera were determined using an automated measurement method based on bleaching of the characteristic color of a 2,2'-azino-bis [3-ethylbenzthiazoline-6-sulfonic acid] (ABTS) radical cation caused by antioxidants [23]. The results are expressed in mmol Trolox equivalents/L.

Measurement of total oxidant status

The TOS levels of the sera were determined using a novel automated measurement method [20]. Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complexes into ferric ions. The oxidation reaction is enhanced by glycerol molecules that are abundantly present in the reaction medium. The ferric ions form a colored complex with xylenol orange in an acidic medium. Therefore, the color intensity, measured spectrophotometrically, is related to the total number of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 equiv./L).

Determination of oxidative stress index

The oxidative stress index (OSI) was calculated from a percent ratio of total peroxide level to the TAS level.

OSI = [TOS (mmol Trolox eqivalent/L) / TAS (μmol H2O2 equivalent/L)] X100

Statistical analysis

Parametric data are expressed as the mean ±standard deviation and categorical data as percentages. The Statistical Package for the Social Sciences (SPSS) version 14 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Nonparametric data were evaluated by the Mann–Whitney U test and categorical data by the chi-squared test. A p value ≤0.05 was considered as significant.

Results

Thirty patients with hydatid cyst and 35 control subjects were recruited for the study. Of the hydatid cyst patients, 11 (36.67%) were male and 19 (63.33 %) were female, and the mean age was 45.3 ±19.44 years. In the control group, 15 (42.86%) individuals were male and 20 (57.14%) were female, with a mean age of 46.9 ±19.5 years. There were no significant differences in age or gender ratio between the patient and control groups (p >0.05; Table 1).

Serum TAS, TOS and OSI levels of patients with hydatid cyst were significantly higher than the control group (p <0.05; Table 2). PON1, and arylesterase activities of patients with hydatid cyst were significantly lower than the control group (p <0.05; Table 2).

Table 1. Demographic data for the patients and the control groups.

	Patient Group n=30	Control Group n=35	P value
Mean age (year)	45.30 ± 19.44	46.90±19.50	0.75
Sex (female/male)	19 / 11	20/15	0.612

Discussion

Hydatid cyst disease is endemic in several parts of the world and continues to be a widespread public health issue in Turkey [2]. The disease is contaminated to humans by gastrointestinal or respiratory intake or transplacental transmission of cestode eggs excreted in the feces of dogs infected with *E. granulosus*. These eggs give rise to oncospheres that penetrate gastrointestinal system

Table 2. TAS, TOS, OSI levels and PON1, arylesterase activities of the patients and the control groups.

	Patient Group Median (min-max); *n=30*	*Control Group* Median (min-max) n=*35*	*P value*
TAS (mmol trolox Equiv./L)	0.89 (0.62-1.39)	1.05 (0.79-1.55)	0.038*
TOS (μmol H2O2 equiv./L)	12.43 (2.81-45.09)	6.43 (2.95-10.86)	0.001*
OSI (%)	12.86 (2.90-57.08)	0.60 (0.37-0.83)	0.001*
PON1 (U/L)	32.50 (21.00-130.00)	92.00 (70.00-114.00)	0.001*
Arylesterase (U/L)	10903.5 (9266.0-11694.0)	16902.0 (14202.0-19602.0)	0.001*

wall and dwell in liver or in other organ systems where they arrive via lymphatic and hematogenous routes [3].

NADPH oxidase system has a prominent role in protection of the host against parasites and is and important source of reactive oxygen species in cells [24]. All of the oxygen consumed during the respiratory burst performed by NADPH oxidase enzyme complex is reduced into superoxide radical ($O2^{-}$) with the transfer of electrons from NADPH, and spontaneous dismutation of $O_2^{\cdot}$ leads to the formation of H_2O_2. The majority of H_2O_2 produced by neutrophils forms hypochloric acid (HOCl) by combining with one of the ions (Cl^-, I^-, Br^-), particularly Cl^-, via MPO enzyme inside the phagosomes or outside the cell [19]. HOCl forms the superoxide radical or hydroxide radical ($OH^{\bullet}$) by combining with Fe^{+2} ions. Elimination half life of the OH• radical is quite short and this is a very unstable molecule. This radical leads so significant injury around itself by forming cross links between protein and lipids, releasing protons or transferring electrons [7]. Therefore MPO enzyme that catalyses the production of HOCl in the organism both has microbicidal activity and causes tissue injury at the site of inflammation through HOCl [18].

There are enzymatic and non-enzymatic antioxidants in organisms which aim to prevent the injury caused by free radicals [8]. The levels of oxidants and antioxidants are at a balance in a healthy human being. Oxidative stress results from increased production of oxidants, reduced level of antioxidants or a combination of both [15]. Several studies have demonstrated that the issue of oxidative stress and antioxidants is involved in the pathogenesis of various parasitic diseases and inflammatory events [25, 26]. Malondialdehyde (MDA), a marker of lipid peroxidation; a non-enzymatic antioxidant, glutathione, and enzymatic antioxidants glutathione peroxidase and superoxide dismutase have been determined in patients with hydatid cyst. Studies have concluded that overall, oxidative stress does have a role in the pathogenesis of hydatid cyst [27-29]. Although the antioxidant/oxidant balance of the body might be measured by separately measuring the activity of antioxidant enzymes and the concentration of antioxidant/oxidant molecules, the overall antioxidant/oxidant TAS [23] and TOS [20] measurements provide easier and faster evaluation. However, we could not find any studies examining the values of TAS and TOS as well as enzymatic activities of PON1 and arylesterase in patients with hydatid cyst in our literature survey. Hence, in this study our objective was to examine the levels of TAS, TOS, OSI, and the activities of PON1 and arylesterase in patients with hydatid cyst.

Results of our study demonstrated that the level of TAS is significantly lower in patients with hydatid cyst compared to the controls, whereas TOS and OSI levels were higher. These results suggest that total oxidative stress is increased during the respiratory burst that occurs as part of the host defense against larval cestodes of *Echinococcus granulosus* and the antioxidant defense mechanisms prove inadequate in these patients. Accordingly, a significant increase is observed in oxidative stress in patients with hydatid cyst. These oxidative compounds turn into toxic substances including peroxynitrite in such cases when the effects of reactive oxygen species cannot be prevented with endogenous and exogenous antioxidants, and cause damage to the basic structural cellular elements including lipids, proteins and nucleic acids. The process results in cell death via necrosis or apoptosis [30, 31]. Therefore, we suggest that oxidative stress is involved in the disease pathogenesis of hydatid cyst and contributes to the inflammation and tissue necrosis. Two separate studies have demonstrated that MDA which is a final product of lipid peroxidation used as a marker of oxidative stress was increased significantly in patients with hydatid cyst [28, 29]. Additionally, other studies have demonstrated that the level of antioxidant enzymes including GSH [29] and glutathione peroxidase, superoxide dismutase were significantly decreased in these patients [27].

PON1 and arylesterase are enzymes of the esterase group that are encoded by the same gene and have similar active centers. Although PON1 is known to exhibit polymorphic changes, the arylesterase enzyme does not have polymorphic changes. Natural substrates of these two enzymes are different; however, PON1 enzyme has the ability to hydrolase phenyl acetate which is the natural substrate of arylesterase. A well known common feature of PON1 and arylesterase is that they are capable of hydrolyzing organophosphates, aryl and alkyl halogens. Additionally, PON1 is protective against the oxidation of LDL and has antioxidant effect

due to its ability to neutralize free radicals including hydrogen peroxide [14, 21, 32]. The activities of PON and arylesterase were found significantly lower in our patient group compared to the controls ($p < 0.05$). Previous studies have demonstrated that the activity of PON1 enzyme was sensitive to oxidative stress and is inactivated by oxidants. Therefore, factors that increase oxidative stress including products of lipid peroxidation have been determined to decrease the activity of PON1 enzyme [33, 34]. Accordingly, it might be suggested that reduced PON1 and arylesterase activity possibly results from increased OSI in these patients.

Serum PON1 is known to exhibit anti-atherosclerotic function by inhibiting LDL oxidation. In vivo LDL oxidation is increased, and therefore atherosclerosis is increased in the absence of PON1 [35]. Additionally, reduced PON1 activity has been determined in certain diseases that accelerate atherogenesis including diabetes and familial hypercholesterolemia, and during myocardial infarction [36].

Hydatid cyst often remains asymptomatic for a prolonged period. Diagnosis is often established incidentally as a result of imaging studies performed for other reasons [1, 2]. Therefore the process of diagnosis and initiation of treatment might take months and even years. The state of reduced PON1 and elevated OSI might persist for a long period in these cases leading to prolonged inadequacy of anti-atherosclerotic effect of PON1. All of these processes create a tendency for atherosclerosis and coronary arterial diseases in patients with hydatid cyst. This tendency should be noted by clinicians particularly in patients with delayed diagnosis of hydatid cyst.

Consequently, oxidative stress is increased and activities of PON1 and arylesterase are decreased in patients with hydatid cyst. Alterations in all of these parameters get involved with the disease pathogenesis by leading to increased tissue necrosis and inflammation. Administration of antioxidant therapy in addition to the routine treatment should be beneficial in these patients. Additionally, non-specific symptoms of the disease often delay the diagnosis, and the increased OSI plus decreased PON1 activities persist for a long period. Persistence of reduced anti-atherosclerotic activity of PON1 creates a tendency for atherosclerosis and cardiac diseases particularly in patients with a delayed diagnosis of hydatid cyst which should be noted by clinicians.

Conflict of interest: The authors report no conflicts of interest.

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