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EDITORIAL

Experimental evidence of obesity as a risk factor for severe acute pancreatitis

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Abstract

The incidence of acute pancreatitis, an inflammation of the pancreas, is increasing worldwide. Pancreatic injury is mild in 80%-90% of patients who recover without complications. The remaining patients may develop a severe disease with local complications such as acinar cell necrosis, abscess and remote organ injury including lung injury. The early prediction of the severity of the disease is an important goal for physicians in management of patients with acute pancreatitis in order to optimize the therapy and to prevent organ dysfunction and local complications. For that purpose, multiple clinical scale scores have been applied to patients with acute pancreatitis. Recently, a new problem has emerged: the increased severity of the disease in obese patients. However, the mechanisms by which obesity increases the severity of acute pancreatitis are unclear. Several hypotheses have been suggested: (1) obese patients have an increased inflammation within the pancreas; (2) obese patients have an increased accumulation of fat within and around the pancreas where necrosis is often located; (3) increase in both peri- and intra-pancreatic fat and inflammatory cells explain the high incidence of pancreatic inflammation and necrosis in obese patients; (4) hepatic dysfunction associated with obesity might enhance the systemic inflammatory response by altering the detoxification of inflammatory mediators; and (5) ventilation/perfusion mismatch leading to hypoxia associated with a low pancreatic flow might reduce the pancreatic oxygenation and further enhance pancreatic injury. Recent experimental investigations also show an increased mortality and morbidity in obese rodents with acute pancreatitis and the implication of the adipokines leptin and adiponectin. Such models are important to investigate whether the inflammatory response of the disease is enhanced by obesity. It is exciting to speculate that manipulation of the adipokine milieu has the potential to influence the severity of acute pancreatitis.

Key words: Acute pancreatitis; Obesity; Adiponectin; Leptin

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INTRODUCTION

The incidence of acute pancreatitis is increasing worldwide[1]. Most episodes of acute pancreatitis are mild and self-limiting, requiring only a short hospitalization[2]. However, 10% of the patients (with a significant proportion of obese patients) develop a severe disease with local and extra-pancreatic complications characterized by early development and persistence of hypovolemia and multiple organ dysfunction[3,4]. Following the initial pancreatic edema, necrosis is the most severe local complication. The patchy areas of nonviable parenchyma are initially sterile but may be infected by bacteria originated mostly from the gut whose permeability increases during the disease. The most important extra-pancreatic complication is lung injury with a high incidence in severe

pancreatitis, ranging from 15% to 55 %[5]. The severity of pulmonary complications varies greatly from mild hypoxemia without clinical or radiological abnormalities to severe acute respiratory distress syndrome. Two peaks of pulmonary complications were observed during the early phase of severe acute pancreatitis, the first peak being described upon admission with new radiological abnormalities by day 5[6]. Hepatic injury is mild in acute pancreatitis but may participate in the propagation of inflammation from pancreas to other organs, mostly lungs[7,8].

INCREASED SEVERITY OF ACUTE PANCREATITIS IN OBESE PATIENTS

Several clinical investigations showed that obesity increases the severity of the disease by favoring local complications within the pancreas and injuries in remote organs as well as by increasing the mortality rate[9-13]. Obesity increases the incidence of early shock, renal and pulmonary failure[14] and extends the hospital stay[15]. However, other studies have questioned such findings[11,16,17].

The mechanisms by which obesity increases the severity of acute pancreatitis is unclear, but one hypothesis might be that obese patients have an increased inflammatory response within the pancreas[11,18]. In the study by Sempere *et al*[12], among 85 consecutive patients with acute pancreatitis, 74% had a mild disease while the remaining patients were severely ill. Serum concentrations of interleukin-1α (IL-1α), IL-1 receptor antagonist (IL1-ra), IL-6, IL-8, IL-10 and IL-12p70 were significantly increased in patients with acute pancreatitis as compared with volunteers, and the concentrations were significantly higher in obese patients. One explanation is that obesity per se induces a chronic inflammatory state[11,19]. A second hypothesis is that obese patients have an increased accumulation of fat within and around the pancreas where necrosis is often located. The risk of pancreatic infection and inflammation would be proportional to the increased amount of peri-pancreatic fat. Accordingly, patients with intra-pancreatic fat are more prone to develop local complications following pancreatic surgery[11,20]. Interestingly, cytokine expression in fat tissue is higher in obese than in lean subjects[21]. In obese patients, the cytokine expression is also higher in visceral than in subcutaneous fat, cytokines being produced mainly by macrophages located in the stroma-vascular fraction of fat tissues[21]. Thus, increase in both peri- and intra-pancreatic fat and presence of inflammatory cells in adipose tissues might explain the high incidence of pancreatic inflammation and necrosis in obese patients. Weight loss improves the inflammatory profile of fat tissue with an increased expression of anti-inflammatory factors such as IL-10 and IL1-ra[21]. Similarly, in inflammatory bowel diseases, visceral fat is also a source of inflammatory signals[22,23]. A third hypothesis is that pancreatic microcirculation is lower in obese than in non-obese patients, which increases the risk of ischemic injury and subsequent local infections. Moreover, obese patients might be immunodeficient, a condition that increases the risk of local infections[24]. Finally, because obesity restricts the movement of the chest wall and diaphragm, inspiratory capacity of obese patients is reduced. Ventilation/perfusion mismatch may lead to hypoxemia that, in conjunction with low blood flow, further decreases tissue oxygenation to the pancreas.

BRIEF OVERVIEW OF THE PATHOPHYSIOLOGY OF ACUTE PANCREATITIS

Although controversial, most observers believe that acute pancreatitis is caused by the dysregulated activation of trypsin within pancreatic acinar cells. Enzyme activation within the pancreas leads to autodigestion of the gland followed by local inflammation. The main factors that trigger the acute disease are pancreatic hyperstimulation (mainly observed in experimental models), gallstones and alcohol abuse in humans. Acute pancreatitis occurs when intracellular protective mechanisms designed to prevent trypsinogen activation or reduce trypsin activity are decreased or overwhelmed. Following the activation of trypsinogen into active trypsin within acinar cells, numerous enzymes such as elastase and phospholipase A2, as well as complement and kinin systems, are activated[25] (Figures 1 and 2). Additionally, inflammation is initiated with local production of mediators such as tumor necrosis factor-α (TNF-α), IL-1and IL-8 from neutrophils, macrophages and lymphocytes[26,27]. In addition to these events, activation of endothelial cells permits the transendothelial migration of leukocytes that release other harmful mediators[28]. Thus, regardless of the initial trigger of the disease, the severity of pancreatic damage is related to the injury of acinar cells and to the activation of inflammatory and endothelial cells. Local complications such as acinar cell necrosis may develop and injury in remote organs (lungs) results from the release of numerous mediators from the pancreas or extrapancreatic organs (Figure 1).

EXPERIMENTAL PANCREATITIS, OBESITY, ADIPONECTINS AND INFLAMMATION

Fat tissues are likely to contribute to the increased inflammation in obese rodents. Thus, adipokines secreted by adipocytes are potent regulators of the inflammatory response, leptin being considered as a pro-inflammatory adipokine, while adiponectin functions as an anti-inflammatory mediator (Table 1). Adipose tissues also produce cytokines that participate in the inflammatory response of obesity and organ dysfunction. Thus, pancreatic necrosis following intrapancreatic duct injection of taurocholic cid (TA) was similar in obese *fa/fa* rats and lean

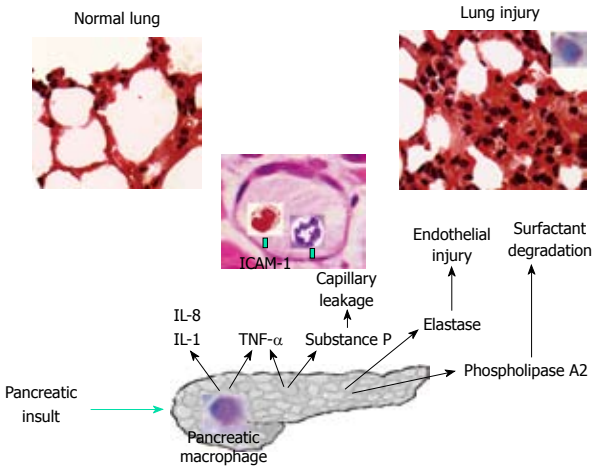

Figure 1 Overview of the major events occurring in experimental acute pancreatitis and pancreatitis-associated lung injury. Inflammatory cells adhere to the endothelial walls *via* the expression of the intercellular molecules (ICAM-1) and translate the local inflammation to remote organs.

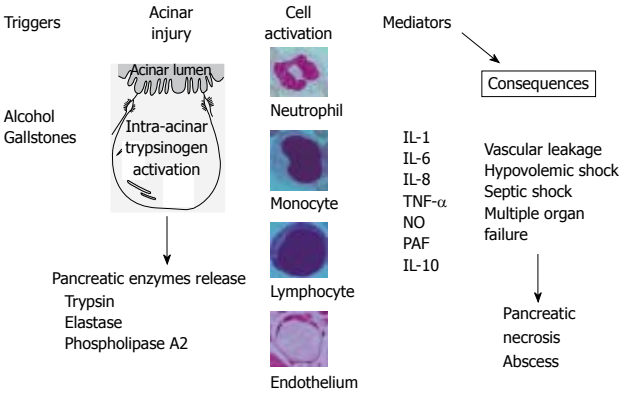

Figure 2 Mediators involved in the pathogenesis of acute pancreatitis. After the acinar cell injury occurs, inflammatory cells will synthesize and release proinflammatory cytokines and chemokines that induce systemic effects (vascular leakage, *etc.*). All these consequences will finally dictate the occurrence of pancreatic necrosis and abscess.

fa/+ rats, but the survival was lower in obese rats[29]. The pancreatic expression of TNF-α and IL-6 was higher in obese than in lean rats while IL-10 expression was lower[30]. TNF-α expression was also higher in liver and lungs from obese rats. Moreover, obese rats with acute pancreatitis had steatohepatitis while livers in lean rats with acute pancreatis were normal. Thus, dysregulation between inflammatory and anti-inflammatory mediators in obese rats is an important issue to explain the increased severity of the disease. These investigators also determined whether high-fat feeding vs. normal diet may influence the severity of a "two-hit" injury (TA-induced pancreatitis followed by intraperitoneal injection of endotoxin 3 h later)[31]. Endotoxin administration lowers the survival rate of lean rats by increasing peripancreatic fat necrosis and systemic inflammatory response while chronic high fat diet does not aggravate pancreatic injury induced by TA plus endotoxin[31].

Obese *fa*/*fa* rats have a mutation with dysfunction of the leptin receptor and develops obesity by week 5[32]. Littermates *fa*/+ rats are used as controls. By week 14, body weight doubles in *fa*/*fa* rats. Restricted feeding does not modify the occurrence of obesity. The obesity is associated with an increase in the number and size of adipocytes. These rats have hyperlipidemia and hypercholesterolemia. The pancreas weight is similar in *fa*/*fa* and *fa*/+ rats but, according to the increased body weight of *fa*/*fa* rats, the ratio between pancreas and body weight is lower in *fa*/*fa* rats[33]. Of note, amylase content is lower in *fa*/*fa* than *fa*/+ rats and treatment with ciglitazone that increases the insulin sensitivity partially prevents this low pancreatic amylase content[34]. Administration of cholecystokinin (CCK) is known to decrease food intake but the obese rats have a higher threshold than lean rats for this effect[35]. Moreover, the exocrine response to cerulein and carbamylcholine is decreased in acini isolated from *fa*/*fa* rats while the response to secretin or vasoactive intestinal peptide is identical[36,37]. When CCK is incubated in isolated acini, less amylase is secreted in *fa*/*fa* rats than in lean rats[37]. In *fa*/*fa* and *fa*/+ rats, the expression of CCK_A and CCK_B receptors is unknown. To overcome the absence of effects on the receptor, circulating leptin expression is increased**.** Leptin mRNA is detected in adipose tissue but not in pancreas, lungs, or liver[38]. The expression of leptin decreases gradually from epididymal to retroperitoneal, subcutaneous, and interscapular brown adipose tissue. In isolated adipocytes, leptin mRNA expression is also significantly higher in *fa*/*fa* than in control rats. Finally, TNF-α protein expression in adipose (perirenal and epididymal) tissues is similar in both strains[33].

The severity of acute pancreatitis has been investigated in other experimental models of obesity, such as *ob*/*ob* and *db*/*db* mice. Both mice are congenitally obese but manifest this phenotype *via* different mechanisms. *Ob*/*ob* mice have a spontaneous mutation of the *ob* (leptin) gene and produce no leptin while *db*/*db* mice have a spontaneous mutation of the leptin receptor and have increased circulating concentrations of leptin. *Ob*/*ob* mice may reach three times the normal weight of wild-type mice. Obesity is characterized by an increase in the number and size of adipocytes. Although hyperphagia contributes to obesity, excess of weight is also

Table 1 Severity of acute pancreatitis and adipokines

Adipocytokine	Effects	Final effect
Leptin	↑ TNF-α ↑ Chemotaxis ↑ Neutrophil activation ↑ IL-6 ↑ T-cell proliferation	Pro-inflammatory
Adiponectin	↓ Endothelial cell adhesion ↓ TNF-α ↓ IL-6 ↓ Phagocytosis ↑ IL-10 ↑ IL-1RA	Anti-inflammatory

Adiponectin may be considered as an anti-inflammatory compound whereas leptin acts as a proinflammatory mediator. Both adipokines may influence the severity of pancreatitis.

observed with a restrictive diet sufficient for lean mice. Interestingly, *ob/ob* mice have impaired pulmonary bacterial clearance of *Streptococcus pneumoniae* and increased pulmonary concentrations of cytokines[39]. *Ob/ob* mice are less hyperglycemic than *db/db* mice. Moreover, in pancreas from *ob/ob* mice, content of triglycerides, free fatty acids, cholesterol and total fat is higher than in lean mice[40]. Serum concentrations of IL-1 and TNF-α are also increased.

In a model of acute pancreatitis induced by two injections of IL-12 plus IL-18, all *ob/ob* mice died within 48 h while all wild-type mice survived[41]. To differentiate the contribution of obesity or leptin deficiency to the severity of the disease, a group of *ob/ob* mice had leptin replacement therapy (obesity with normal leptin). Interestingly, this group had severe acute pancreatitis, suggesting that obesity *per se* and not leptin deficiency was responsible for the severe acute pancreatitis. Moreover, the authors generated "slim" *ob/ob* mice that had a less severe acute pancreatitis, reinforcing the finding that obesity rather that leptin deficiency was responsible for the severity of acute pancreatitis. In another study, three experimental groups received injections of cerulein: C57BL/6J (lean), *ob/ob* (obese mice with leptin deficiency), and *db/db* (obese mice with leptin receptor deficiency and increased circulating leptin) mice[42]. Both *ob/ob* and *db/db* mice developed a significantly more severe disease than wild-type lean mice associated with an increase in pancreatic inflammatory cytokines. Finally, in patients matched for body mass index, the circulating leptin did not correlate with the severity of the disease[43]. These studies confirmed the feeling that leptin production does not relate to the severity of acute pancreatitis.

However, the role of leptin in acute pancreatitis remains puzzling (Table 1). In pancreatitis induced by cerulein injections in lean rats, serum leptin concentrations increased by 12 h and remained high for 36 h[44]. When a more severe disease was induced (arginine model), leptin concentrations were high at 12 and 24 h but were similar at 48 h in both experimental models. Thus, in lean rodents, the serum concentrations of leptin increase in acute pancreatitis but no relationship is found between severity of the disease and circulating leptin concentrations. To further investigate the role of leptin in the severity of the disease, rats with acute pancreatitis were treated with leptin (10 μg/kg ip) after the last cerulein injection[45]. Leptin treatment increased the survival rate over 48 h and this beneficial effect was associated with a reduced serum expression of TNF-α, IL-1, MIP, sICAM and lung nitric oxide. Pancreatic and pulmonary CD40 expression was significantly reduced by leptin as was pancreatic and pulmonary injuries at histological examinations[45].

The anti-inflammatory adipokine adiponectin has also been investigated in experimental pancreatitis. Adiponectin is decreased in obesity and inversely mirrors the severity of experimental pancreatitis[46]. Adiponectin acts through the receptors AdipoR1 and AdipoR2. Both receptors are expressed in rodent pancreas but AdipoR1 expression is significantly decreased in the pancreas of *ob/ob* and *db/db* mice as compared with wild-type lean mice[46]. To investigate the role of adiponectin in the severity of acute pancreatitis, adiponectin knockout (APN-KO) and wild type mice were injected with a low dose of cerulein two weeks after normal or high-fat-diet[47]. Whereas APN-KO mice fed a high-fat-diet treated with cerulein developed pancreatic damage and inflammation, wild-type mice did not. Finally, adenovirus-mediated over-expression of adiponectin attenuates the severity of acute pancreatitis in APN-KO mice[47]. All these data clearly demonstrate that adiponectin plays a protective role in the cerulein model of acute pancreatitis.

INTERACTION OF CHOLECYTOKININ, DIGESTIVE PROENZYMES AND LEPTIN

Confusion on the protective or deleterious role of leptin in acute experimental pancreatitis may also rise from the fact that a crosstalk between CCK and leptin pathways is observed in acinar cells. CCK is produced in endocrine cells present in the mucosa of the small intestine following the ingestion of proteins and fat. CCK stimulates the contraction of gallbladder and relaxes the sphincter of Oddi (facilitating bile secretion into the intestine) and stimulates pancreatic secretion by acinar cells either by a direct effect or through acetylcholine released by the vagus nerve that possesses receptors for CCK. CCK is also a proliferative hormone for the pancreas and by delaying gastric emptying induces satiety. Leptin, produced and secreted from white adipocytes, regulates food intake and energy consumption[48]. Intravenous administration of leptin diminishes the postprandial pancreatic secretions[49]. Administration of leptin does not affect the volume of bile and pancreatic juice while the protein and trypsin output is reduced[49]. The effect of leptin becomes stronger when protein and trypsin secretions are stimulated by CCK. In contrast, leptin does not affect basal and CCK-8-stimulated amylase release in pancreatic acini, suggesting that leptin does not act directly on pancreatic acinar cells but inhibits the secretion of pancreatic enzymes through CCK-vagal-dependent mechanism[49]. In contrast to the intravenous administration, intraduodenal leptin administration to fasted rats increases pancreatic protein and amylase secretions, this effect being related to the stimulation of CCK release through activation of duodeno-pancreatic reflexes[50].

Otsuka Long-Evans Tokushima Fatty (OLETF) rats are spontaneously diabetic rats with polyuria, polydipsia, hyperglycemia, mild obesity and diabetes[51]. These rats do not express the CCK-A receptor mRNA in pancreas. This lack of CCK-A receptors results in a reduced ability to produce nutrient-induced satiety signals which leads to increase in meal size, overall hyperphagia and obesity. Administration of increasing doses of CCK8 induced a biphasic dose-response curve of pancreatic juice and protein secretion in control Long-Evans Tokushima Otsuka (LETO) rats whereas the OLETF rats did not respond to CCK-8[52]. Cerulein injections induce acute

pancreatitis in LETO rats but did not increase serum amylase or lipase activities in OLETF rats.

Finally, the rat pancreatic acinar tumor (AR42J) cell lines do express the leptin receptor[53]. The binding of leptin is specific to the leptin receptor and does not cross-react with CCK pathway. Leptin does not modify basal amylase release but inhibits amylase release stimulated by CCK. Leptin alone has no effect on intracellular Ca^{2+} mobilization but pre-treatment with leptin enhances the Ca^{2+} response to CCK. Thus, AR42J cells express a functional leptin receptor that modulates the action of CCK on Ca^{2+} mobilization and amylase release[53]. Relationship between enzyme release from acinar cells and signals of satiety such as leptin in lean and obese rodents are complex and further investigations are needed.

CONCLUSION

The prevalence of obesity has increased worldwide. Despite numerous clinical investigations, the precise mechanisms involved in the pathogenesis of acute pancreatitis remain elusive, and currently no specific medical therapy is available beyond general support. Investigating the mechanisms, by which acute pancreatitis develops from novel angles such as obesity, offers potentially new observations that may ultimately lead to the development of useful treatment. It is exciting to speculate that manipulation of the adipokine milieu has the potential to influence the severity of acute pancreatitis. Thus, investigations along these lines are warranted.

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