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Endothelial markers are associated with pancreatic necrosis and overall prognosis in acute pancreatitis: A preliminary cohort study

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ABSTRACT

Background: Endothelial injury is believed to play an important role in the evolution of pancreatic microcirculatory dysfunction and pancreatic necrosis (PN) in patients with acute pancreatitis (AP). The aim of this study was to investigate the role of three endothelial markers (von Willebrand factor, vWF; E-selectin; endothelial protein C receptor, EPCR) in the early phase of AP, especially the relationship between endothelial markers and PN.
Methods: From March 2015 to March 2016, 57 AP patients admitted within 72 h of symptom onset in our hospital were included for this study. Blood samples were taken on admission and the clinical characteristics and outcomes of these patients were recorded. The levels of vWF, E-selectin and EPCR were measured using ELISA for analysis and compared with other severity markers of AP.
Results: All the three markers were significantly different in healthy control, mild, moderate and severe AP patients. Moreover, the endothelial markers, especially vWF, also showed significant difference in patients with different extent of PN, as well as those with or without MODS. Additionally, the levels of endothelial markers correlated well with other commonly used markers of AP severity.
Conclusion: Elevated endothelium-related mediators (vWF, E-selectin and EPCR) appear to participate in the development of PN and may be a potential indicator of overall prognosis. Our results may help clinicians better understand the pathophysiological process of the development of PN.

1. Introduction

Acute pancreatitis (AP) is an inflammatory condition usually takes a mild, self-limiting disease course. However, severe acute pancreatitis (SAP) complicated by persistent organ failure develop in around 20% patients, resulting in a mortality as high as 30% [1–3]. As an important complication of AP, PN develops in around 15% of AP patients, and the occurrence of PN generally confers a high risk of mortality, especially if the necrotic segment becomes infected [4–8]. At present, numerous biomarkers have been assessed for early detecting the occurrence of PN, including creatinine, urea nitrogen, hematocrit, etc. [8–10] Nevertheless, the majority of these markers only reflect the general severity of the disease, rather than being directly involved in the pathophysiological process of the development of PN.

Recent studies have demonstrated that microcirculatory disturbance of pancreas occurs in the acute phase of AP is closely related to the development of PN [11–14]. As a pivotal mechanism in the pathogenesis of AP, microcirculatory disorder and dysfunction can severely influence the pancreatic perfusion and lead to ischemia and hypoxia of pancreas, which directly result in infarction of pancreatic tissue, namely, PN. Vascular endothelial injury and coagulative derangements have been recognized as two core pathological processes in the microcirculatory changes of AP patients [14–17].

Coagulation changes during the AP course and markers such as D-dimer and antithrombin-III (AT-III) have been well studied in

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previous literature [18–20]. Various endothelial markers were also evaluated in AP patients repeatedly [21–25]. However, limited attention has been paid to the relationship between PN and endothelial markers. The study conducted by Lu et al. suggested thrombomodulin (TM), a vascular endothelial marker which promotes activation of the anticoagulant protein C and inhibits the procoagulant properties of thrombin, may be a potential marker of PN in AP patients [26]. However, Lu and his colleagues did not include other important endothelial parameters and they did not compared TM with other commonly used severity markers of AP.

Therefore, in the present study, we aimed to investigate the role of endothelial markers in the early phase of AP, especially the relationship between endothelial markers and PN. The levels of von Willebrand factor (vWF, a protein mediates platelet activation in the subendothelium of damaged blood vessels), E-selectin (a glycoprotein mediates the early endothelial-neutrophil adhesion in inflammation) and endothelial protein C receptor (EPCR, a membrane protein functions as a primary receptor for protein C activation on endothelium) of AP patients were measured for analyses.

2. Materials and methods

This study was conducted at the Department of General Surgery in Jinling Hospital, a tertiary referral center in China between March 2015 and March 2016. The study was reviewed and approved by the Institutional Medical Ethics Committee. All study participants gave their verbal informed consent.

2.1. Patients

In the present study, all consecutive adult AP patients (age≥18 years) who were admitted to our center (SICU or general wards) within 72 h from symptom onset between March 2015 and March 2016 were screened. General diagnostic criteria for AP were defined according to the revised Atlanta criteria: 1) abdominal pain consistent with AP; 2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; 3) characteristic findings of AP from abdominal imaging. The diagnosis of AP requires two of the above-mentioned three features. Exclusion criteria included prior attacks of acute pancreatitis, a known history of coagulative disorders, receiving surgical intervention before admission, pregnancy, and combining with other serious abdominal diseases. All patients received standard medical therapy and were followed until discharge from the hospital or hospital death [27,28].

2.2. Data collection

Baseline data including age, sex, body mass index (BMI), etiology, the acute physiology and chronic health (APACHE) II score, the sequential organ failure assessment (SOFA) score, and the bedside index of severity in acute pancreatitis (BISAP) score were recorded on admission. The diagnosis of hyperlipidemic acute pancreatitis was made when 1) serum TG levels is higher than 1000 mg/dL within 24 h of disease onset or 2) if the estimation of TG has been delayed (>24 h), the TG level needed to be higher than 500 mg/dL and other etiology of AP should be excluded.[29,30] The diagnostic criteria of acute biliary pancreatitis was as follows: 1) gallstones or biliary sludge could be detected by transabdominal ultrasound, CT or other examinations or 2) if not, the serum level of ALT needed to be more than 60 U/L and other etiology of AP should be excluded.[31] Alcoholic pancreatitis was diagnosed unless a person has a history of over 5 years of heavy alcohol consumption (>50 g per day).[28] Patients without hyperlipidemia, gallstones, and alcohol history were screened to exclude other rare causes: 1) hypercalcemia and hyperparathyroidism; 2) pancreatobiliary tumors; 3) autoimmune pancreatitis(mainly IgG4); 4) anatomic and physiologic anomalies like pancreas divisum. If still no definite cause could be confirmed, patients were diagnosed as idiopathic pancreatitis. Organ failure was defined as a score of 2 or more using the modified Marshall scoring system.[32] Multiple-organ dysfunction syndrome (MODS) was defined as combined dysfunction of 2 major organ systems. The classification of AP and diagnoses of local complications were made based on the revised Atlanta classification of acute pancreatitis [1].

2.3. Measurements

In all study patients, blood samples were taken at the time of admission, kept at 4 °C, centrifuged (3000 rpm for 15 min) within 30 min of collection, aliquoted, and stored at −80 °C until analysis. The following endothelial markers were measured: serum vWF concentration (ELISA; Abcam, ab108918), serum E-selectin concentration (ELISA; Cloud-Clone, SEA029Hu) and serum EPCR concentration (ELISA; Cloud-Clone, SEA022Hu). The measurement of vWF, E-selectin and EPCR was performed by the same well-trained investigator following the manufacturer's instructions. The concentrations of D-dimer, AT-III, CRP and PCT were determined using the same blood sample in the central lab of Jinling Hospital.

2.4. Statistical analysis

All analyses were performed using SPSS 22.0 for windows (IBM Analytics, Armonk, NY). Data are expressed as median (interquartile range) for continuous variables and frequencies (proportions) for categorical variables. Mann-Whitney *U* test, Kruskal-Wallis test and chi-squared test were used as the circumstances required. In addition, Spearman correlation analysis was made to assess the relationships between 2 variables. All statistical tests were two-tailed, and the statistical significance was considered as $P < 0.05$.

3. Results

3.1. Patient characteristics

The flow chart of patient selection was displayed in Fig. 1. Among all 407 AP patients, 57 eligible patients were enrolled in the final analysis. Table 1 shows the detailed demographic data and

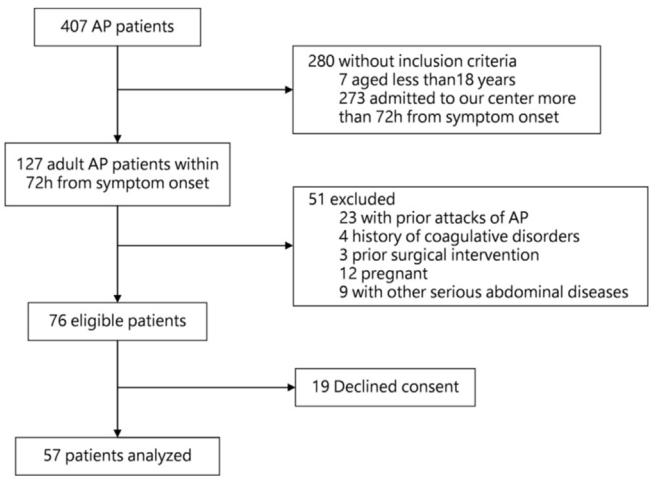

Fig. 1. Study flowchart.

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