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The diagnostic value of calcium binding protein S100A8/A9 and S100A12 in acute pancreatitis

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ABSTRACT

Background: S100A8/A9 and S100A12 which are the major calcium-binding proinflammatory proteins secreted by granulocytes, has been proposed to be related to distinct disease states of inflammatory origin. This study aims to explore the circulating levels of S100A8/A9 and S100A12 in acute pancreatitis (AP) and reveal their relationship with conventional inflammatory markers.

Material and Method: Serum S100A8/A9 and S100A12 were determined in AP patients (male/female: 17/13) by using a specific enzyme-linked immunosorbent assay (ELISA) method at both onset and remission and in 30 healthy controls (male/female: 17/13).

Results: Significantly higher S100A8/A9 and S100A12 levels were found in AP patients compared to healthy controls ($p<0.001$). Circulating levels of S100A8/9, S100A12 and C-reactive protein (CRP) were found to be elevated in AP patients at disease onset compared with remission. The correlation analysis demonstrated a significant association between S100A8/A9 and S100A12 ($r=0.366$, $p=0.047$). The cut-off level for S100A8/A9 for detecting AP was ≥54.4 ng/ml with a sensitivity and specificity of 96.7% and 73.3% (AUC: 0.958). The optimum cut-off level for S100A12 for detecting AP was ≥350.25 ng/ml with a sensitivity and specificity of 73.3% and 76.7% (AUC: 0.752) respectively.

Conclusion: Circulating S100A8/A9 and S100A12 levels were found to be elevated in AP patients. Both of these markers might serve as an additional tool in the diagnostic workup in AP since S100A8/A9 and S100A12 were significantly correlated with CRP.

Keywords: Acute pancreatitis, S100A8/A9, S100A12, CRP, inflammation

INTRODUCTION

Acute pancreatitis (AP) is one of the most encountered gastrointestinal reason for emergency department (ED) admission and shows an annual incidence up to 12 to 45 per 100,000 population (1). An increase in serum amylase and lipase levels with an acute onset of abdominal pain continues to be the most widely used diagnostic criteria of AP. Although both of these enzymes are usually used for the diagnosis, their popularity does not appear to be justified because of their low specificity in which elevated levels could also be observed in perforated gastric or duodenal ulcers, kidney diseases, gastrointestinal obstruction, tubo-ovarian disease, and mesenteric infarction (2). Although there are several additional diagnostic assays including urinary trypsinogen-2 and trypsinogen activation peptide exist, they are unfortunately less widely available. Therefore there is an eager need for better noninvasive diagnosing markers that can help identify the exact diagnosis at an earlier time point, and evaluate the efficacy of medical treatment.

Amongst a number of calcium-binding proteins (CBP), S100 protein family consists the mostly encountered one. From this CBPs, S100A8, S100A9, and S100A12, are very well defined by a distinctive expression pattern,

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with strong prevalence in myeloid origin cells (3). In this context, the S100A8/A9 heterocomplex and the S100A12 are elements of the calgranulin family and released from inflammatory cells of the myeloid lineage. It has been suggested that increased circulating S100A8/A9 and S100A12 levels might be an indicator of a subclinical inflammation in which increased levels were reported in distinct disease states including inflammatory bowel disease, otitis media, alcoholic liver cirrhosis, Hodgkin lymphoma, and myocarditis (4-10). Unfortunately, there is no literature data that reveals the possible role of these CBPs in AP pathophysiology.

Based on the emerging roles of S100A8/A9 and S100A12 in inflammation-associated diseases, we designed the current trial to examine the possible involvement of S100A8/A9 and S100A12 in AP and to determine whether these two parameters are correlated with conventional inflammatory markers commonly used to evaluate inflammatory response in AP course.

MATERIAL AND METHOD

The study was approved by the Çanakkale Onsekiz Mart University Clinical Researches Ethics Committee (Date: 27.11.2019, Decision No: 2019-19). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Participants

Thirty patients with AP (M/F: 17/13) admitted to the ED of Çanakkale Onsekiz Mart University (COMU) and hospitalized whether to a regular ward or intensive care unit (ICU) were initially recruited for the study. After treatment, all patients achieved remission and were included in the main analysis. Thirty healthy subjects (M/F: 17/13) were recruited from healthy individuals seeking a routine health check-up who had no previous history of acute/chronic inflammatory disorders, or a history of any drug use. Exclusion criteria of the study included; patients referred from an outside hospital, patients with an inflammatory and malignant condition including inflammatory bowel disease, otitis media, alcoholic liver cirrhosis, Hodgkin lymphoma, chronic pancreatitis and myocarditis. Each of the 30 patients was diagnosed with AP within 12 h of admittance to ED and this assessment was based on the revised Atlanta classification that includes physical examination with the presence of abdominal pain, elevated levels of serum lipase and/or amylase (more than three times from upper normal limit), and characteristic computed tomography (CT) or magnetic resonance imaging (11). After hospitalization, each patient was closely followed up until discharge from the hospital. Remission of AP was defined as the disappearance of symptoms and radiologic imaging findings after the initial medical treatment.

Clinical and Laboratory Assessment

Clinical, demographic and biochemical parameters of each patient were recorded. The obtained data include; age, gender, and disease severity Routine hemogram and laboratory parameters including lipase, amylase, lipase, alanine aminotransferase, aspartate aminotransferase, albumin, creatinine, calcium, glucose, lactate dehydrogenase, C-reactive protein (CRP) and sedimentation rate (ESR) were recorded. Fasting serum samples were obtained from each study participant at both the onset and remission of the disease after overnight fasting without any anticoagulant use. Blood samples were left on the clot, and serum was separated from cellular elements by centrifugation (3,000 rounds per minute for 15 minutes) within two hours after blood sampling. All serum samples were stored at -80°C until the analysis was performed.

S100A 8/9 and S100A 12 Assay

S100A 8/9 levels were measured by a double antibody Enzyme-linked immunosorbent assay (ELISA) kit, from Bioassay Technology Laboratory made in Shangai China, Catalogue Number E4010Hu. S100A 12 levels were measured using commercially available ELISA kits from Bioassay Technology Laboratory made in Shangai China, Catalogue Number E3074Hu.

Statistical Analysis

Frequencies and percentages (%) were used to express categorical variables. Continuous variables were expressed median and interquartile range (IQR). The Shapiro–Wilk test was used to evaluate the normality assumption for the continuous variables. Mann–Whitney U test was performed for analyzing differences between two groups in conditions with the existence of non-normally distributed continuous variables. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test. Spearman's correlation test was used to perform correlation analysis. ROC analysis was used to calculate the areas under the receiving operator curves (AUROC) with 95% confidence intervals for S100A8-9 and S100A12 to predict acute pancreatitis. Statistical evaluations were performed by using SPSS19.0 for Windows (IBM Corp., Armonk, NY, USA). P values below 0.05 were accepted as significant.

RESULTS

A total of 30 patients with AP and 30 control subjects were enrolled in this study. Thirteen (43.3%) AP patients and 13 (43.3%) of the healthy controls were female. Median age of AP patients was 67.0 (57.0-75.0) years and healthy controls had a median age of 63.5 (48.5-76.3) years. No significant differences were demonstrated between study groups in respect to age and sex. The median serum

S100A 8/9 levels in patients with AP was significantly elevated (p<0.001) compared with healthy control group [102.2(64.7-177.5)] (ng/mL) vs 51.2(43.9-55.4) (ng/mL)]. Similarly the median serum S100A12 levels in patients with AP was significantly elevated (p<0.001) compared with healthy control group [409.5(304.8-711.8) (ng/mL) vs 312.4(268.1-346.2) (ng/mL)]. **Table 1** demonstrates the clinical, demographic characteristics and biochemical values of the study groups. **Figure 1** demonstrates the median S100A 8/9 and S100A12 levels of the AP patients at the onset and remission compared with those of the healthy controls.

Table 1. Demographic characteristics and laboratory values of the acute pancreatitis patients and controls

	Acute pancreatitis (n=30)	Control group (n=30)	p
Age (years)	67.0 (57.0-75.0)	63.5 (48.5-76.3)	0.280
Sex (F/M)	17/13	17/13	1.00
Amilaz (U/L)	1123.0 (514.0-1922.0)	64.5 (42.0-82.3)	<0.001
Lipaz (U/L)	1908.0 (1178.0-3912.0)	37.0 (28.5-52.0)	<0.001
ALT (U/L)	35.0 (15.0-173.0)	16.0 (13.75-23.25)	0.004
AST (U/L)	40.0 (23.0-227.0)	21.0 (16.0-30.3)	<0.001
ALP (U/L)	114.0 (78.0-197.0)	76.5 (53.25-93.5)	<0.001
GGT (U/L)	142.0 (37.0-298.0)	27.0 (12.8-36.3)	<0.001
Total Bilirubin (mg/dl)	1.0 (0.6-3.0)	0.5 (0.33-0.73)	0.001
WBC (/mm³×10³)	11.4 (9.0-14.7)	6.7 (5.4-8.4)	<0.001
Hemoglobin (g/dL)	13.0 (11.5-14.5)	12.7 (11.6-13.6)	0.416
Platelet (/mm³×10³)	248.0 (208.0-310.0)	221.5 (169.0-280.0)	0.109
CRP (mg/L)	5.9 (2.7-13.6)	0.40 (0.2-0.7)	<0.001
Sedimentation (mm/h)	34.0 (17.0-60.0)	15.0 (11.0-20.3)	0.003
S100A8/A9 (ng/mL)	102.2 (64.7-177.5)	51.2 (43.9-55.4)	<0.001
S100A12 (ng/mL)	409.5 (304.8-711.8)	312.4 (268.1-346.2)	<0.001

ALT: Alanine aminotransferase, AST: Aspartate aminotrasferase, ALP: Alkaline Phosphatase, GGT: Gamma Glutamyl Transferase, WBC: White Blood Count, CRP: C-Reactive Protein

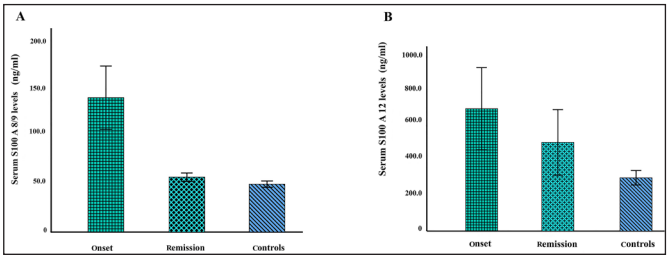

Figure 1. Bar plots and corresponding error bars of (A) median S100A 8/9 and S100A 12 levels of the acute pancreatitis patients and controls; (B) median S100A 8/9 and S100A 12 levels of the acute pancreatitis patients at onset and remission

The comparison of serum inflammation markers in conjunction with S100A 8/9 and S100A12 are given in **Table 2**. Both S100A 8/9 and S100A12 were found to be elevated at onset of the disease compared with remission. Likewise, white blood cell (WBC), CRP and ESR values were significantly elevated in AP patients at onset of the disease. Spearman correlation analysis revealed a significant correlation between CRP and S100A 8/9 (r=0.467, p=0.009) and S 100A 12 (r=0.555, p=0.001) (**Figure 2**). Moreover, both S100A 8/9 and S100A12 levels were found to be correlated at the onset of the disease (r=0.366, p=0.047) (**Table 3**).

Table 2. Comparison of serum S100A8/A9 and S100A12 levels and other markers of inflammation at onset and remission of acute pancreatitis

	Onset	Remission	p
WBC (/mm³×103)	11.4 (9.0-14.7)	6.8 (5.15-8.7)	<0.001
Neutrophil (/mm³×10³)	10.3 (6.9-13.1)	4.5 (2.9-5.7)	<0.001
Lymphocyte (/mm³×10³)	1.1 (0.7-1.4)	1.4 (1.1-1.9)	0.047
Platelet (/mm³×10³)	248.0 (208.0-310.0)	240.0 (188.5-350.0)	0.976
CRP (mg/dL)	5.9 (6.7-13.6)	0.8 (0.5-1.5)	<0.001
Sedimentation (mm/h)	34.0 (17.0-60.0)	17.0 (11.5-26.0)	0.007
S100A8/A9 (ng/mL)	102.2 (64.7-177.6)	54.2 (49.7-59.9)	<0.001
S100A12 (ng/mL)	409.5 (304.8-711.8)	282.9 (242.7-564.5)	0.015

WBC: White Blood Count, CRP: C-Reactive Protein

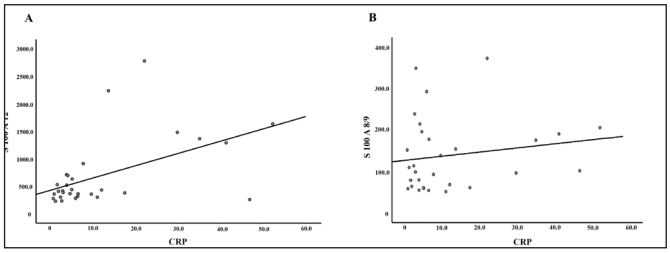

Figure 2. Correlations of (A) S100A 8/9 with CRP; (B) S100A 12 with CR

The Receiver Operating Characteristic (ROC) curve analysis revealed that the ideal S100 A8/9 level cut-off points for determining AP was ≥54.4 ng/ml with a sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of 96.7%, 73.3%, 95.7 and 78.4 respectively (AUC: 0.958). The optimum S100A12 level cut-off value for determining AP was ≥350.25 ng/ml with a sensitivity, specificity, NPV and PPV of 73.3, 76.7%, 74.2 and 75.9, respectively (AUC: 0.752) (**Table 4**). **Figure 3** demonstrates ROC curve analysis to predict acute pancreatitis.

Table 3. Correlation analysis of study variables at onset of acute pancreatitis

	S100A8/9		S100A 12		Sedimentation		CRP	
	r	p	r	p	r	p	r	p
WBC	0.036	0.851	0.118	0.535	0.487	0.010	0.258	0.169
CRP	0.467	0.009	0.555	0.001	0.309	0.117	-	-
Sedimentation	0.326	0.097	0.091	0.651	-	-	-	-
S100A12	0.366	0.047			-	-	-	-

WBC: White Blood Count, CRP: C-Reactive Protein

Table 4. ROC analyses of S100A8/A9 and S100A12 with other conventional inflammation markers to determine acute pancreatitis

Acute pancreatitis vs controls	AUC	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC (/mm³×10³)	0.849	7.1	93.3	60.0	70.0	90.0
CRP (mg/dl)	0.959	1.0	93.3	83.3	84.8	92.6
Sedimentation (%)	0.731	16.5	70	63.3	65.6	67.9
S100 A8/9 (ng/ml)	0.958	54.4	96.7	73.3	78.4	95.7
S100 A12 (ng/ml)	0.752	350.25	73.3	76.7	75.9	74.2

WBC: White Blood Count, CRP: C-Reactive Protein, AUC: Area Under Curve, PPV: Positive Predictive Value, NPV: Negative Predictive Value, ROC: Reciever Operating Characteristics

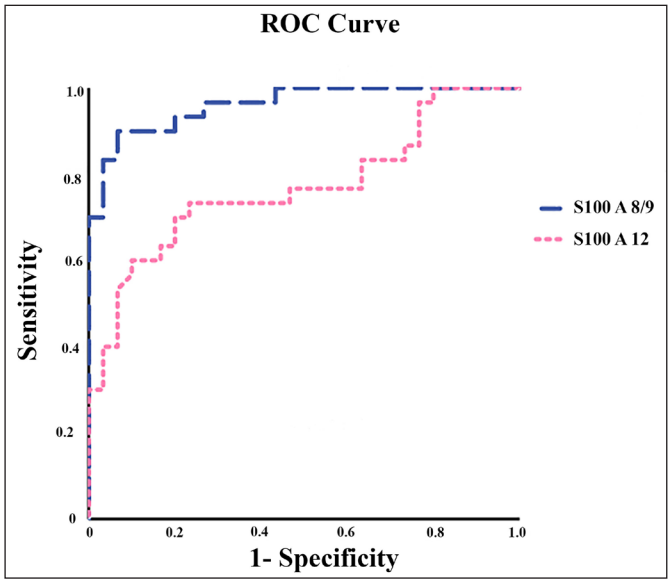

Figure 3. Receiver operating characteristic curves of study parameters to predict acute pancreatitis

DISCUSSION

This study demonstrated that S100A8/A9 and S100A12 levels are increased in AP compared to healthy controls. Moreover, in AP patients after remission was achieved, S100A8/A9 and S100A12 levels were returned to normal values compatible with healthy controls. In addition, circulating S100A8/A9 and S100A12 levels were found to have high specificity, sensitivity, and predictive values in patients with AP suggesting that both of these markers could be regarded as useful serum markers of inflammation in these patient group. Thus, our findings add new and relevant proof to the growing body of evidence on the role of proinflammatory S100 proteins in AP patients with a prospect for potential diagnostic and therapeutic strategies

At present, the severe form of AP is associated with an exceptionally high mortality rate rising to 30% due to rapid inflammatory development and complex pathophysiological conditions during the disease course (12,13). Therefore, there is an urgent and compelling need to determine the inflammatory status in AP patients especially in the very first days of hospital admission (14). In order to accomplish this goal and to determine the existence and the severity of pancreatic inflammation, clinical and biochemical evaluations are generally used in clinical practice (15). Unfortunately, the precise molecular mechanisms underlying pancreatic inflammation and destruction is still challenging (16). In this context, this study for the first time uncovered the potential role of two CBPs, S100A8/A9 and S100A12, in AP patients and investigated their roles in inflammation by analysing their correlation with conventional inflammation markers.

The S100 protein family involves over 20 members which are expressed entirely in vertebrates and exert intra- and extracellular regulatory properties (17). Of the S100 protein family, S100A8, S100A9 and 100A12 are strictly associated with inflammation (17-20). S100A8 and S100A9, both of which are different proteins, constitute the greater part of the calcium-binding capability in phagocytes and arise a heterocomplex to create the structure of calprotectin (21). S100A8/A9 heterocomplex increase the secretion of nuclear factor kappa B and proinflammatory mediators upon Toll-like receptor 4 (TLR4) stimulation. Furthermore, the S100A8/A9 is substantially responsive to oxidative stress and has a key function in the scavenging of the oxidants and the maintenance of tissue components and proteins (17,22) Although, there is no literature data revealing a possible role of S100A8/A9 heterodimer in pancreatitis, a recent paper by Gammal et al. (23) the role of S100A8/A9 protein in chronic pancreatitis, intraductal papillary mucinous tumour and adenocarcinoma of the pancreas

was investigated. Authors' reported that in all of these three diseases S100A8/A9 serum levels were increased and they suggested that S100A8/A9 heterodimer levels could help to distinguish patients with malignant and/ or inflammatory disease from normal and non-malignant pathological conditions. In this study, we also revealed that S100A8/A9 heterodimer is increased in AP and we think that this finding is important because it provides mechanism that centers S100 protein family in the pathophysiology of AP.

The other calcium binding protein that is investigated in the present study is S100A12 which is a protein that is specifically expressed in granulocytes and early differentiation stages of monocytes (24). S100A12 has been demonstrated to be present on circulating leukocytes and is considered a susceptible marker for the local inflammatory process related to oxidative stress. Similarly to S100A8/A9, S100A12 is considered phagocyte-specific, displays pro-inflammatory activities and has already been related to distinct diseases of inflammatory origin, including inflammatory bowel disease, otitis media, hepatitis B-related acute-on-chronic liver failure and juvenile idiopathic arthritis (4,5,25,26). Even though there is no data in humans on the relation between S100A12 and AP, there is one study in literature exploring a potential effect of S100A12 on severity evaluation and curative effect of severe AP in a mice model of AP (27). This experimental mice model shows huge promise that S100A12 can be used to monitor the development and prognosis of severe AP. Furthermore, the inhibition of S100A12 expression, the excessive activation of neutrophils demonstrated to be controlled, which will weaken the inflammatory reaction of severe AP by reducing the release of inflammatory mediators.

This study has several limitations that need to be addressed. First, we accept that the relatively low number of patients recruited for this study limits us to generalize our findings. Second, although we found that S100A8/A9 and S100A12 are sensitive markers of inflammation, our study does not clearly address whether these findings are specific for AP. Third, it would be noteworthy of examining the other factors such as oxidative stress marker expression, in order to fully understand the pathophysiological role of S100A protein family in AP associated inflammatory response.

CONCLUSION

It is apparent that the upregulation of S100A8/A9 heterocomplex and S100A12 is not limited to the boundaries of pancreas region, but is also reflected systemically and consequently observed in patient serum. Furthermore elevated levels of S100A8/A9 and s100A12 is related to AP development and significantly correlated with CRP. These findings suggest that S100A8/A9 heterocomplex and S100A12 in serum might be a potential biomarker of AP with providing significant information regarding ongoing inflammatory status in AP patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Çanakkale Onsekiz Mart University Clinical Researches Ethics Committee (Date: 27.11.2019, Decision No: 2019-19).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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