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The role of serum tenascin-c and procalcitonin in predicting the severity of acute pancreatitis

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Abstract

Acute pancreatitis (AP) constitutes an activation of a variety of enzymes secreted by the pancreas and is a continuing inflammatory process where the pancreas damages itself. Although a variety of factors reported to have an association with disease severity, the role of Tenascin-C and procalcitonin in the pathophsiology of the disease has not been clearly elucidated yet. Therefore, this study aimed to assess whether tenascin-C and procalcitonin would be useful in predicting disease severity and prolonged hospital stay in conjunction with several prognostic scoring systems. A total of 44 AP patients (male/female: 24/20), and 40 healthy subjects (male/female: 20/20) were enrolled in this study. Tenascin-C and procalcitonin levels with other markers of inflammation were measured for all study participants. Prognostic scoring systems were used as to predict the disease severity in AP patients. Serum tenascin-C levels was higher in AP patients at onset of the disease compared with healthy controls. There were statistically significant and positive differences identified between serum Tenascin-C with Atlanta (p=0.000 r=0.538), Ranson (p=0.041 r=0.310) and Imrie (p=0.039 r=0.312) scoring systems. There was a statistically significant and positive correlation between CRP with serum tenascin-C (p=0.015 r=0,366) levels. Serum tenascin-C levels had high sensitivity (76.5%) and specificity (77.8%) for prediction of severe pancreatitis according to the Atlanta scoring system (AUC:0.809). The present study demonstrated that tenascin-C and procalcition levels are elevated in AP. Moreover, the appraisal of tenascin-C levels in patients with AP in conjunction with other markers of inflammation may provide additional information in estimating AP severity.

Keywords: Acute Pancreatitis, tenascin-c, procalcitonin, prognostic markers

Introduction

Acute pancreatitis (AP) begins with activation of a variety of enzymes secreted by the pancreas and is a continuing inflammatory process where the pancreas damages itself. This frequently observed clinical situation may occur in a broad spectrum from mild edematous pancreatitis to necrotizing pancreatitis that may cause serious morbidity and mortality.

Of deaths linked to AP, 65% occur within the first 2 weeks and 80% within the first 1 month. As a result, the clinical progression of AP is associated with patients receiving early diagnosis and early prognosis predictions.Additionally, it is important to predict clinical complications and to determine situations which may lead to mortality. Due to the limited findings about the disease in patients in the early period, there is still a need for simple and easy-to-use inflammatory markers and scoring systems [1].

Tenascins are a group of extracellular matrix glycoproteins expressed during development of multicellular organisms and playing a role in a variety of pathological processes like inflammation, tissue injury, tumor angiogenesis and metastasis [2]. Tenascin-C expression in adults is generally limited to the region with temporary tissue injury and tenascin-C level returns to normal after tissue repair is completed. Contrary to this, tenascin-C is continuously high in inflammatory situations, and is widespread in remodeling during tissue healing and autoimmune diseases [3].

Procalcitonin (PCT), found at undetectable levels in the blood of healthy people, occurs at high levels in blood in situations like inflammation, infection and organ failure that may cause tissue injury and is rapidly released by neuroendocrine tissue present in organs like thyroid gland C cells, lungs and liver. As a result, it has been used as a good marker of tissue injury and infection in recent years [4].

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In spite of many studies performed about the inflammatory role of the tenascin-C molecule, there is no study performed with AP patients. In this study, we aimed to analyze the role of tenascin-C and procalcitonin in AP patients to predict disease severity.

Material and Methods

This study prospectively included 44 AP patients admitting to Çanakkale Onsekiz Mart University Training and Research Hospital between March 2019 and March 2020. The control group comprised 40 healthy individuals attending the gastroenterology clinic with no comorbid disease or medication use.

Exclusion criteria for the study were patients younger than 18 years, with tests performed at any external center, patients attending with second pancreatitis attack within the last 1 week (accepted as the same attack), patients with chronic liver diseases, diseases progressing with acute or chronic inflammation or with pancreas cancer.

Patient age, sex, smoking and alcohol use, body mass index (BMI), duration of hospital admission, and pancreatitis etiology were recorded. To determine disease severity, the Ranson score was used at time of first diagnosis and in the 48th hour, while the Imrie score was calculated in the 48th hour (Imrie <3 points mild AP, ≥3 severe AP).

According to Atlanta criteria, patients were grouped as mild, moderate and severe. Patients without organ failure and local-systemic complications were included in the mild group. Patients without permanent organ failure with local-systemic complications or with temporary organ failure without any complications (<48 hours) were included in the moderate group. Patients developing permanent organ failure (organ failure accepted as systolic blood pressure <90 mmHg, PaO2 below 60 mmHg, creatinine values above 2 mg/dL after rehydration) were included in the severe patient group.

Blood samples were taken from patients within the first 12 hours after admission to the ward. Samples were centrifuged for 5 minutes at 5000 rpm to separate serum. Serum samples were placed in Eppendorf tubes and stored at -80 °C. Tenascin-C and PCT antigen levels quantitatively determined by using ELISA kits (Shanghai Sunredbio (SRB) Technology Co. Ltd. China).

All statistical analyses were completed using SPSS version 22.0 (SPSS Inc., Chicago, IL, United States). Continuous data are expressed as mean and standard deviation, while categoric data are expressed as number and percentage. Normal distribution of continuous variables was tested with the Shapiro-Wilk test. Data with normal distribution were compared with the chi-square test, while data without normal distribution were compared with the Mann Whitney U test. Continuous data for three variables were compared with the Kruskal-Wallis test. Comparisons between groups used the Bonferroni correction. For categoric data, chi-square and Fisher tests were used as appropriate. Correlation analyses were performed with the Spearman correlation analysis. Diagnostic value for prediction of lengthened admission duration and severity of acute pancreatitis by inflammatory markers was investigated with the ROC curve analysis. P<0.05 was accepted as the level of statistical significance.

Results

Demographic characteristics showed 20 of the patient group were women (45%) and 24 were men (55%), while the sex distribution in the control group was 20 women (50%) and 20 men (50%). Mean age of cases in the patient group was 65.45±13.68 years, while mean age of cases in the control group was 62.40±15.69 years.

In the patient group, the proportion of smokers was 18.1% with alcohol use at 18.1%, while in the control group the proportion of smokers was 17.5% with alcohol use at 15%. The BMI in the patient group was 28.59±5.58 kg/m^2, while in the control group it was 25.57±4.60 kg/m^2.

The AP etiologies of patients were biliary pancreatitis in 22 patients (50%), chronic alcohol use in 3 patients (6.8%), hyperlipidemia in 4 patients (9%), other causes in 5 patients (medication use, tumor, post-ERCP, autoimmune pancreatitis, etc.) (11.3%) and idiopathic in 10 patients (22.7%). Mean duration of hospital stay was 6.45±3.37 days (Table 1).

Table 1. Demographic and clinical information for individuals included in the study

	Acute Pancreatitis (n:44)	Controls (n:40)
Age (year)	65.45±13.68	62.40±15.69
Gender, female, n(%)	20 (%45)	20 (%50)
Smoking, n(%)	8 (%18)	7 (%17)
Alcohol use, n(%)	8 (%18)	6 (%15)
BMI (kg/m2)	28.59±5.58	25.57±4.60
Length of stay in the hospital (day)	6.45±3.37	-
Etiology, n(%)		
Biliary	22 (%50)	-
Alcohol	3 (%6)	-
Hyperlipidemia	4 (%9)	-
Idiopathic	10 (%22)	-
Others	5 (%11)	-

The Tenascin-C levels at time of first diagnosis, discharge and in the control group were 2997±1869 pg/ml, 1183±1044 pg/ml, and 1619±1260 pg/ml, respectively. PCT was identified as 867±755 pg/ml at diagnosis, 236±127 pg/ml at discharge and, 264±203 pg/ml in the control group. There were statistically significant differences identified between serum tenascin-C (p=0.000) and PCT (p=0.000) between first diagnosis and remission. There were also significant differences present between serum tenascin-c (p=0.000) and PCT (p=0.000) levels at time of diagnosis in patients and in the control group.

The CRP values in patients were 11.81±12.81 mg/dl at onset, 1.15±0.99 mg/dl at remission, while they were 0.77±1.00 mg/dl in the control group (Table 2).

There were statistically significant and positive differences identified between serum tenascin-C with Atlanta (p=0.000 r=0.538), Ranson (p=0.041 r=0.310) and Imrie (p=0.039 r=0.312) scoring systems. These had moderate level of correlation according to correlation coefficients. There was a statistically significant and positive correlation between CRP with serum tenascin-C (p=0.015 r=0.366) Our study did not identify a difference between PCT values with scoring systems (Table 3).

Serum tenascin-C levels had a sensitivity of 76.5% and specificity of 77.8% for prediction of severe pancreatitis according to the Atlanta scoring system. PCT had sensitivity of 68.8% and specificity of 41.7%, WBC had sensitivity of 70.6% and specificity of 37%, CRP had sensitivity of 47.1% and specificity of 77.8% and ESR had sensitivity of 85.7% and specificity of 61.5% (Table 4) (Figure 1A).

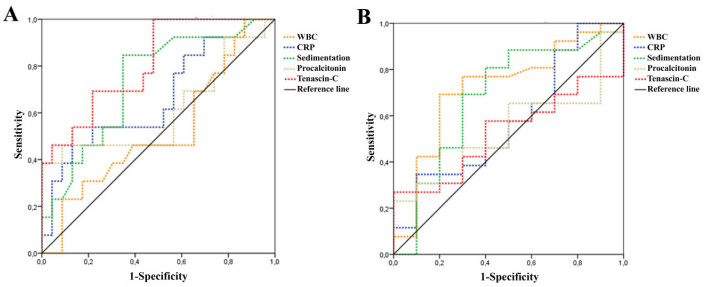

Figure 1. ROC curve analysis demonstrating the role of Tenascin-c and Procalcitonin with other markers of inflammation in predicting (A) severity of acute pancreatitis according to Atlanta scoring system (B) length of hospital stay.

Serum tenascin-C had sensitivity of 53.3% and specificity of 42.9% to predict patients with 4 days hospital admission (lengthened admission duration). PCT had sensitivity of 66.7% and specificity of 38.5%, WBC had sensitivity of 80% and specificity of 64.3%, CRP had sensitivity of 53.3% and specificity of 50% and ESR had sensitivity of 69% and specificity of 63.6% (Table 5) (Figure 1B).

The distribution intervals of serum tenascin-C levels at time of first diagnosis and discharge for patients and in the control group are shown on box-plot graphs (Figures 2).

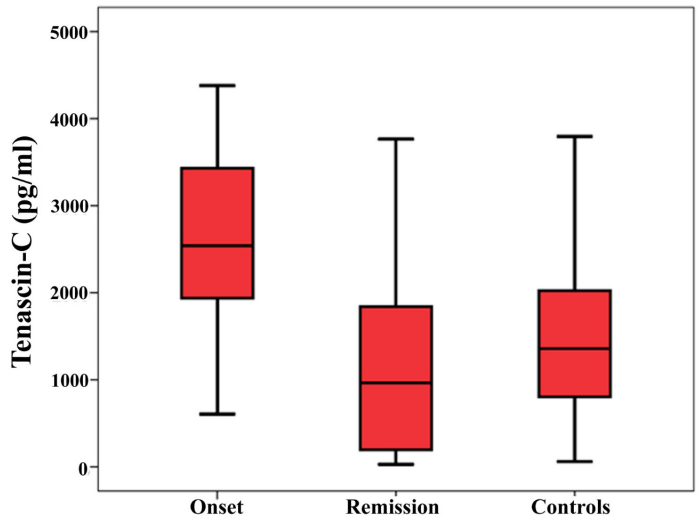

Figure 2. Serum Tenascin-C levels of acute pancreatitis patients on admission and remission in comparison to healthy controls.

Table 2. Comparison of Laboratory data and differences for groups included in the study

	Onset	Remission	Controls	
WBC (/mm³×10³)	13.01±6.08	7.09±2.19	7.36±2.75	1-3
Hb (g/dl)	12.98±2.20	11.51±1.81	12.62±1.92	2-3
Hct (%)	39.39±6.51	34.99±5.26	37.38±5.20	2-3
Plt (/mm³×10³)	259±81	270±113	242±112	-
Glucose (mg/dl)	153.45±51.83	117.17±37.05	113.62±25.87	1-3
AST (U/L)	146.22±159.43	25.03±13.54	24.70±13.23	1-3
Creatinine (mg/dl)	1.04±0.59	1.29±2.16	0.84±0.21	1-3
BUN (mg/dl)	18.27±9.45	12.76±9.21	15.12±4.99	2-3
Albumin (g/dl)	3.97±0.59	3.47±0.40	4.22±0.40	1-2-3
LDH (U/L)	416.31±362.97	189.84±42.99	181.37±37.14	1-3
Amylase (U/L)	1456±1023	65.56±27.38	61.50±22.74	1-3
Lipase (U/L)	3369±3233	43.04±18.53	39.77±19.88	1-3
Calcium (mg/dl)	9.02±0.67	8.73±0.69	9.22±0.59	1-2-3
Tenascin-C (pg/ml)	2997±1869	1183±1044	1619±1260	1-3
PCT (pg/ml)	867±755	236±127	264±203	1-3
CRP (mg/dl)	11.81±12.81	1.15±0.99	0.77±1.00	1-2-3
ESR (mm/s)	35.98±24.96	20.51±12.51	19.85±12.38	1-3

P<0.005 for 1- Onset-Controls; 2- Remission-Controls; 3- Onset-Remission

Table 3. Correlation of tenascin-C and procalcitonin values with different scoring systems and inflammatory markers

	Tenascin-C		Procalcitonin	
	r	p	r	p
Atlanta	0.538	0.000	0.301	0.059
Ranson	0.310	0.041	0.256	0.111
Imrie	0.312	0.039	0.207	0.200
Balthazar	-0.109	0.483	0.083	0.609
WBC(/mm³×10³)	-0.045	0.773	0.153	0.345
CRP(mg/dl)	0.366	0.015	0.034	0.835
ESR(mm/s)	0.002	0.991	0.106	0.537

Table 4. Role of tenascin-C and other inflammatory markers in predicting severity of pancreatitis according to Atlanta scoring system

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV
Tenascin-C (pg/ml)	2700	0.809*	76.5	77.8	68.4	84.0
PCT (pg/ml)	470	0.609	68.8	41.7	44.0	66.7
WBC(/mm³×10³)	9800	0.520	70.6	37.0	41.4	66.7
CRP(mg/dl)	11.5	0.662	47.1	77.8	57.1	70.0
ESR(mm/s)	29.5	0.731*	85.7	61.5	54.5	88.9

***:p<0.05**

Table 5. Role of tenascin-C and other inflammatory markers in predicting prolonged length of hospital stay

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV
Tenascin-C (pg/ml)	2300	0.527	53.3	42.9	66.7	30.0
Procalcitonin (pg/ml)	400	0.535	66.7	38.5	69.2	35.7
WBC (/ mm³×10³)	10000	0.721	80.0	64.3	82.8	60.0
CRP (mg/dl)	6.35	0.577	53.3	50.0	69.6	33.3
ESR (mm/h)	25	0.681	69.0	63.6	83.3	43.8

Discussion

In this study, it was revealed that high serum tenascin-C at time of first admission for AP had lowered by time of discharge and returned to normal. Additionally, serum tenascin-C levels were found to be positively correlated with Atlanta, Imrie and Ranson scoring systems and with CRP. Serum tenascin-C was observed to have high sensitivity and specificity to predict severe pancreatitis according to the Atlanta scoring system. In spite of this, it had lower sensitivity and specificity to predict lengthened admission duration compared to PCT, WBC, CRP and ESR.

Acute pancreatitis is an acute inflammatory disease of the pancreas causing systemic inflammatory response syndrome with significant morbidity and mortality rates [5]. Most patients experience the disease with mild progression, with mortality rates up to 20% and severe AP development reaching rates of 10-30% [6-7]. There are many systemic changes observed related to pancreatitis pathophysiology. The earliest of these changes is blockage of release of pancreatic enzymes, in spite of continuing synthesis. Intra-acinar activation of these enzymes with continuing synthesis is accepted as one of the basic mechanisms in the onset of pancreatitis [8]. Experimental models of AP showed microcirculatory changes like vasoconstriction, capillary stasis, reduced oxygen saturation and progressive ischemia occur in the early period. These changes cause increased vascular permeability and swelling of the gland (edema or interstitial pancreatitis). Activation of granulocytes and macrophages cause the release of proinflammatory cytokines (tumor necrosis factor, IL-1, IL-6, IL-8), arachidonic acid metabolites (prostaglandins, platelet activating factor and leukotrienes), proteolytic and lipolytic enzymes, and reactive oxygen metabolites [9]. The tenascin-C molecule acts in inflammation regions in correlation with increased TNFα, IL-6, and serum inflammatory markers in many studies, similar to the mechanism of pancreatitis pathophysiology [10].

Serum tenascin-C levels were significantly different in the patient group between first admission and discharge. The inflammatory process is triggered in the organ and surroundings from the time the pathology begins in AP patients. Linked to this, there are many studies showing serum levels of acute phase reactants like PCT, CRP, leukocyte count and ESR are increased in AP [11-14]. It is considered that the tenascin-C molecule level in serum begins to increase in response to the initiation of inflammation in pancreatic and/or peripancreatic tissues. At discharge, serum levels of tenascin-C molecule had returned to normal, as with other acute phase reactants, as an indicator of significant clinical amelioration in AP patients.

Tenascin-C (AUC=0.527) had 53.3% sensitivity, 42.9% specificity, 66.7% PPV and 30.0% NPV to predict lengthened duration of admission. No marker in our study (PCT, WBC, CRP, ESR) including tenascin-C was identified to have statistically significant difference to predict lengthened hospital stay. It may be considered that the reason for this is the inadequate level of complicated pancreatitis cases among patients included in our study. Considering the effect of tenascin-C at molecular level, inclusion of higher numbers of patients with complicated pancreatitis (like aseptic necrosis, infected necrosis) may cause a change in the sensitivity and specificity values obtained in our study.

A study by Kumar et al. identified that PCT levels were more valuable compared to CRP, Ranson criteria and CTSI scoring systems to predict severe pancreatitis [15]. Bülbüller et al. compared the Ranson criteria and APACHE II scoring system with PCT levels to predict severe pancreatitis in their study. PCT values had 100% sensitivity and 84% specificity for prediction of severe pancreatitis [16]. In our study, PCT levels (AUC=0.609) had 68.8% sensitivity, 41.7% specificity, 44.0% PPV and 66.7% NPV for prediction of severe AP according to the Atlanta scoring system. To predict lengthened duration of hospital admission, PCT values (AUC=0.535) were identified as 66.7% sensitivity, 38.5% specificity, 69.2% PPV and 35.7% NPV.

In our study, the serum PCT values at time of diagnosis had regressed at time of discharge. Additionally, the PCT values were not identified to be correlated with Atlanta, Ranson, and Imrie scoring systems and other inflammation markers (WBC, CRP, ESR). PCT levels are reported to be unaltered in limited local infections like tonsillitis, sinusitis, cystitis, uncomplicated skin/soft tissue infections, abscesses or empyema [17-18]. In our study, the lack of correlation of PCT values with scoring systems and other inflammatory markers and low observation of sensitivity and specificity compared to other studies is thought to be due to most of these markers increasing in bacterial infections and the low rate of complications that may be associated with bacterial infection (like abscess, necrosis) in our patients. Additionally, the fact that PCT values were only monitored in patients at two times, diagnosis and discharge, may have caused this result. Measurements at more frequent intervals may cause changes to these results.

In spite of the lack of a single ideal serum marker to predict severity, CRP is a beneficial marker for necrosis with 80% sensitivity and specificity. However, as highest CRP values are only reached after 48 hours, it is necessary to measure them 48 hours after onset of clinical symptoms. The peak levels for CRP occur 24 to 48 hours after the onset of pancreatitis [19-22]. As a result, when CRP levels are measured in the early stage in AP patients, they do not reflect the disease severity. The sensitivity and positive predictive values for serum CRP levels in severe pancreatitis patients were reported as 83-100% and 37-77% [23]. In our study, CRP had sensitivity of 47.1%, specificity of 77.8%, PPV 57.2% and NPV 70.0% to predict severe pancreatitis. Low sensitivity of CRP values may be associated with our patient group including a population with comorbid diseases. As shown in many studies, CRP is a molecule which does not just increase in the inflammatory process, but increases in many clinical situations like chronic inflammatory processes, tissue necrosis, post-operative situations and obesity [24-26].

Limitations of our study include the low number of patients with AP diagnosis as our center is a tertiary health facility. Additionally, the low number of patients may be caused by being a single-center, prospective study. Homogeneous case distribution may not be observed due to being an advanced stage health facility.

Conclusion

In conclusion, This study showed that tenascin-C levels and procalcitonin levels are increased at the start of disease and fell in the remission period in AP patients. Additionally, the importance of tenascin-C to determine disease severity along with other inflammatory markers and scoring systems for AP was reported. We think that tenascin-C can be considered an important marker of AP and potential indicator for disease activity. If our data can be confirmed in advanced studies, we believe standardized values for the tenascin-C molecule may ease diagnosis of AP and be an important parameter for patient follow-up.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
The approval was obtained from comu clinical researches ethics committee with the decision dated 27.03.2019 and numbered 07-07.

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