

# Impaired thiol/disulfide homeostasis in patients with mild acute pancreatitis

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## ABSTRACT

**Background/Aims:** The aim of this study was to compare the dynamic thiol/disulfide (SS) homeostasis and ischemia-modified albumin (IMA) concentration between healthy subjects and patients with mild acute pancreatitis (AP).

**Materials and Methods:** A total of 28 patients with AP (AP group) and 35 age- and sex-matched healthy individuals (control group) were included in this study. Serum thiols/SS and IMA concentrations were measured and compared between the two groups.

**Results:** The mean serum native thiol (SH) and total thiol (TT) levels were significantly lower in the AP group than in the control group (224.7±80.3 µmol/L vs. 314.66±87.5 µmol/L,  $p<0.001$  and 273.3±76.8 vs. 346.9±79 µmol/L,  $p<0.001$ , respectively). SS levels were significantly higher in the AP group than in the control group (24.2±11.1 µmol/L vs. 16.1±9.9 µmol/L,  $p<0.054$ ). There were no differences in the IMA concentration and the mean IMA/albumin ratio (IMAR) between both the groups.

**Conclusion:** We found that mild AP may affect serum thiol and SS levels, and cause impaired thiol/SS homeostasis.

**Keywords:** Acute pancreatitis, thiol/disulfide, ischemia-modified albumin

## INTRODUCTION

Acute pancreatitis (AP) is an important gastrointestinal problem that causes a significant number of hospitalizations worldwide (1). Although its common etiologic factors (i.e., alcoholism in Western countries, idiopathic causes in our country, and gallstones common to both regions) are well known (2,3), its pathogenesis has not been fully understood. Realization of its causative agents and determination of the pathophysiology are essential for the successful management of AP (1).

Ischemia-modified albumin (IMA), a novel marker of oxidative stress (OS), is produced as a result of damaged albumin under hypoxic conditions (4). IMA levels have been reported to increase in many diseases, such as pre-eclampsia, appendicitis, and inflammatory bowel diseases (5-7). Information regarding the association between IMA and pancreatitis is limited and only includes the results obtained from one experimental study in rats and one in humans (8,9).

Thiols are one of the most important antioxidant barriers in humans, and thiol/disulfide (SS) homeostasis is a relatively novel OS marker (10). It includes functional

sulfhydryl groups [(SS)+(SH)], which are the molecules responsible for oxidation and anti-oxidation. Thiol/SS homeostasis has been demonstrated to participate in anti-oxidant protection and detoxification in previous studies (11,12). Increased OS has a crucial role in the pathogenesis of many diseases (13). It has been shown that increased OS may have a role in the pathogenesis of idiopathic recurrent AP. Many recent studies have reported on thiol levels and thiol/SS homeostasis in patients with chronic hepatitis, ulcerative colitis, and coronary artery disease (14-17); however, till date, only one study has been conducted on patients with AP (18). To the best of our knowledge, no studies have been conducted with regard to IMA.

Therefore, the aim of this study was to evaluate the thiol/SS homeostasis and IMA in a mild form in patients with AP for the first time using a novel method.

## MATERIALS AND METHODS

A total of 28 patients with AP and 35 age- and sex-matched healthy individuals were included in this prospective study. This research was conducted in accordance with the principles of the 2008 Declaration of

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Helsinki and was approved by the Local Ethics Committee of Harran University School of Medicine. Each participant provided written informed consent before commencing the study protocol. Serum thiol/SS homeostasis and IMA concentration were measured and compared between the two groups.

### Inclusion criteria

Patients with AP who were admitted to our hospital within 72 hours after onset of disease and presented with significant abdominal pain of pancreatic origin were included in the study.

### Exclusion criteria

Patients with the following conditions were excluded: (a) surgical intervention or endoscopic therapy previously, (b) diabetes mellitus, (c) comorbid diseases, such as renal failure, liver diseases, and malignancy that might affect the OS parameters, (d) any complications of AP, such as pseudocyst or bile duct obstruction, (e) pregnant and lactating women, and (f) age of <18 years.

### Diagnosis of AP

The diagnosis of AP was made in the presence of appropriate clinical and biochemical findings, which were supported by results from imaging techniques, such as ultrasonography, computed tomography, and magnetic resonance imaging with magnetic resonance cholangiopancreatography.

### Stored blood sample tests

Serum IMA concentrations were measured as described by Bar-Or et al. (19). The total thiol (TT), native thiol, and SS concentrations were measured in the serum samples using a new method defined by Erel and Neselioglu (11).

### Statistical analysis

The analyses were performed using SPSS ver. 20.0 package program (Statistical Package for the Social Sciences, Chicago, Illinois, USA). Significance level was accepted as  $p < 0.05$ .

### RESULTS

The mean age of the patients in the AP group (28 patients) was  $48.3 \pm 19.5$  years (range 22-83) and in the control group (35 subjects) was  $46.5 \pm 12.2$  years (range 27-69). There were 19 females (68%) in the AP group and 21 (60%) in the control group. No significant differences were noted in the demographic features between both the two groups. According to the revised Atlanta classification (20), all our patients were diagnosed with mild AP.

**Table 1.** Dynamic thiol/disulfide homeostasis and IMA concentrations in the AP and control groups.

	AP group (Mean $\pm$ SD)	Control group (Mean $\pm$ SD)	p
Native thiol (SH), $\mu\text{mol/L}$	224.7 $\pm$ 80.3	314.66 $\pm$ 87.5	$p < 0.0001$
Total thiol (TT), $\mu\text{mol/L}$	273.3 $\pm$ 76.8	346.9 $\pm$ 79	$p < 0.0001$
Disulphide (SS), $\mu\text{mol/L}$	24.2 $\pm$ 11.1	16.1 $\pm$ 9.9	$p < 0.05$
Disulphide/native thiol (SS/SH)	14.2 $\pm$ 13.1	6.1 $\pm$ 5.4	$p < 0.05$
Disulphide/total thiol (SS/TT)	9.92 $\pm$ 6.2	5.08 $\pm$ 3.9	$p < 0.01$
Thiol/total thiol (SH/TT)	80.1 $\pm$ 12.4	89.83 $\pm$ 7.8	$p < 0.01$
IMA	0.91 $\pm$ 0.46	0.84 $\pm$ 0.61	$p > 0.05$
IMAR	0.26 $\pm$ 0.11	0.25 $\pm$ 0.13	$p > 0.05$

AP: Acute pancreatitis; IMA: Ischemia-modified albumin; IMAR: IMA/albumin ratio.

The mean serum native thiol (SH) and TT levels were significantly lower in the AP group than in the control group ( $224.7 \pm 80.3 \mu\text{mol/L}$  vs.  $314.66 \pm 87.5 \mu\text{mol/L}$ ,  $p < 0.0001$  and  $273.3 \pm 76.8$  vs.  $346.9 \pm 79 \mu\text{mol/L}$ ,  $p < 0.0001$ , respectively). SS levels were significantly higher in the AP group than in the control group ( $24.2 \pm 11.1 \mu\text{mol/L}$  vs.  $16.1 \pm 9.9 \mu\text{mol/L}$ ,  $p < 0.04$ ).

There were significant differences in the SS/SH, SS/TT, and SH/TT ratios between the AP and control groups ( $14.2 \pm 13.1$  vs.  $6.1 \pm 5.4$ ,  $p < 0.04$ ;  $9.92 \pm 6.2$  vs.  $5.08 \pm 3.9$ ,  $p < 0.01$ ; and  $80.1 \pm 12.4$  vs.  $89.83 \pm 7.8$ ,  $p < 0.01$ , respectively). Further, there was no correlation between the thiol/SS homeostasis components, C-reactive protein (CRP), and the time of hospital stay.

No significant differences were noted between the IMA concentration and mean IMA/albumin ratio (IMAR) in patients with and without AP (for both cases:  $p > 0.05$ ). The results are summarized in the Table 1.

### DISCUSSION

Few previous studies have revealed the role of serum OS parameters and IMA in patients with AP. Baser et al. were the first to show that OS was positively related with the inflammatory process and severity of the disease in patients with AP. They found an increase in serum OS parameters (TOS and OSI) and IMA levels, in addition to a decrease in the serum total antioxidant status level in patients with mild AP (8). Contrary to this study, we used serum thiols, SS, and thiol/SS and IMA/albumin ratios as

OS parameters. Our results were compatible with those of Baser et al., except for IMA, in that while serum thiol (total and native) levels were decreased because of OS, serum SS and IMA levels and IMAR values did not increase simultaneously in mild AP. In addition, Topaloglu et al. showed that serum IMA has a role as a marker in the monitoring of inflammation process during pancreatitis in an experimental rat model (8,9).

Although there are limited studies on the relationship of OS and IMA with AP, the pathophysiologic role of OS in patients with chronic pancreatitis (CP) and idiopathic recurrent AP has been studied widely in the recent years. Increased OS has been implicated in the pathogenesis of CP. McPherson et al. have speculated that the increased OS in patients with CP results from one or more of the following causes: generation of free radicals due to cytochrome P450 induction, exposure to a chemical that undergoes bioactivation, and insufficiency of micronutrients that are required to balance antioxidant capacity. They have also reported several beneficial effects of antioxidant therapy (i.e., a significant reduction in pain and OS levels) in patients with CP (21). Additionally, Bopanna et al. have found that the concentration of several OS markers [such as 4-hydroxynonenol (4-HNE), malondialdehyde (MDA), and serum superoxide dismutase] was increased and that of antioxidant markers (such as ferric reducing ability of plasma, glutathione peroxidase (GPX), and vitamin C) was decreased in patients with idiopathic recurrent AP (16). They suggested that OS plays a role in the pathogenesis of idiopathic recurrent AP and that the correction of oxidant-antioxidant balance is an important therapeutic target in preventing the progression of the disease.

Atlanta classification has been used to evaluate the severity and to predict the clinical course of AP using computed tomography severity index (CTSI) and modified CTSI (20). According to this classification method, our patients presented with mild AP. We evaluated the correlations of serum thiols, SS, and IMA levels (OS parameters) with CRP and time of hospital stay (AP parameters) and found no significant correlations between the OS and AP parameters.

The limitations of this study were that the number of patients studied for this evaluation was less, and there were no patients with moderate and severe forms of AP.

## CONCLUSION

It was found that the SH and TT levels were decreased, whereas the SS levels were increased in patients with

mild AP. Further, the SS/SH and SS/TT ratios were increased and the SH/TT ratio was decreased in these patients. However, IMA and IMAR values were similar between the AP and control groups. Based on the findings of our study, we suggest that while serum thiol (total and native) concentrations were decreased because of OS, with a simultaneous increase in the serum SS levels, IMA and IMAR values did not change in mild AP.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Local Ethics Committee of Harran University.

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - A.U.; Design - A.U.; Supervision - A.U.; Resources - A.U.; Materials - R.Y.; Data Collection and/or Processing - R.Y.; Analysis and/or Interpretation - Ö.E., A.K.; Literature Search - T.S.; Writing Manuscript - Ç.C.; Critical Reviews - A.U., T.S.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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## REFERENCES

1. van Dijk SM, Hallensleben ND, van Santvoort HC, et al. Dutch Pancreatitis Study Group. Acute pancreatitis: recent advances through randomised trials. *Gut* 2017; 66: 2024-32. [CrossRef]
2. Chen HZ, Ji L, Li L, Wang G, Bai XW, Cheng CD, Sun B. Early prediction of infected pancreatic necrosis secondary to necrotizing pancreatitis. *Medicine (Baltimore)* 2017; 96: e7487. [CrossRef]
3. Tamer A, Yaylacı S, Demirsoy H, et al. Akut Pankreatitli Olgularımızın Retrospektif Değerlendirilmesi. (Retrospective Analyses of the Acute Pancreatitis) *Sakaryamj* 2011; 1: 17-21. [CrossRef]
4. Karatas GA, Kaban I, Aka N, Mentese A, Aker F, Uras AR. The Role of Ischemia Modified Albumin and D-dimer as Early or Late Biochemical Markers in Ovarian Torsion. *J Obstet Gynaecol Res* 2017; 43: 895-901. [CrossRef]
5. Seshadri Reddy V, Duggina P, Vedhantam M, Manne M, Varma N, Nagaram S. Maternal serum and fetal cord-blood ischemia-modified albumin concentrations in normal pregnancy and preeclampsia: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2018; 31: 3255-66. [CrossRef]
6. Nazik S, Avci V, Küskü Kiraz Z. Ischemia-modified albumin and other inflammatory markers in the diagnosis of appendicitis in children. *Ulus Travma Acil Cerrahi Derg* 2017; 23: 317-21. [CrossRef]
7. Guntas G, Sahin A, Duran S, et al. Evaluation of Ischemia-Modified Albumin in Patients with Inflammatory Bowel Disease. *Clin Lab* 2017; 63: 341-7. [CrossRef]

8. Topaloglu N, Kucuk A, Tekin M, et al. Serum Ischemia-Modified Albumin Levels in Experimental Model of Acute Pancreatitis. *J Coll Physicians Surg Pak* 2015; 25: 395-8.
9. Baser H, Can U, Karasoy D, et al. Evaluation of oxidant/anti-oxidants status in patients with mild acute -pancreatitis. *Acta Gastroenterol Belg* 2016; 79: 23-8.
10. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. *Clin Biochem* 2014; 47: 326-32. [\[CrossRef\]](#)
11. Altıparmak IH, Erkuş ME, Sezen H, et al. The relation of serum thiol levels and thiol/disulphide homeostasis with the severity of coronary artery disease. *Kardiol Pol* 2016; 74: 1346-53. [\[CrossRef\]](#)
12. Uyanikoglu H, Sak ME, Tatli F, et al. Serum ischemia modified albumin level and its relationship with the thiol/disulfide balance in placenta percreta patients. *J Obstet Gynaecol* 2018; 38: 1073-7. [\[CrossRef\]](#)
13. Ulusoy S, Ayan NN, Dinc ME, Is A, Bicer C, Erel O. A new oxidative stress marker for thiol-disulphide homeostasis in seasonal allergic rhinitis. *Am J Rhinol Allergy* 2016; 30: 53-7. [\[CrossRef\]](#)
14. Dertli R, Keskin M, Biyik M, et al. Dynamic thiol-disulfide homeostasis is disturbed in hepatitis B virus-related chronic hepatitis and liver cirrhosis. *Turk J Med Sci* 2018; 48: 985-92. [\[CrossRef\]](#)
15. Neselioglu S, Keske PB, Senat AA, et al. The relationship between severity of ulcerative colitis and thiol-disulphide homeostasis. *Bratisl Lek Listy* 2018; 119: 498-502. [\[CrossRef\]](#)
16. Bopanna S, Nayak B, Prakash S, Shalimar, Mahapatra SJ, Garg PK. Increased oxidative stress and deficient antioxidant levels may be involved in the pathogenesis of idiopathic recurrent acute pancreatitis. *Pancreatol* 2017; 17: 529-33. [\[CrossRef\]](#)
17. Soyalp M, Yalcin M, Oter V, Ozgonul A. Investigation of procalcitonin, IL-6, oxidative stress index (OSI) plasma and tissue levels in experimental mild and severe pancreatitis in rats. *Bratisl Lek Listy* 2017; 118: 137-41. [\[CrossRef\]](#)
18. Köseoğlu H, Alışık M, Başaran M, et al. Dynamic thiol/disulphide homeostasis in acute pancreatitis. *Turk J Gastroenterol* 2018; 29: 348-53. [\[CrossRef\]](#)
19. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. *J Emerg Med* 2000; 19: 311-5. [\[CrossRef\]](#)
20. Sahu B, Abbey P, Anand R, Kumar A, Tomer S, Malik E. Severity assessment of acute pancreatitis using CT severity index and modified CT severity index: Correlation with clinical outcomes and severity grading as per the Revised Atlanta Classification. *Indian J Radiol Imaging* 2017; 27: 152-60. [\[CrossRef\]](#)
21. McPherson SJ, O'Reilly DA, Sinclair MT, Smith N. The use of imaging in acute pancreatitis in United Kingdom hospitals: findings from a national quality of care study. *Br J Radiol* 2017: 20170224. [\[CrossRef\]](#)