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CASE CONTROL STUDY

Resistin is not an appropriate biochemical marker to predict severity of acute pancreatitis: A case-controlled study

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Abstract

AIM: To assess levels of serum resistin upon hospital admission as a predictor of acute pancreatitis (AP) severity.

METHODS: AP is both a common and serious disease, with severe cases resulting in a high mortality rate. Several predictive inflammatory markers have been used clinically to assess severity. This prospective study collected data from 102 patients who were diagnosed with an initial acute biliary pancreatitis between March 2010 and February 2013. Measurements of body mass index (BMI) and waist circumference (WC) were obtained and serum resistin levels were analyzed at the time of hospital admission using enzyme-linked immunosorbent assay. Additionally, resistin levels were measured from a control group after matching gender, BMI and age.

RESULTS: A total of 102 patients (60 females and 42 males) were diagnosed with acute gallstone-induced pancreatitis. The mean age was 45 years, and mean BMI value was 30.5 kg/m^2 (Obese, class Ⅰ). Twenty-two patients (21.6%) had severe AP, while eighty-eight patients had mild pancreatitis (78.4%). Our results showed that BMI significantly correlated with pancreatitis severity (P = 0.007). Serum resistin did not correlate with BMI, weight or WC. Furthermore, serum resistin was significantly higher in patients with AP compared to control subjects (P < 0.0001). The mean resistin values upon admission were 17.5 ng/mL in the severe acute biliary pancreatitis group and 16.82 ng/mL in the mild AP group (P = 0.188), indicating that resistin is not an appropriate predictive marker of clinical severity.

CONCLUSION: We demonstrate that obesity is a risk factor for developing severe AP. Further, although there is a correlation between serum resistin levels and AP at the time of hospital admission, resistin does not adequately serve as a predictive marker of clinical severity.

Key words: Acute pancreatitis; Resistin; Body mass index; Waist circumference

Core tip: Several predictive inflammatory markers have been used to predict pancreatitis severity. Peri-pancreatic adipose tissue synthesizes and secretes adipose-specific proteins, termed adipocytokines. One of these proteins, resistin, has immunomodulatory and metabolic activity. This novel adipose-driven protein, produced by pancreatic islets, may represent a useful additional marker for predicting acute pancreatitis (AP) severity. We found that serum resistin levels were significantly higher in patients with acute biliary pancreatitis compared to control subjects; however, resistin failed to

serve as a predictive marker of clinical severity. Our study did find, however, that obesity correlated with severity of acute biliary pancreatitis. Based on the increased levels in AP patients upon hospital admission, we suggest that resistin could be used as a new diagnostic marker.

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INTRODUCTION

Acute pancreatitis (AP) is a potentially life-threatening acute inflammatory condition of the pancreas. Gallstones are the most common cause of AP, representing close to 60% of all cases[1]. Notably, the incidence of AP is increasing in North America and Europe[2,3] paralleled with an increase in the prevalence of obesity[4]. Obesity is a chronic low-grade inflammatory state characterized by high circulating levels of pro-inflammatory cytokines[5]. A large amount of visceral fat surrounding the pancreas may easily promote the inflammation in AP[6], and a strong correlation has been determined between peri-pancreatic visceral adipose tissue volume and AP severity[6]. In fact, a new severity scoring system including obesity as an independent predictor for AP outcome has been proposed[7]. Obesity is also associated with higher levels of inflammatory markers[8], potentially of predictive value. Experimental biochemical markers have been studied to assess disease severity, including trypsinogen activation peptide, interleukin-6, interleukin-10, procalcitonin, phospholipase A2 and C-reactive protein[9]. In AP, pancreatic injury leads to a massive release of pancreatic lipase that causes digestion of peri-pancreatic adipose tissue[10] which becomes infiltrated by significant quantities of monocytes. This process leads to the synthesis and secretion of adipose-specific proteins, termed adipocytokines[11], which serve as new predictive markers[10] with potent immunomodulatory[11,12] and metabolic activities. The metabolic and pro-inflammatory changes seen in AP might be partially caused by these proteins[10]. One of these novel adipocytokines, resistin, is produced by white and brown adipose tissues[13,14]. Recently, resistin has been described as serving as a marker of monocyte activation and it can be used to detect early inflammation of peri-pancreatic adipose tissue. Our study investigates the ability of serum resistin levels upon hospitalization to predict clinical severity of AP.

MATERIALS AND METHODS

A group of 102 patients with an initial attack of acute biliary pancreatitis were included in this prospective study between March 2010 and February 2013. They were admitted to the surgical ward at King Fahd Hospital, Saudi Arabia. Study protocols were approved by an institutional review board. All patients provided written informed consent, and underwent a routine medical history and clinical examination. The diagnosis of AP was based on acute upper abdominal pain with an elevated serum amylase of at least three times the upper normal limit, which peaks approximately 24 h after the onset of attack[15] and/or serum lipase. Gallstone pancreatitis was diagnosed based on radiologic findings of a gallstone or bile duct dilatation by abdominal ultrasonography and liver biochemical tests including serum alanine transaminase ($\geq$ 65 U /L), serum bilirubin level (> 18.1 Umol/L), and alkaline phosphatase (> 137 U/L). A combination of ultrasonography and blood tests provide a sensitivity of 95%-98%[16]. None of the patients had ever consumed alcohol and none had a history of drug consumption known to cause pancreatitis. Serum calcium and lipid profiles were tested to exclude hypercalcemia or hyperlipidemia-induced pancreatitis. Patients without obvious cause of AP underwent endoscopic retrograde cholangiopancreatography (ERCP). Computed tomography contrast-enhanced abdominal scans were used to predict pancreatic parenchymal injury 48 h after hospital admission. We graded the severity of pancreatitis radiologically into five distinct groups from A to E according to the Balthazar-Ranson scoring system[17], while clinical severity evaluation was carried out using the Ranson and APACHE Ⅱ scores within 48 h after admission. An Atlanta criterion was adopted to define mild AP as absence of the criteria of severe AP[18]. Severe AP was defined as the presence of at least one of the following criteria: pancreatic necrosis > 30%, pancreatic abscess, pseudocyst, systolic blood pressure < 90 mmHg, $pO_2 \leq$ 60 mmHg, creatinine > 2 mg/dL after rehydration, gastrointestinal bleeding > 500 mL in 24 h, or death[19]. Furthermore, late complications like pancreatic pseudocyst and abscesses were followed up in the outpatient clinic after 4-8 wk by computed tomography abdominal scan based on clinical presentation.

Exclusion criteria

Patients were excluded from the study based on the following: (1) diabetes mellitus; (2) presence of morbidities possibly affecting patient weight, such as hypothyroidism or pregnancy; (3) alcohol consumption; (4) history of episodes of idiopathic and chronic recurrent pancreatitis; (5) drug-induced and pancreatic divisum; (6) ERCP pancreatitis; (7) hyperlipidemia or hypercalcemia induced pancreatitis; and (8) patients with symptoms for more than 48 h. Obesity was classified by body mass index (BMI), which was measured by weight in kilograms divided by height in meters squared (kg/m^2) as recommended by the World Health Organization[20]. Waist circumference (WC) was measured in the standing position at the height of the umbilicus, while the subject breathed out gently using a circumference measuring tape (Seca

Table 1 Patient characteristics (n = 102)

Patient characteristics	Result
Age (yr, mean ± SD)	45 ± 17.5
Gender (male/female)	41.2%/58.8%
Body mass index (kg/m², mean ± SD)	30.5 ± 6.89
Underweight	2.0%
Normal	26.4%
Overweight	21.6%
Obese	43.1%
Morbid obesity	6.9%
Central obesity	
Waist circumference (cm, mean ± SD)	94.9 ± 16.74
Death (mortality)	3.9%
Severity of pancreatitis	
Mild	78.4%
Severe	21.6%
Complications	
Local	21.6%
Acute fluid collection	45.4%
Pancreatic necrosis	45.4%
Pancreatic pseudocyst	9.2%
Pancreatic abscess	0%
Thrombosis	0%
Systemic	18.6%
Shock	15.8%
Pulmonary insufficiency	42.2%
Renal failure	10.5%
GIT bleeding	10.5%
DIC	10.5%
Severe metabolic disturbance	10.5%

GIT: Gastrointestinal; DIC: Disseminated intravascular coagulation.

200, Hamburg, Germany). Venous blood samples from the antecubital vein of patients were collected. Samples were collected into vacuum tubes containing EDTA. After sampling, the tubes were immediately centrifuged at 1.5 *g* for 10 min. Aliquots of serum were stored at -20 ℃ and routine hematology and biochemistry tests were performed. All biochemical measurements were carried out by the same team of laboratory technicians using the same methods throughout the study period. Samples were collected from AP patients at time of hospital admission. We enrolled a control group of 102 persons with matched BMI, gender and age, because serum resistin concentration increases in obesity, and is positively correlated with BMI, insulin resistance or body fat[21-23]. Resistin plasma samples for both test patients and control groups were stored at -80 ℃ and diluted 100-fold and stored until biochemical analysis was completed. One technician performed the analysis in a blinded fashion. Resistin concentrations for both groups were measured by using ELISA.

ELISA assay conditions: Serum was quantitatively assayed for resistin using a sandwich enzyme immunoassay. Standards and samples were sandwiched by immobilized antibody and biotinylated polyclonal antibodies specific for resistin. Samples were analyzed using the Bio-plex suspension array system, which included a fluorescent reader and Bio-plex Manager analytic software at the Taibah University Biochemical Department. Mean values of duplicate readings were calculated for each standard and sample in a blinded fashion. The cut-off value of resistin was 15 ng/mL.

Statistical analysis

Data was analyzed using SPSS software (version 15; SPSS Inc., Chicago, IL). Means and standard deviations were used to describe demographic variables. Serum resistin levels and additional continuous variables were analyzed using correlation tests. Receiver operating characteristics curves were used to evaluate the ability of serum resistin level to predict the severity of AP and the relationship with BMI. The χ^2 test was used to calculate the association between classified variables and to estimate the relationship between levels of resistin, and different variables. A P-value less than 0.05 (two-tailed) was considered to be statistically significant. Differences between study groups were tested by paired t-test. Kruskal-Wallis and Mann-Whitney U tests were also used to confirm results.

RESULTS

Our study consisted of 102 patients (60 females and 42 males) diagnosed with an initial first attack of acute gallstone-induced pancreatitis. The mean age was 45 years, and mean BMI value was 30.5 kg/m^2 (Obese, class I). Patient characteristics are summarized in Table 1. None of the patients had ever consumed alcohol or had a history of drug consumption. Twenty-three patients who were initially recruited to the study were excluded due to a history of recurrent pancreatitis. Of these, 13 had metabolic (hyperlipidemia, hypercalcemia) recurrent pancreatitis, whereas 10 patients did not have an underlying cause of the recurrent pancreatitis so underwent ERCP. Three patients had two separately draining pancreatic ducts (pancreatic divism) and 2 patients had chronic pancreatitis due to presence of pancreatic duct stones.

We investigated the relationship between severity of pancreatitis and risk factors such as age, gender, BMI, WC, and body weight. Our results showed that only BMI significantly correlated with severity of acute biliary pancreatitis (P = 0.007; Table 2). Data on serum resistin levels were available for this cohort upon hospital admission. Serum resistin concentration did not correlate with BMI, weight or WC in our patients (not shown). The mean resistin values at admission were 17.5 ng/mL in the severe acute biliary pancreatitis group and 16.82 ng/mL in the mild AP group (P = 0.188; not shown). Serum resistin concentration was significantly higher in patients with AP compared with control subjects (Figures 1 and 2). Resistin concentrations upon admission correlated with AP. Receiver-operator curve and area under the curve (AUC) delineate sensitivity and specificity of serum resistin concentration as an inflammatory marker on the day of admission in AP, AUC > 97% and cutoff value: 15 ng/mL (Figures 3A and B), but resistin failed to serve as a predictive marker of clinical severity in AP (P = 0.188; Figure 2). Moreover,

Table 2 Relationship between severity of pancreatitis and body mass index *n* (%)

Patient characteristics	Patients (*n* = 102)	Mild pancreatitis (*n* = 80)	Severe pancreatitis (*n* = 22)	χ^2
Body mass index (kg/m²)				0.007
Underweight	2 (2.0)	2 (2.5)	0 (0)	
Normal	27 (26.4)	23 (28.7)	4 (18.1)	
Overweight	22 (21.6)	13 (16.2)	9 (40.9)	
Obese	44 (43.1)	39 (48.7)	5 (22.7)	
Morbid obesity	7 (6.9)	3 (3.7)	4 (18.1)	

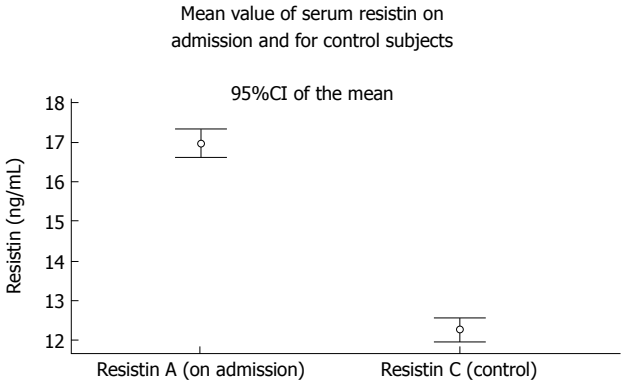

Figure 1 Significant difference between resistin level in acute biliary pancreatitis patients and control subjects (*P* = 0.000).

we studied the correlation between serum resistin levels and both serum calcium level and extent of pancreatic fatty necrosis by CT scan, but there was no significant correlation (P = 0.271 and 0.431, respectively). Further, we analyzed the relationship between serum resistin levels and BMI in both groups (AP patient and controls); however, there was no significant difference when using non-parametric correlation and Spearman's test (P = 0.271 and 0.437, respectively).

DISCUSSION

AP is a highly variable disease in terms of severity. Many scoring systems and experimental inflammatory markers have been developed for early detection of severe AP. Obesity is a chronic low-grade inflammatory state characterized by high levels of circulating proinflammatory cytokines[5]. Therefore, a large amount of visceral fat surrounding the pancreas may easily exacerbate the inflammation in AP[6]. Obesity may also be linked to the severity of AP. It is generally accepted that obesity is associated with an increased risk of AP development; therefore larger abdominal adiposity and higher WC often accompany severe pancreatitis[24]. Pancreatic microcirculation is lower in obese patients compared to those who are non-obese, which increases the risk of ischemic injury and subsequent local infections[25]. Furthermore, obesity is also associated with higher levels of inflammatory markers[8]. In AP, pancreatic injury leads to a massive release of pancreatic lipase that leads to digestion of peri-pancreatic adipose tissue[10] which becomes infiltrated by significant quantities of monocytes. This creates adipocytokines[11], one of which is resistin[12] which has potent immunomodulatory[11,13] and metabolic activities. Resistin has been identified in pancreatic islets[26], the gastrointestinal tract, monocytes, spleen, white blood cells and plasma. Recently, resistin was shown to serve as a marker of monocyte activation[27]. Thus, resistin can be used for detection of early inflammation of peri-pancreatic adipose tissue infiltrated by monocytes. Importantly, human resistin mRNA expression is higher in abdominal adipose tissue than in subcutaneous adipose tissue[28], therefore we chose to investigate the serum level of resistin in AP patients to assess its potential value for detecting pancreatitis severity specifically induced by adipose tissue inflammation. Until now, resistin has not been reported in purely acute biliary pancreatitis patients of a substantial sample size.

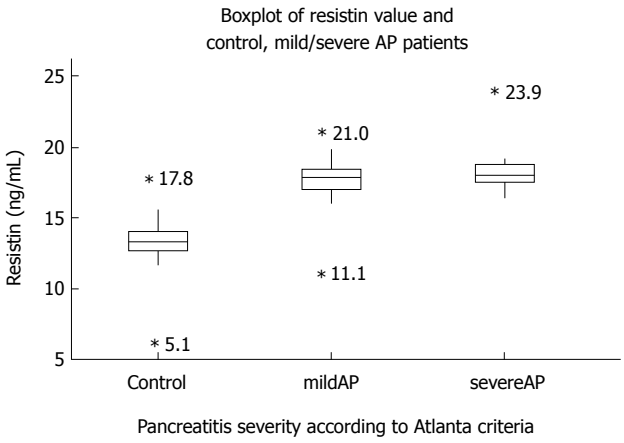

Figure 2 Box plot graph delineates the difference variation between acute pancreatitis patients (mild/severe) and control group.

A majority of patients in our study had acute gallstone-induced pancreatitis. Our results showed that: (1) obesity significantly correlated with severity of acute biliary pancreatitis; (2) serum resistin concentration was significantly higher in patients with AP compared with control subjects; (3) resistin failed to serve as a predictive marker of AP severity; (4) no correlation exists between serum resistin levels and either serum calcium or extent of pancreatic fatty necrosis by CT scan; and (5) no relationship exists between serum resistin levels and BMI for either group.

A previously reported meta-analysis of 739 cases showed that obesity (BMI $\geqslant$ 30 kg/m^2) was a significant risk factor for AP severity[29], similar to our results that BMI > 30 kg/m^2 is associated with severe pancreatitis (P = 0.007; Table 2). Additionally, serum levels of resistin have been reported in 50 patients with AP, showing that 40% had biliary pancreatitis. In this example, the level of resistin correlated with Ranson and APACHE Ⅱ scores[27], suggesting that resistin concentration upon hospital admission may serve as an early predictive marker

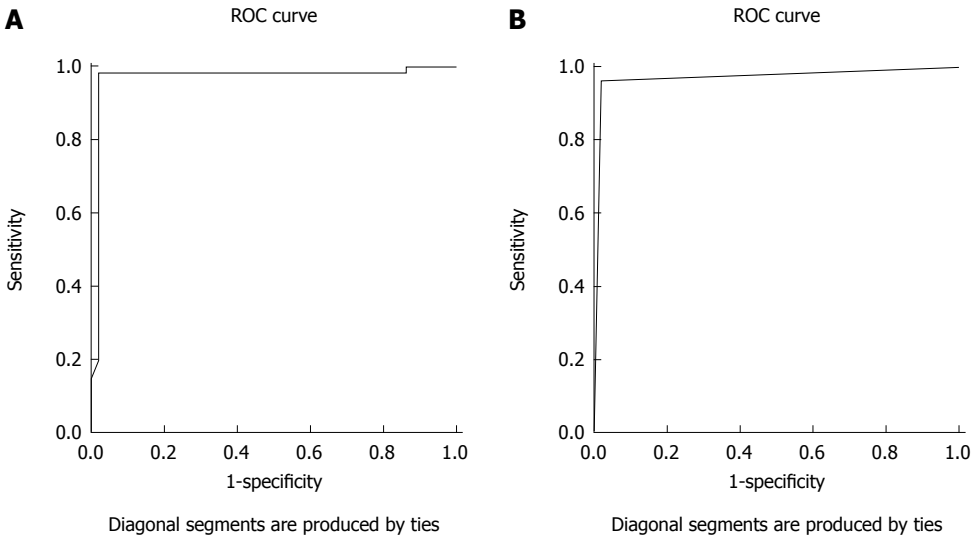

Figure 3 Receiver-operator curve and area under the curve. A: Receiver-operator curve (ROC) and area under the curve (AUC) delineate sensitivity and specificity of serum resistin concentration (day of admission), AUC > 97%, *P*-value < 0.0001; B: ROC and AUC of serum resistin value on admission. Cutoff value: 15 ng/mL and positive predictive value: 97%.

of peri-pancreatic necrosis and clinical severity for AP[27]. However, these studies used a small sample size and 40% of the patients had biliary pancreatitis with resistin levels measured over the first 10 d after admission (mean value), which is not reflective of the single initial value alone. Our study, however, had twice the sample size and most of the pancreatitis cases were biliary in origin, which has not previously been extensively studied. Additionally, we measured the serum resistin levels in our patients within a few hours after a confirmed diagnosis of acute biliary pancreatitis upon hospital admission.

Leśniowski *et al*[30] measured serum resistin in 30 AP patients and concluded that the serum concentration of resistin may represent a useful additional marker of inflammatory response in AP; however, the study did not report data for its ability to predict clinical severity. Adrych *et al*[31] demonstrated that serum resistin concentration is elevated in a small cohort of patients with chronic pancreatitis of alcoholic origin (n = 50)[31]. Many inflammatory markers, such as trypsinogen activation peptide, interleukin-6, interleukin-10, procalcitonin, phospholipase A2 and C-reactive protein, have been used to assess the severity of pancreatitis[32-34]. In our study, we used a biochemical marker that specifically reflects the inflammation of peri-pancreatic adipose tissue. In addition, our study was designed with strict exclusion criteria to eliminate any confounding variables that affected patients' weight or BMI. We noticed that a large fraction of our patients had acute biliary pancreatitis and did not consume alcohol, leaving the possibility that alcoholic AP might behave quite differently. However, it would be quite difficult to select an obese population without hyperlipidemia, hypertension or other morbidities strongly associated with obesity. It is likely that a portion of the population is undiagnosed for multiple risk factors. Exploration of an inflammatory marker, such as resistin, reflects the severity burden of AP and is superior over other scoring approaches. Before resistin can be used widely in the clinical setting, our results must be confirmed by larger and multi-center studies. The use of new pancreatic injury markers of inflammatory response appears very promising, although most have been studied mainly in a research setting so their clinical impact remains to be determined.

Obesity is a clear risk factor for severe AP. We demonstrate that there is a correlation between serum resistin and AP upon hospital admission, but this marker failed to serve in a predictive manner with regard to clinical severity.

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COMMENTS

Background

Acute pancreatitis (AP) is a potentially life-threatening acute inflammatory condition of the pancreas. Notably, the incidence of AP is increasing with a correlated increase in obesity.

Research frontiers

In AP, pancreatic injury leads to synthesis and secretion of adipose-specific proteins, termed adipocytokines. One of these adipocytokines, resistin, can be used to detect early inflammation of peri-pancreatic adipose tissue. This study investigates the ability of serum resistin levels upon hospitalization to predict clinical severity of AP.

Innovations and breakthroughs

The authors demonstrate that there is a correlation between serum resistin and AP upon hospital admission, but this marker failed to serve in a predictive manner with regard to clinical severity.

Applications

Resistin serum levels can be used as a diagnostic marker for AP, as levels are increased upon hospital admission.

Peer review

This article deals with an important issue, based on the known sequential events of obesity preceding severe AP. The task of investigating a potential predictive marker of fat necrosis will provide a useful clinical tool.

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