

The thiol-disulphide homeostasis in patients with acute pancreatitis and its relation with other blood parameters

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ABSTRACT

BACKGROUND: Acute pancreatitis is a common disease seen in emergency departments because of abdominal pain. The present study aims to evaluate the relation between measurements of thiol-disulphide parameters in patients diagnosed with acute pancreatitis and other blood parameters.

METHODS: A total of 56 (56%) patients, who were admitted to the emergency department, and 44 (44%) healthy volunteers participated in this study. A total of 100 samples were taken from the participants. Detailed blood samples were taken from the patients at the time of arrival at the hospital. The thiol-disulphide level in serum was examined using a brand new method that was developed by Erel and Neşelioğlu in the venous blood samples of the patients who were diagnosed with acute pancreatitis during the admission. The data were evaluated in the computer medium.

RESULTS: Gallstones were defined as the etiology of AP in 41 patients (73.2%); in one patient, hypertriglyceridemia (1.7%); in four patients, alcohol use (7.1%), and idiopathic 10 patients (17.8%). While the blood thiol levels were low, the disulfide levels were high at a significant level. No statistically significant relations were detected between the amylase, lipase, neutrophil lymphocyte ratio (NLR), which are other blood parameters, and thiol-disulphide balance parameters.

CONCLUSION: The disruption of the thiol-disulphide balance may play a role in the pathogenesis of acute pancreatitis. In acute pancreatitis, since the thiol level is decreased in the blood, administration of the complementary therapies for this thiol deficiency may contribute to the treatment of the disease.

Keywords: Acute pancreatitis; oxidative stress; thiol-disulphide homeostasis.

INTRODUCTION

Thiols, in other words, mercaptans, are in -SH group.^[1] Generally, the plasma thiol pool is made up of thiols like albumin and low-molecular-weight cysteinylglycine, cysteine (Cys), homocysteine, glutathione and γ -glutamylcysteineprotein.^[2]

Thiol-disulphide homeostasis is extremely important. Thiol/Disulphide Ratio (TDR) is very important in the detoxification process. In previous studies, the findings showed that TDR had several effects on antioxidant protection, signal transduction, enzymatic regulation, apoptosis and cellular signal mechanisms.^[3,4]

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In some diseases, the Thiol-Disulphide Ratio was examined. This ratio was measured unilaterally until 2014, and with the help of the new method that was developed by Erel and Neşelioglu,^[5] it is, nowadays, possible to measure it bilaterally.^[6]

Acute pancreatitis (AP) is rare in clinical practice and its prevalence is approximately 80 per 100.000 people.^[7,8] Severe AP occurs with persistent organ failure. The mortality and morbidity rates of severe AP are also high.^[9,10] In recent years, a moderately severe AP has been reported as consisting of patients with transient organ failure or local/systemic complications without persistent organ failure.^[9,11]

In this study, we aim to examine the thiol/disulphide homeostasis parameters, which constitute homeostasis occurring in the maintenance of many physiological mechanisms that are necessary for organisms and patients with AP.

MATERIALS AND METHODS

This study was approved by the ethical board of Yildirim Beyazıt University (date: 03.12.2014, no: 208). A total of 56 (56%) patients, who were admitted to the emergency department, and 44 (44%) healthy volunteers participated in this study. A total of 100 samples were taken from the participants. AP diagnosis was considered as detection of two of the three necessary diagnosis criteria, which are (a) abdominal pain consistent with AP; (b) serum lipase or amylase levels being higher than three times the maximum limit of normal; and (c) the common findings obtained with abdominal imaging methods.^[7]

The exclusion criteria in the present study were patients who had chronic pancreatitis, malignant illnesses, renal failures, liver failures, heart failures, myocardial infarctions, rheumatic illnesses, psychiatric patients, and patients who had immunosuppressive disorders. The reason for this exclusion was that these diseases or conditions might affect the thiol/disulphide homeostasis.

Detailed blood samples were taken from the patients at admission. The thiol-disulphide ratio was examined with a brand-new method that was developed by Erel and Neşelioglu^[5] at the admission of the patients who were diagnosed with acute pancreatitis.

Thiol-Disulphides Homeostasis Parameters Measurement

Thiol/Disulphide Homeostasis tests were measured using an automated spectrophotometric method described by Erel and Neşelioglu. For short, disulphide bonds were first reduced to form free functional thiol groups with sodium borohydride. Unused reductant sodium borohydride was consumed and removed with formaldehyde to prevent the reduction of DTNB (5,5'-dithiobis-(2-nitrobenzoic) acid), and all of the

thiol groups, including reduced and native thiol groups, were determined after the reaction with DTNB. Half of the difference between the total thiols and native thiols provides the dynamic disulphide amount. After the determination of native and total thiols, disulphide amounts, disulphide/total thiol percent ratios (SS/SH+SS), disulphide/native thiol percent ratios (SS/SH) and native thiol/total thiol percent ratios (SH/SH+SS) were calculated.^[5]

Measurement of the IMA (Ischemia-Modified Albumin)

Measurement of IMA levels was obtained using venous blood samples on admittance within one hour. Specimens were stored for 30 minutes at room temperature and then centrifuged at 3500 rpm for five minutes. Latter samples were transferred to Eppendorf tubes and stored at -80°C until analysis. Albumin Cobalt Binding Test was used to detect the presence of Ischemia Modified Albumin (IMA). This test was performed by adding 50 mL 0.1% cobalt (II) chloride (CoCl₂, 6H₂O) (Sigma-Aldrich Chemie GmbH Riedstrasse 2, Steinheim, Germany) to the patient serum. After mixing, followed by 10 minutes of incubation to allow for albumin cobalt binding, 50 mL 1.5 mg/mL dithiothreitol was added. After mixing, followed by two minutes of incubation, 1.0 mL of a 0.9% sodium chloride solution was added to reduce the binding capacity. The blank was prepared similarly with distilled water instead of dithiothreitol. The absorbance of samples was measured at 470 nm using a spectrophotometer. The results were expressed as absorbance units (ABSU).^[12]

Ferroxidase Measurement

Ferroxidase levels were measured using the method described by Erel O.T. This method is automated, colorimetric and based on the enzymatic oxidation of ferrous ion to ferric ion. The results were expressed in units per liter serum.^[13]

Albumin, urea and creatinine tests were performed using Roche cobas c501 device using commercial kits of Roche.

Neutrophil, lymphocyte and platelet levels were measured using the Sysmex hematology device.

Statistical Analyses

The data were analyzed with the SPSS for Windows 16.0 Package Program. Firstly, descriptive statistics were given. The ratio comparisons in 2x2-eyed tables were performed with the Chi-Square test. The normality analysis of the continuous data was carried out with the Kolmogorov-Smirnov Test, and it was accepted as a result of the test that the data with a value of $p < 0.05$ were not distributed normally. The Independent Samples t-test was employed for the data that showed the normal distribution in the comparisons made between two groups, and the Mann-Whitney U-test was employed for the data that did not show normal distribu-

tion. The Spearman Correlation Test was employed for the analysis in the analysis of the data that were not normally distributed, and the Pearson Correlation Test was employed in the normally distributed data. The P-value was employed for statistical significance, and the results that were $p < 0.05$ were considered to be statistically significant.

As a result of the correlation analyses, no parameters were determined that had a correlation with the hospitalization time at a significant level. NLR had a weak correlation with amylase ($p=0.018$, $\rho: 0.333$) and lipase ($p=0.031$, $\rho: 0.306$). No relations were detected between the thiol/disulphide homeostasis parameters and amylase and/or lipase.

RESULTS

The study group consisted of 56 (56%) patients, and 44 (44%) healthy volunteers applying to the emergency department. A total of 100 samples were taken from the participants. The mean age of the Control Group was 64 (Min-max: 21–80), and the mean age of the Study Group was found to be 57 (Min-max: 18–92). There were no differences between the two groups concerning age distribution at a statistically significant level. In the Control Group, the male gender was 38.6%, and in the Study Group, it was 39.3%. This difference was not found to be statistically significant (Table 1).

The AP etiology was gallstones in 41 of the patients (73.2%), hypertriglyceridemia in one patient (1.7%), alcohol use in four patients (7.1%), and was idiopathic in 10 patients (17.8%).

The in-hospital mortality was determined as 1.8% (1 case) in the Study Group. The 28-day mortality was also determined to be 1.8% (1 case). The mean hospitalization was determined as five days (min-max: 1–41; IQR:3) (6.05 days on average).

According to the Balthazar Classification and the CTSI (Computed Tomography Severity Index), 32 patients in the Study Group had AP, 32 had mild AP (0-4 points), 20 had moderate-severe AP (4–6 points), and four patient had severe AP (7–10 points).^[14]

The hematologic and biochemical parameters, thiol/disulphide homeostasis parameters, IMA and ferroxidase average and median values and the statistical analysis of the differences of the Patient and Control Group are given in Table 1. The findings showed that all of the creatinine, neutrophil, neutrophil/lymphocyte ratio, thiol/disulphide homeostasis parameters, IMA and ferroxidase values were different at a statistically significant level between the groups (Figs. 1–3). In the Patient Group, the neutrophil, neutrophil/lymphocyte ratio, disulphide and IMA were higher at a significant level and the creatinine, NT, TT, index-1, and ferroxidase were lower at a significant level (Table 1).

Table 1. Biochemical and hematological parameters in patient and control groups

	Acute pancreatitis patient / Control group												p
	Control						Patient						
	Mean	SD	Min	Med	Max	95% CI*/ IQR**	Mean	SD	Min	Med	Max	95% CI*/ IQR**	
Albumin*	4.38	0.36	3.74	4.32	5.06	4.27–4.49	4.31	0.42	3.4	4.31	5.22	4.26–4.47	0.371
Ure**	35.2	11.8	18.2	34	66.7	19.0	32.1	14.7	13	27.4	82	12.0	0.066
Creatinin**	0.9	0.16	0.56	0.95	1.28	0.22	0.9	0.81	0.3	0.8	6.5	0.32	0.011
Neutrophil**	4645	1811	2210	4330	10100	2088	8996	4156	2700	8450	24100	3880	<0.001
Lymphocyte*	2068	1053	300	1885	6700	1748–2388	1746	1013	200	1600	5000	1465–1986	0.124
Platelets* (x10 ³)	269	74	88	259	431	246–291	252	81	111	235	456	235–281	0.295
NLR**	2.92	2.3	0.45	2.23	12.94	1.7	7.33	5.95	1.6	5.77	31	7.19	<0.001
Native Thiol*	436.4	65.2	278.4	436.2	578.3	416.6–456.2	352.1	109.1	93.5	342.6	710	332.9–392.2	<0.001
Disulphide*	16.22	7.41	3.85	15.38	33	13.97–18.47	21.39	14.55	0.45	19.58	71.1	17.43–25.75	0.024
Total Thiol*	468.8	65.1	305.5	470.9	607.3	449.0–488.6	394.9	108.2	96.7	389.7	735.7	376.9–434.6	<0.001
Index1**	0.038	0.018	0.008	0.039	0.073	0.026	0.068	0.058	0.001	0.055	0.273	0.039	0.005
Index2**	0.035	0.016	0.008	0.036	0.064	0.022	0.056	0.039	0.001	0.049	0.177	0.032	0.005
Index3**	0.930	0.031	0.872	0.929	0.984	0.044	0.888	0.079	0.647	0.901	0.998	0.064	0.005
IMA**	66.7	9.4	50.8	70.5	84	18.1	73.7	9.3	35.8	74	97	6.8	<0.001
Ferrosidaz**	567	185.8	309.7	514.6	1054.1	255.1	461.5	224.2	40	472.5	1247.7	184	0.025

*Independent Samples-t test; Mean±SD ve 95% CI. **Mann-Whitney-U test; Median (Min-Max) ve IQR.

NLR: Neutrophil lymphocyte ratio; IMA: Ischemia-modified albumin; SD: Standard deviation; Min: Minimum; Max: Maximum; CI: Confidence interval; IQR: Interquartile interval. Index1: disulphide/native thiol. Index2: disulphide/total thiol. Index3: native thiol/total thiol.

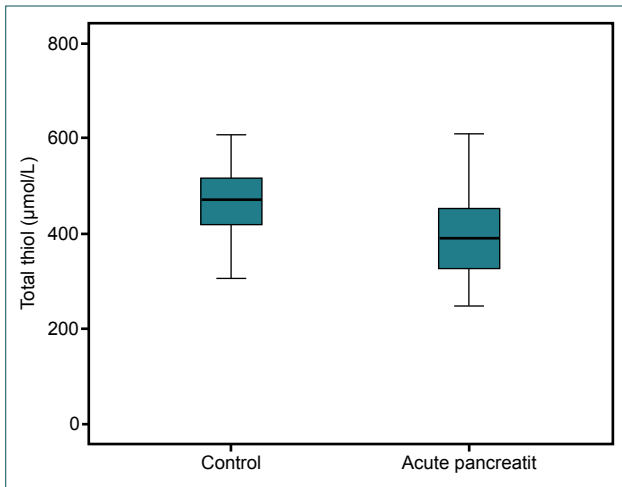


Figure 1. The total thiol distribution in the patient and control group.

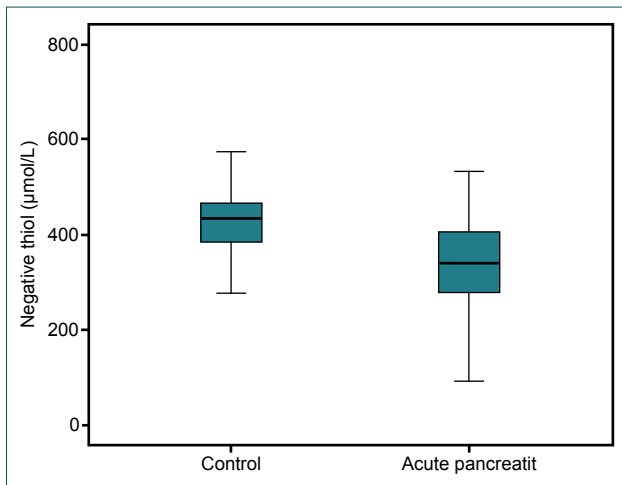


Figure 2. The native thiol distribution in the patient and control group.

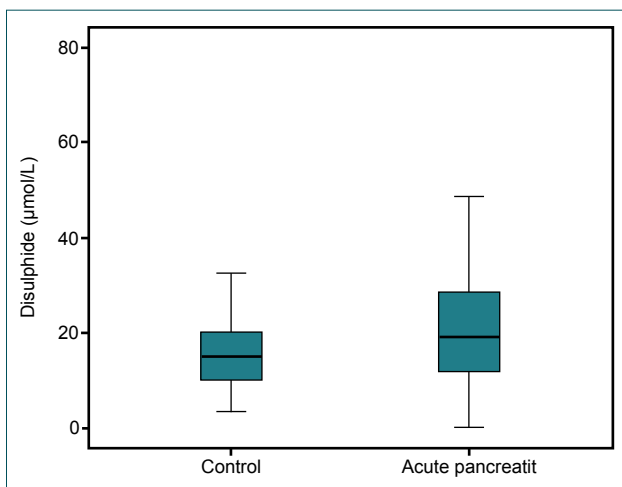


Figure 3. The disulphide distribution in the patient and control group.

DISCUSSION

The dynamic thiol/disulphide homeostasis has a crucial significance in detoxification, antioxidant protection, apoptosis,

signal transduction, regulation of enzymatic activity, as well as transcription factors and cellular signaling mechanisms.^[3,4] Since thiols have continuous interaction with almost all of the physiological oxidants, they are essential antioxidant buffers.^[15,16] Thiol protein groups constitute a significant antioxidant group and are responsible for 52.9% of the total serum antioxidant capacity in healthy people.^[17] A new and automated testing system was proposed by Erel and Neselioglu^[5] to determine the dynamic thiol/disulphide homeostasis. Total serum thiol and native thiol levels are measured; and disulphide concentrations are computed in this method. This test shows the changes in favor of the thiol or disulphide.

Acute pancreatitis is a fascinating disease. The two most common etiologies of acute pancreatitis are gallstones and excessive alcohol consumption. The diagnosis of acute pancreatitis is made with a combination of history, physical examination, computed tomography scan, and laboratory evaluation. Differentiating patients who will have a benign course of their pancreatitis from patients who will have severe pancreatitis is challenging to the clinician.

Releasing active pancreatic enzymes into the bloodstream initiates an inflammatory cascade, which is involved in stimulating the production of many inflammatory cytokines, including interleukins and tumor necrosis factor- α . This cytokine storm can be determined by several serum markers. C-reactive protein (CRP) is the most widely studied and used serum marker to assess the severity of AP. Aside from CRP, many other acute-phase reactants and inflammatory markers, including cytokines, have been studied to assess the severity of AP. Recently, several studies investigated the thiol-disulphide and IMA levels in disorders in which oxidative stress plays an important role in the pathogenesis, including diabetes, cirrhosis, end-stage renal disease, sepsis, and inflammatory bowel disease. Ischemia and oxidative stress are the major determinants of forming IMA, and an increase in serum IMA levels was demonstrated in ischemic disorders and in disorders that oxidative stress contributes to its pathogenesis. Oxidative stress and the production of free radicals are responsible for the progression of pancreatic inflammation, and triggering the generation of inflammatory cytokines is the key event in the pathogenesis of acute pancreatitis.^[18]

We concluded that thiol-disulphide levels decreased as oxidative stress increased in acute pancreatitis. This study aims to compare the thiol-disulphide homeostasis and other blood parameters levels of patients with AP and healthy controls, and to investigate thiol-disulphide homeostasis as a marker of disease severity.

In the present study, disulphide/total thiol and disulphide/native thiol rates increased in favor of disulphide at a significant level. However, the native thiol levels decreased. The thiol level, native thiol level, and native thiol/total thiol percent ratios were lower.

The findings showed that in the thiol/disulphide homeostasis tests that the homeostasis shifted towards the thiol or disulphide side. When the novel method was used, low thiol/disulphide homeostasis was detected in some clinical settings (such as hyperemesis gravidarum, acute myocardial infarction, non-ST elevation myocardial infarction, and Type I Diabetes Mellitus).^[15,19-21]

Reduced glutathione is the basic non-protein thiol in the cells of all mammals and constitutes a significant antioxidant. In animal AP models, its decrease in pancreatic tissue was shown in previous studies.^[22-24] In thiol measurements, these studies employed pancreatic tissue; however, in our study, the thiol/disulphide homeostasis parameters were measured in serum with a novel, easy and full-automatic method in AP patients. The low-molecular-weight thiols and disulphides were evaluated in a study conducted on animal models with AP by Moreno et al.,^[25] who considered disulphide stress as a specific OS type that was associated with mixed disulphides, especially protein cysteinylated, and oxidation of thiols like gamma-glutamylcysteine, cysteine, and homocysteine. However, they did not report any glutathione oxidation or changes in protein glutathionylation. It was also determined that reduced glutathione level reduced in the pancreatic tissue of rats with AP.^[25]

Thiol levels were investigated in studies conducted on animals with pancreatitis, and the thiol-disulphide homeostasis parameters have been examined in humans for the past few years. In our study, the disulphide/total thiol and disulphide/native the thiol rates increased at a significant level in favor of disulphide. However, the native thiol and total thiol levels decreased. The thiol-disulphide homeostasis increased in favor of disulphide. Similar results were obtained in a study that was conducted before ours.^[26]

In our study, we obtained similar results with different tests that showed oxidative stress in tissues. There are several other studies that examined plasma oxidative stress.^[25,27,28] We determined that this homeostasis shifted in favor of disulphide by examining the thiol-disulphide homeostasis in AP.

Among OS markers, there are ischemia-modified albumin, protein carbonyls and superoxide dismutase, which increase among AP in different trials.^[27-29] In a recent meta-analysis study, it was reported that antioxidant therapy had possible benefits for AP, which might be considered as a proof that decreases in the antioxidant levels occurring in AP pathogenesis.^[30,31]

The neutrophil lymphocyte ratio, which is examined in the serum, may be considered as an indirect indicator of the immune response capacity of the host. The reason why NLR indicates that the prognosis is bad may be due to that tumors make metastasis through cytokines and chemokines, and that the mechanism in which the dominance of neutrophils may suppress the cytotoxic T cells. In the first 48 hours, the increase in the NLR is related to severe acute pancreatitis and

is an independent negative prognostic marker in AP.^[32] In the present study, we could not detect any statistically significant relation between the blood thiol-disulphide homeostasis parameters and serum NLR.

The findings suggest the thiol/disulphide homeostasis deficiency may have a role in the AP pathogenesis. Complementing with thiol compounds like N-Acetyl Cysteine (NAC) may be a target for AP therapy. NAC is considered as a free radical collector and stimulates the glutathione synthesis.^[30,31] In the study, the findings suggest that mixed antioxidant supplementation with NAC could reduce the hospital stay and the rate of complications in AP patients.^[33,34]

Conclusion

The disruption of thiol-disulphide homeostasis may have a role in the pathogenesis of acute pancreatitis. Since the thiol level is decreased, administering complementary treatment for thiol deficiency may contribute to the healing of the disease.

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ORIJİNAL ÇALIŞMA - ÖZET

Akut pankreatitli hastalarda tiyol-disülfid dengesi ve diğer kan parametreleri ile ilişkisi

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AMAÇ: Akut pankreatit (AP) karın ağrısı nedeniyle acil serviste sıklıkla görülen bir hastalıktır. Bu çalışma AP tanısı konulan hastalarda, kanda tiyol-disülfid parametrelerinin ölçümü ve diğer kan parametreleri ile ilişkisinin değerlendirilmesi amaçlandı.

GEREÇ VE YÖNTEM: Çalışmaya acil servise başvuran 56 (%56) hasta ve 44 (%44) sağlıklı gönüllü olmak üzere toplam 100 örnek alındı. Hastalardan geliş anında detaylı kan örnekleri alındı. Akut pankreatit tanısı konan hastaların başvurusu sırasında ki venöz kan örneklerinden Erel ve Neşelioglu tarafından geliştirilen yepyeni bir yöntemle serumda tiyol-disülfid düzeyi çalışıldı. Veriler bilgisayar ortamında değerlendirildi.

BULGULAR: Akut pankreatitin etiyolojisi 41 hastada (%73.2) safra taşı, bir hastada (%1.7) hipertrigliseridemi, dört hastada (% 7.1) alkol kullanımı ve 10 hastada (%17.8) idiyopatik idi. Kan tiyol düzeyleri düşük iken, disülfid düzeyleri anlamlı derecede yüksekti. Diğer kan parametreleri olan amilaz, lipaz, NLR (nötrofil lenfosit oranı) ile tiyol-disülfid dengesi parametreleri arasında istatistikî açıdan anlamlı fark bulunamadı.

TARTIŞMA: Akut pankreatit de patogenezde tiyol-disülfid dengesinin bozulması rol oynayabilir. AP’de kanda tiyol düzeyi azaldığından bu tiyol eksikliğini tamamlayıcı tedavilerin verilmesi hastalığın iyileşmesine katkıda bulunabilir.

Anahtar sözcükler: Akut pankreatit; oksidatif stres; tiyol-disülfid dengesi.

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