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BRIEF ARTICLE

Value of adipokines in predicting the severity of acute pancreatitis: Comprehensive review

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Abstract

AIM: To analyze the prognostic value of adipokines in predicting the course, complications and fatal outcome of acute pancreatitis (AP).

METHODS: We performed the search of PubMed database and the systemic analysis of the literature for both experimental and human studies on prognostic value of adipokines in AP for period 2002-2012. Only the papers that described the use of adipokines for prediction of severity and/or complications of AP were selected for further analysis. Each article had to contain information about the levels of measured adipokines, diagnosis and verification of AP, to specify presence of pancreatic necrosis, organ dysfunction and/or mortality rates. From the very beginning, study was carried out adhering to the PRISMA checklist and flowchart for systemic reviews. To assess quality of all included human studies, the Quality Assessment of Diagnostic Accuracy Studies tool was used. Because of the high heterogeneity between the studies, it was decided to refrain from the statistical processing or meta-analysis of the available data.

RESULTS: Nine human and three experimental studies were included into review. In experimental studies significant differences between leptin concentrations at 24 and 48 h in control, acute edematous and acute necrotizing pancreatitis groups were found (P = 0.027 and P < 0.001). In human studies significant differences between leptin and resitin concentrations in control and acute pancreatitis groups were found. 1-3 d serum adiponectin threshold of 4.5 μg/mL correctly classified the severity of 81% of patients with AP. This threshold yielded a sensitivity of 70%, specificity 85%, positive predictive value 64%, negative predictive value88% (area under curve 0.75). Resistin and visfatin concentrations differ significantly between mild and severe acute pancreatitis groups, they correlate with severity of disease, need for interventions and outcome. Both adipokines are good markers for parapancreatic necrosis and the cut-off values of 11.9 ng/mL and 1.8 ng/mL respectively predict the high ranges of radiological scores. However, the review revealed that all nine human studies with adipokines are very different in terms of methodology and objectives, so it is difficult to generalize their results. It seems that concentrations of the leptin and resistin increases significantly in patients with acute pancreatitis compared with controls. Serum levels of adiponectin, visfatin and especially resitin (positive correlation with Acute Physiology and Chronic

Health Evaluation Ⅱ, Ranson and C-reactive protein) are significantly different in mild acute pancreatitis and severe acute pancreatitis patients, so, they can serve as a markers for the disease severity prediction. Resistin and visfatin can also be used for pancreatic and parapancreatic necrosis prediction, interventions needs and possible, outcome.

CONCLUSION: High levels of adipokines could allow for prediction of a severe disease course and outcome even in small pancreatic lesions on computed tomography scans.

Key words: Adipokines; Acute; Pancreatitis; Severity; Prediction

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INTRODUCTION

Acute pancreatitis (AP) is a common disease with a wide spectrum of severity. Its incidence is about 30-113 cases per 100 000 individuals, with the overall mortality rate of 10%-15%[1-4]. Most episodes of AP are mild and self-limiting, but up to 10%-20% of patients develop severe AP with mortality ranging from 29% to 43%[5,6]. Over past two decades mortality rate in early phase of AP associated with the systemic inflammatory response syndrome decreased significantly, but mortality in the late phase remains high. It is believed that the cause of death in late phase is predominantly linked to the development of infected necrosis and septic complications[7], thus resulting in multiple organ failure and severe sepsis[8,9]. Because of the systemic complications and high mortality, a considerable interest in the early prediction of the disease course and severity remains.

Pancreatic enzyme levels poorly correlate with the severity of AP, thus prognosis is commonly based on clinical scores. The first disease specific prognostic score was proposed by Ranson in 1974, which later was complemented by a number of pancreatitis specific and organ failure scores, including Glasgow/Imrie (1984), Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ (1985), Multiple Organ Dysfunction Score (1995), Sequential Organ Failure Assessment (1998), Pancreatitis Outcome Prediction (2007), Bedside Index of Severity in Acute Pancreatitis (2009), and many others. Although, the accuracy of such scores is high enough (Table 1)[10-14], all of them are multifactorial and rather uncomfortable for everyday use, so a great attention is still given for seeking a single prognostic marker. The most widely explored and described single predictor is C-reactive protein (CRP), which remains very useful, because it is accurate, cheap, and widely available. However, its concentration reaches a peak on third day of the disease, so it has a greatest prognostic value approximately 48 h after the onset of the symptoms. Optimal cut-off value recommended by almost all societies for disease course prediction is 150 mg/L. CRP has sensitivity of 80%, specificity of 84% with area under curve (AUC) 0.84 in predicting severity of the disease 48 h after admission with a cut-off of 150 mg/L[15]. There is little data on the value of CRP on prediction of development of pancreatic necrosis. Some studies demonstrated that a cut-off of as low as 71 mg/L is sufficient to predict development of clinically significant (volume > 30%) necrosis with a sensitivity of 78.79%, specificity of 71.43% and AUC 0.766[12].

The main problem remains, that neither prognostic scores nor single predictors can't accurately predict the disease course and severity, development of pancreatic or peripancreatic necrosis, and outcomes during the first hours or even days of hospitalization. Therefore, there is a great stimulus for seeking new accurate and easy to use predictors. Perhaps, the least studied group of predictors in AP is adipokines, including adiponectin, leptin, resistin and visfatin.

Adiponectin is being produced exclusively in adipocites and plays an important role in the inhibition of the inflammatory response[16,17]. Adiponectin depresses nuclear factor kappa B signaling in endothelial cells and adipocytes, induces the anti-inflammatory cytokine interleukin (IL)-10 and IL-1 receptor antagonist in leukocytes[18-20].

Leptin is an adipocyte-derived hormone that acts centrally in the hypothalamus to regulate body waste and peripherial energy expenditure[21]. The presence of leptin and expression of its receptors have been detected in other tissues, also in pancreas[22]. This suggests, that leptin may modulate pancreatic function and inflammatory response in pancreatitis.

Resistin and visfatin are the adipohormones, produced by neutrophils, macrophages, bone marrow and WAT[23,24]. They can induce the synthesis of pro-inflammatory cytokines, such as IL-6, IL-1β, tumor necrosis factor alpha, that is why their role in inflammatory response has been suggested[24-27].

It is now widely accepted, that white adipose tissue is an active endocrine organ, which is also involved in pathogenesis of AP. Peripancreatic fat cells necrosis might cause a massive release of cytokines (IL-1, IL-6, tumor necrosis factor) and adipokines, that possibly cause multiorgan dysfunction and whole body metabolic changes. It is hypothesized that the extent of peripancreatic fat-cell necrosis determines the severity of pancreatitis, and an early increase of adipocyte-specific marker proteins might serve as predictor of the clinical course[28].

Table 1 Pancreatitis prediction scores

Score	Sensitivity (%)			Specificity (%)			AUC		
	Course	Necrosis	Mortality	Course	Necrosis	Mortality	Course	Necrosis	Mortality
Ranson, 1974	84	77	100	90	88	77	0.94	0.85	0.95
Glasgow/Imrie, 1984	70	82	89	83	73	70	0.84	0.82	0.80
APACHE Ⅱ, 1985	70	63	100	72	69	66	0.78	0.72	0.90
MODS, 1995	73	69	89	81	74	90	0.84	0.78	0.93
SOFA, 1996/1998	76		87	69		90	0.81		0.93
POP, 2007	83	51	78	71	95	86	0.86	0.71	0.89
BISAP, 2009	38	33	57	92	91	88	0.81	0.78	0.82

APACHE: Acute Physiology and Chronic Health Evaluation; MODS: Multiple Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment; POP: Pancreatitis Outcome Prediction; BISAP: Bedside Index of Severity in Acute Pancreatitis; AUC: Area under curve.

Table 2 Reviewer judgments of methodological quality of included human studies according to the Quality Assessment of Diagnostic Accuracy Studies tool

	Konturek *et al*[30]	Leśniowski *et al*[33]	Duarte-Rojo *et al*[34]	Tukiainen *et al*[35]	Sharma *et al*[36]	Schäffler *et al*[37]	Schäffler *et al*[38]	Schäffler *et al*[39]	Daniel *et al*[40]
Patients spectrum	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Selection criteria	Unclear	No	No	No	Yes	No	No	No	Yes
Reference standart	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Period between IT and RS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Verification	Unclear	Yes	No	Yes	Yes	No	No	No	Yes
Same RS	No	Yes	No	No	Yes	No	No	No	Yes
RS independence on IT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IT replication	Yes	No	No	No	No	No	Yes	Yes	Yes
RS replication	No	No	No	No	No	No	No	No	No
IT interpretation	No	No	No	No	No	No	No	No	No
RS interpretation	Yes	No	No	No	No	No	No	No	No
Data in practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Report	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Withdrawals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	8 yes	7 yes	6 yes	8 yes	9 yes	7 yes	8 yes	8 yes	11 yes

IT: Index test; RS: Reference standart.

The aim of this study is to analyze and review the available information about the prognostic value of adipokines in predicting the course of AP, development of pancreatic and peripancreatic necrosis, infectious complications, need for interventional treatment, and fatal outcome. The main objective of the study is to compare the prognostic value of adipokines with already well established single predictors and multifactorial scores in the clinical context.

MATERIALS AND METHODS

We performed the search of PubMed database (service of the United States National Library of Medicine that includes citations from MEDLINE and other life science journals for biomedical articles) and the systemic analysis of the literature for both experimental and human studies on prognostic value of adipokines in AP for period 2002-2012. Keywords (keywords and textwords) for the search were adipokines, adipocitokines, visfatin, resistin, adiponectin, leptin, acute pancreatitis, pancreatic necrosis, peripancreatic necrosis. Further we searched the references of identified articles to find additional sources of information. Only articles in English language were included in the analysis. Dual publications were excluded. All identified papers (title, abstract and subsequently full text) were independently evaluated by two investigators. Only the papers that described the use of adipokines for prediction of severity and/or complications of AP were selected for further analysis. To be included in the systematic review, each article had to contain information about the levels of measured adipokines, diagnosis and verification of AP, to specify presence of pancreatic necrosis, organ dysfunction and/or mortality rates. All disagreements were resolved by discussion with other two investigators. From the very beginning study was carried out adhering to the PRISMA checklist and flowchart for systemic reviews.

To assess quality of all included human studies the Quality Assessment of Diagnostic Accuracy Studies tool was used[29]. Quality assessment was performed independently by three researches and all disagreements were resolved by review and discussion with the fourth investigator. The result of the human studies quality assessment is shown in Table 2. Based on the judges' evaluation 8 of 9 studies got seven or more "yes", so the overall quality of included studies was good. However, all studies were very different. Four of them analyzed only one adipo-

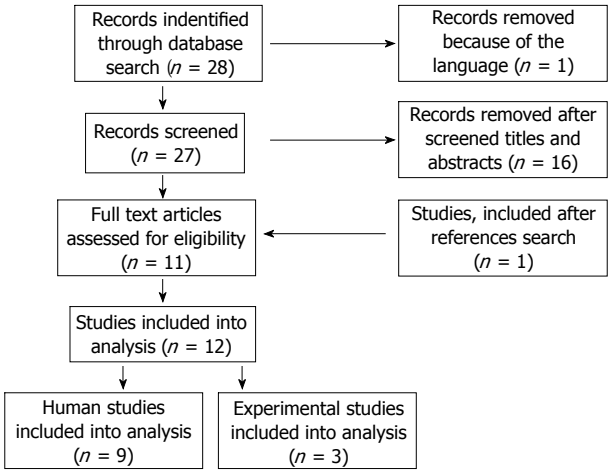

Figure 1 Selection of the studies for systematic review (PRISMA flowchart). Records identified through database search, *n* = 28.

kine, two adipokines were analyzed in three studies, and the remaining two studies analyzed three adipokines. In two studies adipokines concentration was measured only in control and AP groups, without distinction of mild and severe acute pancreatitis.

Statistical analysis

Because of the high heterogeneity between the studies, lack of the uniform diagnostic criteria and high variation of the assessed adipokines profile it was decided to refrain from the statistical processing or meta-analysis of the available data.

RESULTS

Through database search 28 records were identified. After screening the titles and abstracts, 16 records were removed, because adipokines were not used for prediction of the disease course. One record was removed because of the language. In reference search one additional study was found. So, nine human and three experimental studies were further analyzed (Figure 1).

All three experimental studies were performed on rats. The only one adipokine leptin was analyzed. In all studies significant differences between leptin concentrations in control and acute pancreatitis groups was found[30-32], one study analyzed leptin concentrations in control, acute edematous pancreatitis (AEP) and acute necrotizing pancreatitis (ANP). Significant difference at 12 h was found between controls and ANP group. At 24 and 48 h significant difference was found between controls and both AEP and ANP groups[32] (Table 3).

All nine human studies (Table 4) with adipokines are very different in terms of methodology and objectives, so it is difficult to generalize their results. It seems that concentrations of the leptin and resistin increases significantly in patients with AP compared with controls. Serum levels of adiponectin, visfatin and especially resitin (positive correlation with APACHE Ⅱ, Ranson and CRP) are significantly different in severe acute pancreatitis (SAP), mild acute pancreatitis (MAP) patients, so, they can serve as a markers for the disease severity prediction. Resistin and visfatin can also be used for pancreatic and parapancreatic necrosis prediction, interventions needs and possible, outcome.

Table 3 Summary of the experimental studies on the prognostic value of adipokines in rats

Study	Groups	*n*	Leptin, ng/mL	*P* value
Konturek *et al*[30]	AP	6-8	7.5 (4.3-18.4)	$P < 0.01$[1]
	Controls	6-8	2.1 (1.0-11.8)	
Yavuz *et al*[31]	AP	10	1.92 ± 0.1	
	CP	10	1.86 ± 0.13	
	Controls	10	0.78 ± 0.12	$P < 0.001$
Kerem *et al*[32]	AEP	30		$P < 0.001$[2]
	ANP	30		
	Controls	30		$P = 0.027$ and $P < 0.001$

AP: Acute pancreatitis; CP: Chronic pancreatitis; AEP: Acute edematous pancreatitis; ANP: Acute necrotizing pancreatitis; CIP: Caerulein-induced pancreatitis. [1]The induction of CIP resulted in a significant increase of plasma levels of leptin; [2]At 12 h leptin levels in ANP was higher than in controls, at 24 and 48 h leptin levels in AEP and ANP were higher than in controls.

DISCUSSION

Human studies (Table 4) began in 2002, when Konturek *et al*[30] found, that median plasma leptin levels in AP were significantly increased as compared with controls. In 2007, Leśniowski *et al*[33] found a significant differences between resistin concentrations in AP and control groups.

In study of Duarte-Rojo *et al*[34] there was no significant independent association between leptin serum levels and severity of AP or fatal outcome. The similar results are published from Tukiainen *et al*[35]: on admission plasma leptin levels do not correlate with AP severity. This study also did not confirm correlation between adiponectin levels and severity of AP. Despite of this, in 2009, Sharma *et al*[36] has shown, that 1-3 d serum adiponectin threshold of 4.5 μg/mL correctly classified the severity of 81% of patients with AP. This threshold yielded a sensitivity of 70%, specificity 85%, positive predictive value 64%, negative predictive value 88% (AUC 75%).

Promising results are published from Schäffler *et al*[37-39] group. They began their trial in 2006 and finished in 2011 with 41 SAP and 9 MAP patients. This study has shown, that resistin and visfatin concentrations has significant differences between MAP and SAP groups, they correlate with severity of disease, need for interventions and outcome. Both adipokines are good markers for parapancreatic necrosis and the cut-off values of 11.9 ng/mL and 1.8 ng/mL respectively allow to predict the high ranges of radiological scores. These results are consistent with Daniel *et al*[40] study in 2010, which demonstrates, that resistin and visfatin may be possibly used for AP prognosis and disease monitoring.

Although Schäffler group provides some cut-off values of adipokines, which are associated with high radiological

Table 4 Summary of the human studies on the prognostic value of adipokines

Study	Patients and methods	Results	Conclusions
Konturek *et al*[30]	Prospective observational study (n = 45) Diagnosis of AP based on Atlanta criteria Adipokines studied: leptin Adipokines evaluated between 48-72 h of illness onetime AP (n = 15) *vs* controls (n = 30)	Leptin: AP/controls- 7.5 (4.3-18.4) ng/mL/2.1 (1.0-11.8) ng/mL	Median plasma leptin levels in AP were significantly increased as compared with controls
Duarte-Rojo *et al*[34]	Prospective observational study (n = 52) Diagnosis of AP based on typical clinical manifestations with at least a 3-fold increase of serum amylase and/or lipase Whenever uncertainty about diagnosis existed, CT-scan was performed to confirm/rule out AP Severe AP was considered when patients developed one or more local or systemic complications according to the Atlanta classification of AP Adipokines studied: leptin Adipokines evaluated onetime during the 1 d of hospital stay MAP (n = 38) *vs* SAP (n = 14)	There was no statistically significant association between leptin serum levels and severity of AP There was no difference in leptin measurements between patients favorable and fatal outcomes (P = 0.34) Time of evolution from onset of pain did not alter leptin values There was a positive correlation of BMI and leptin (r = 0.476, P < 0.001) in the whole group Predicted severity by modified Ranson's criteria correlated with Atlanta criteria (r = 0.414, P = 0.002); however, it did not correlate with leptin levels	Results do not support human leptin as a major pro-inflammatory signal involved in AP, nor as a protective and anti-inflammatory mediator It seems neither to be the link between obesity and a higher rate of complications in AP; nor a prognostic marker
Tukiainen *et al*[35]	Prospective observational study (n = 24) AP and SAP defined by Atlanta criteria Adipokines studied: leptin, adiponectin Adipokines evaluated on admission, on days 2-4, and on days 5-7 MAP (n = 12) *vs* SAP (n = 12)	In patients with SAP highest value of CRP was 349 mg/L (284-476 mg/L), with MAP 119 mg/L (11-367 mg/L) Leptin on admission SAP/MAP [6.1 (1.6-72.9) ng/L]/[9.0(2.5-36 .5) ng/L], (P > 0.05); on days 2-4, 7.7 (1.6-13.9) ng/L/3.8(1.6-12.9) ng/L, (P > 0.05) Adiponectin on admission SAP/MAP, [5642 (1201-19 400) ng/L]/[6314 (1980-24 340) ng/L], (P > 0.05)	Plasma levels of adiponectin and leptin do not correlate with AP severity on admission and during the first week of the disease
Schäffler *et al*[37]	Pilot prospective observational study (n = 23) Diagnosis of AP was based on clinical, laboratory and radiological findings during CT and/or ultrasound examination Adipokines studied: leptin, adiponectin, resistin Adipokines evaluated daily for 10 d after admission SAP (n = 20) *vs* MAP (n = 3) and patients with high points *vs* low points on radiological scores	Balthazar score: 4 (1-5), Schroeder score: 5 (1-7), Necrosis score: 2(1-4) Ranson: 3 (0-7), Apache II: 12 (4-37) Resistin has a significant positive correlation with Ranson score (r= 0.6, P = 0.002) and with Apache II score (r = 0.5, P = 0.019) Resistin: intervention group/no intervention, 32.4 ± 10.7 ng/L/15.8 ± 5.1 ng/L, P = 0.026 Leptin and relative changes in leptin values were positively and significantly correlated with CRP levels (r = 0.6, P = 0.007 and P = 0.003, respectively) Resistin cut-off value of > 9.2 ng/mL (10 d mean value) can provide a PPV of 91.9% in predicting Schroder score of > 3 (specificity 85%, sensitivity 75%, AUC 0.9, P < 0.0001) Leptin cut-off value of 15.0 ng/mL can provide a PPV of 88% in predicting Schroder score of > 3 (specificity 85%, sensitivity 50%, AUC 0.72, P < 0.0001) Day 1 resistin proved to predict a Schroder score > 3 with a PPV of 93.3%, cut-off 6.95 ng/mL, specificity 87.5%, sensitivity 93.3%; AUC 0.9, P = 0.002)	Serum adipokines might be the new useful early markers of disease severity in AP
Leśniowski *et al*[33]	Prospective observational study (n = 79) All AP was classified as grade B according to Balthazar CT score Adipokines studied: adiponectin, resistin Adipokines evaluated onetime during the first day of hospitalization AP (n = 39) *vs* controls (n = 40)	Resistin: AP/controls, 8.38 ± 4.87 ng/mL/3.58 ± 1.51 ng/mL, P < 0.05 Adiponectin: AP/controls, 119.38 ± 61.75 ng/mL/133.77 ± 55.38 ng/mL, P > 0.05 CRP: AP/controls, 23.21 ± 8.75 ng/mL/3.95 ± 1.06 mg/L, P < 0.01 Weak positive correlation between serum resistin and CRP was observed (r = 0.57, P < 0.05) No correlation between selected adipocytokines and BMI was noticed	Serum concentrations of resistin may possibly represent the useful early marker of inflammatory response in AP
Sharma *et al*[36]	Prospective observational study (n = 60) Diagnosis of AP based on Atlanta criteria SAP was defined as the presence of cardiovascular, pulmonary, and/or renal system dysfunction during the initial hospital admission during for at least 48 h Adipokines studied: adiponectin Adipokines evaluated on admission and subsequently up to 30th hospital day MAP (n = 27) *vs* SAP (n = 33)	Serum adiponectin levels from days 1 to 3 were significantly lower for patients with SAP [median 3.74 (0.83-8.92) μg/L] than those with MAP [6.58 (1.31-15.37) μg/L], P = 0.02 Serum adiponectin levels from days 4 to 7 were lower for patients with SAP [median 4.53 (0.94-18.2) μg/L] than those with MAP [8.06 (2.11-17.72) μg/L], P = 0.01 1-3 d serum adiponectin threshold of 4.5 μg/mL correctly classified the severity of 81% of patients with AP This threshold yielded a sensitivity of 70%, specificity 85%, PPV 64%, NPV 88%, AUC 0.75	Serum adiponectin levels are significantly lower in patients with SAP than those with MAP and could serve as inverse marker of systemic inflammatory response to pancreatic injury

Daniel *et al*[40]	Prospective observational study (n = 62) Diagnosis of AP was based on at least threefold elevated serum amylase level, as well as ultrasonography and CT In all cases AP was classified as C according to Balthazar's CT score and as severe according to Ranson's criteria (3 points) Adipokines studied: resistin Adipokines evaluated on 1, 2, 3 and 5 d of hospitalization SAP (n = 32) *vs* controls (n = 30)	On first day of observation , the median serum CRP level was 51.9 ± 46.1 mg/L, significantly higher than in control group (3.44 ± 3.04 mg/L, P = 0.01), and further increased at third day of hospitalization (102.6 ± 55.1 mg/L, P < 0.05), slightly decreasing on fifth day of hospitalization (78 ± 47.7 mg/L) The values observed at third and fifth day of hospitalization were significantly higher than in the control group (P < 0.001) One day of admission and third day of the hospitalization the mean serum resistin concentration was 12.9 ± 6.38 ng/mL and 17.4 ± 4.23 ng/mL, respectively Both values were significantly higher than in the control group (4.06 ± 2.63 ng/mL, P < 0.05) At fifth day of hospitalization serum resistin concentration increase further to 25.8 ± 8.14 ng/mL, which was significantly higher than at first and third day (P < 0.05) of hospital stay Significant correlation between CRP and resistin (r = 0.43, P < 0.05) during the hospital stay was found	Resistin may be useful early marker in edematous form of AP
Schäffler *et al*[38,39]	Prospective observational study (n = 50) Diagnosis of AP was based on clinical, laboratory and radiological findings during CT and/or ultrasound examination All patients were divided into three groups: first - with higher radiological score's points, second - with lower radiological score's points and third - no CT scan (mild pancreatitis) Adipokines studied: leptin, adiponectin, resistin, visfatin Adipokines were measured daily from admission till 10 d of hospital stay SAP (n = 41) *vs* MAP (n = 9) and patients with high points *vs* low points on radiological scores	Balthazar score: 4.0 (1-5), Schroeder score: 4.5 (1-7), Necrosis score: 1.5 (1-4), Ranson: 3 (0-8), Apache II: 12 (0-45) Admission resistin levels has positive an significant correlation with Apache II score (r = 6, P < 0.001) and with Ranson score (r = 0.4, P = 0.013) Admission resistin cut-off value of > 11.9 ng/mL can provide a PPV of 89% in predicting Schroeder score of > 3 (specificity 80%, sensitivity 70%, AUC 0.8, P < 0.002) Admission resistin cut-off value of > 11.9 ng/mL can serve as a positive predictor of a Balthazar score > 3 and Necrosis score > 2 Admission visfatin cut-off value of > 1.8 ng/mL can provide a PPV of 93.3% in predicting Schroeder score of > 3 (specificity 81.8%, sensitivity 93.3%, AUC 0.89, P < 0.001, likehood ratio 5.1, post-test probability 93.0%) Admission visfatin concentration can also predict Necrosis score > 2 (PPV 48.3, specificity 40.0%, sensitivity 93.8%, AUC 0.77, P < 0.004, likehood ratio 1.5, post-test probability 70.0%) and Balthazar score > 3 (PPV 79.3, specificity 57.1%, sensitivity 88.9%, AUC 0.74, P < 0.011, likehood ratio 2.1, post-test probability 55.0%)	Resistin and visfatin levels are highly elevated in patients with SAP when compared to patients with MAP Both adipokines levels are positively correlated with clinical severity, clinical end points and needs for interventions A single measurement of serum resistin or visfatin on the day of admission is a highly significant and positive predictive marker in predicting peripancreatic necrosis

AP: Acute pancreatitis; SAP: Severe acute pancreatitis; MAP: Mild acute pancreatitis; BMI: Body mass index; CRP: C-reactive protein; AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value; CT: Computed tomography.

scores ranges, there is no precise cut-off values in order to predict disease severity on admission, development of pancreatic and parapancreatic necrosis, infectious complications, need for interventional treatment and fatal outcome. Therefore it is difficult to compare the prognostic value of adipokines with other prognostic systems.

It is clear, that obesity complicates the course of acute pancreatitis and it is associated with higher incidence of local complications, organ failure and increased mortality risk[41,42]. Adipose tissue doesn't accumulate contrast, making it difficult to evaluate it's necrosis on computed tomography (CT) scans. Thus, adipokines could be a useful markers for adipose tissue necrosis. High levels of adipokines could allow for prediction of a severe disease course and outcome even in small pancreatic lesions on CT scans, but further research is needed. Therefore, it is appropriate to initiate a multicenter study, with a sufficient number of AP patients and controls. All patients must be evaluated with the same clinical score, adipokines should be investigated all at once and CT scans should be standardized in time. We believe, that such a study could provide a more definitive answer about the value of the adipokines in predicting the course and the outcomes of AP in a clinical setting.

COMMENTS

Background

Acute pancreatitis (AP) is a common disease with a wide spectrum of severity. The main problem remains, that neither prognostic scores nor single predictors can't accurately predict the disease course and severity, development of pancreatic or peripancreatic necrosis, and outcomes during the first hours or even days of hospitalization. Therefore, there is a great stimulus for seeking new accurate and easy to use predictors. Perhaps, the least studied group of predictors in AP is adipokines. The aim of this study was to analyze the prognostic value of adipokines in predicting the course, complications and fatal outcome of AP.

Research frontiers

It is now widely accepted, that white adipose tissue is an active endocrine organ, which is also involved in pathogenesis of AP. Peripancreatic fat cells necrosis might cause a massive release of and adipokines, that possibly cause multi-organ dysfunction and whole body metabolic changes. It is hypothesized that the extent of peripancreatic fat-cell necrosis determines the severity of pancreatitis, and an early increase of adipocyte-specific marker proteins might serve as predictor of the clinical course.

Innovations and breakthroughs

It seems that concentrations of the leptin and resistin increases significantly in patients with AP compared with controls. Serum levels of adiponectin, visfatin

and especially resitin (positive correlation with Acute Physiology and Chronic Health Evaluation Ⅱ, Ranson and C-reactive protein) are significantly different in mild and severe AP patients, so, they can serve as a markers for the disease severity prediction. Resistin and visfatin can also be used for pancreatic and parapancreatic necrosis prediction, interventions needs and possible, outcome.

Applications

Adipokines could be a useful markers for adipose tissue necrosis. High levels of adipokines could allow for prediction of a severe disease course and outcome even in small pancreatic lesions on computed tomography scans, but further research is needed.

Terminology

AP: Acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems; Mild AP: Associated with minimal organ dysfunction an uneventful recovery; Severe AP: Associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst; Adipokines: Cytokines secreted by adipose tissue.

Peer review

In the current review, the authors have presented the current knowledge on the role of adipocytokines in predicting severity of AP. The search criteria were scientific and the data has been presented in an easily comprehensible manner.

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