

Experimental acute pancreatitis models relevant to lipids and obesity

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1. Introduction and Background

While severity in conventional animal models of AP is related to etiology, this rarely happens in human disease. Most obese individuals do not experience an episode of acute pancreatitis (AP) during their lifetime, but those who do develop AP are more prone to severe acute pancreatitis (SAP) and associated morbidity and mortality (1). In this entry, we will discuss the relevance of obesity and lipids as potential modifiers of the course and outcome of AP in the light of limitations posed by conventional models of acute pancreatitis and suggest relevant improvisations with examples in various *in vitro* and *in vivo* systems.

From the perspective of pancreatitis and its experimental models, visceral fat depots can be divided into intrapancreatic and those around the pancreas i.e. peripancreatic fat. Both of these can contribute to SAP in humans. The human facts relevant to the nature and amounts of lipid used in the sections on experimental models are: 1. More than 30% body weight may be contributed by adipose tissue during obesity. 2) Obesity is associated with SAP (32, 43, 45, 46) and is defined as a BMI of $>30 \text{ kg/m}^2$ in western countries or $>25 \text{ kg/m}^2$ in the East. 3) Clinical studies from the west (12, 36, 44, 47, 81, 89) and Asia (91, 98, 110, 111) report increased SAP above the corresponding BMIs. 4) There is a higher consumption of polyunsaturated fatty acid (PUFA) (42, 84, 88, 103) in Asia compared to the west (41, 42, 88). 5) Dietary PUFAs accumulate in visceral adipocytes (88). 6) 80-90% of adipocyte mass may comprise triglyceride. 7) Intra pancreatic fat increases with

BMI (86) and may comprise an average of about 20% pancreatic area in obese individuals. 8) Peripancreatic fat may commonly range from 2-9 Kg in obese individuals. Both these depots may be hydrolyzed in pancreatitis contributing to SAP. While further details on obesity related human data are provided in the chapter "Relationship between obesity and pancreatitis" (63), in this section we shall focus on studying the impact of obesity in animal models of pancreatitis.

Limitations of Current Animal Models in the Context of Human AP

Current animal models of acute pancreatitis are classified for severity on the basis of an inducer/etiology causing pancreatic necrosis (54). This is a significant limitation since severity in human AP is unrelated to pancreatic necrosis or etiology, with the exception of hypertriglyceridemic pancreatitis (25, 26, 55). Rat caerulein pancreatitis is considered milder due to the lesser pancreatic necrosis (54, 72) while, mouse caerulein pancreatitis is considered a severe acute pancreatitis model due to the higher amount of acinar necrosis ranging from 5-30% (45, 54, 57). In both these models, the pancreas returns to baseline after a few days of inducing AP. Similarly, lung injury in these is mild and transient with no evidence of impaired gas exchange.

In contrast, development of necrosis during human AP may not result in worse outcomes. While severe pancreatic necrosis is defined as development of pancreatic parenchymal necrosis of more than 30% during human disease (31), a prospective human study from the United Kingdom

showed no/minimal relationship between the extent of necrosis and outcome (56). SAP and early mortality in human AP can occur with minimal pancreatic necrosis (16, 32, 61) due to systemic complications or sustained organ failure (31). A number of studies have documented that only about half of patients with necrotizing pancreatitis develop organ failure (46, 78, 97).

Taurocholate induced pancreatitis in rats is considered severe due to the extensive pancreatic hemorrhagic necrosis noted in this model (5, 54, 72). To induced AP 3 to 5% solutions of bile salts such as sodium taurocholate are injected locally into the bilio- pancreatic duct, aimed at stimulating severe biliary acute pancreatitis (5). This results in a local concentration of 60 to 100 mM, which is 5 to 100 fold above the critical micellar concentration (94) which can cause a detergent like effect on cell membranes in the pancreatic acinar cells. Currently while no published study has verified the appropriateness of these concentrations of bile salts in relevance to human disease, our unpublished data shows bile acid concentrations to average at 25 μ M in pancreatic collections from patients with biliary AP. A recent review by Lerch and Gorelick also questioned the injection of bile acids/salts as a model for biliary acute pancreatitis (54).

Clinically, it is often difficult to establish the causal agents responsible for the severity in human acute pancreatitis, since markers and mediators of disease are indistinguishable. Animal models allow initiation and inhibition of steps relevant to the patho-physiology of the disease and are thus important in establishing causality. Several potential targets like trypsin (6, 7, 9, 14, 18, 75, 90, 100, 101) and reactive oxygen species (2) have been considered of therapeutic relevance since their levels may be increased in acute pancreatitis. However clinical trials of acute pancreatitis targeting reactive oxygen species (2) trypsin (6, 7, 9, 14, 18, 75, 90, 100, 101) and inflammatory mediators (43) have shown limited benefits, although these targets seem scientifically sound in animal models. The discord between modification

of outcomes and interpretation of animal models can be seen in the lack of evidence of clinical improvement despite more than 70 trials of serine protease and trypsin inhibition over the last six decades (6, 7, 9, 14, 18, 75, 90, 100, 101). Thus, based on i) lack of relevance of etiology to outcomes, ii) lack of accurate parameters used to define systemic injury, iii) limited clinical benefits of attractive therapeutic targets in animal models and iv) overemphasis of pancreatic necrosis in defining AP severity we need to interpret the relevance of conventional AP models with caution.

2. Role of Obesity and Lipids in Acute Pancreatitis

Obesity is known to be associated with worse acute pancreatitis outcomes (3, 19, 29, 68, 74, 81, 89, 91) and several clinical and epidemiological studies have shown that patients with increased intra-abdominal fat or higher body mass index (BMI) are at an increased risk for developing SAP (33, 68, 85, 111). The two other clinical clues to lipids worsening AP outcomes are i) hypertriglyceridemic pancreatitis generally being severe (13, 25, 26, 55, 106) and ii) AP patients receiving intravenous total parenteral nutrition including IV lipids having worse outcomes (77, 79, 109). Recent reports from North America show the usage of parenteral nutrition to be as high as 40 to 60% in patients with acute pancreatitis (95, 105). The prevalence of organ failure is reported to be more than 50% in patients receiving parenteral nutrition containing intravenous lipid emulsions (77, 79, 109). IV lipids may result in high systemic fatty acid concentrations, 6 to 8 fold above normal (38), consistent with levels found in the serum of patients with SAP (27, 73). These associations of obesity/ lipids in causing worse outcomes suggest the role of fat as a common modifier of AP outcomes. In the following sub sections, we will discuss the mechanistic, translational and potential therapeutic relevance of obesity in the context of *in vitro* and *in vivo* models of acute pancreatitis.

***In vitro* Models of Fat Mediated Severe Acute Pancreatitis**

The purpose of an *in vitro* model is to replicate the pathophysiology occurring *in vivo* in a reductionist manner. Therefore, the design of fat induced pancreatic damage model should simulate the *in vivo* environment. Several studies show evidence of pancreatic parenchymal necrosis around fat necrosis. (4, 48, 62, 67). Physiologically, adipocytes and the neighboring pancreatic acinar cells do not allow their contents to communicate with each other. Acinar cells physiologically secrete digestive enzymes present in zymogen granules from their apical region into the duct lumen; however, an insult which causes pancreatitis can result in basolateral leakage of

lipases into the surrounding adipocytes (20, 21, 30, 34, 48, 50) and consequent lipolysis of adipocyte triglyceride, producing free fatty acids(FFA). This is seen histologically as positive Von Kossa staining (4, 62) and high FFA levels in pancreatic necrosis collections (28, 62, 71).

This pathologic *in vivo* lipolytic flux between adipocytes and acinar cells can be simulated *in vitro* using a trans-well system which allows macro molecular diffusion between the acinar and adipocyte compartments, while preventing cellular contamination of the individual compartments (**Figure 1**) (4, 62).

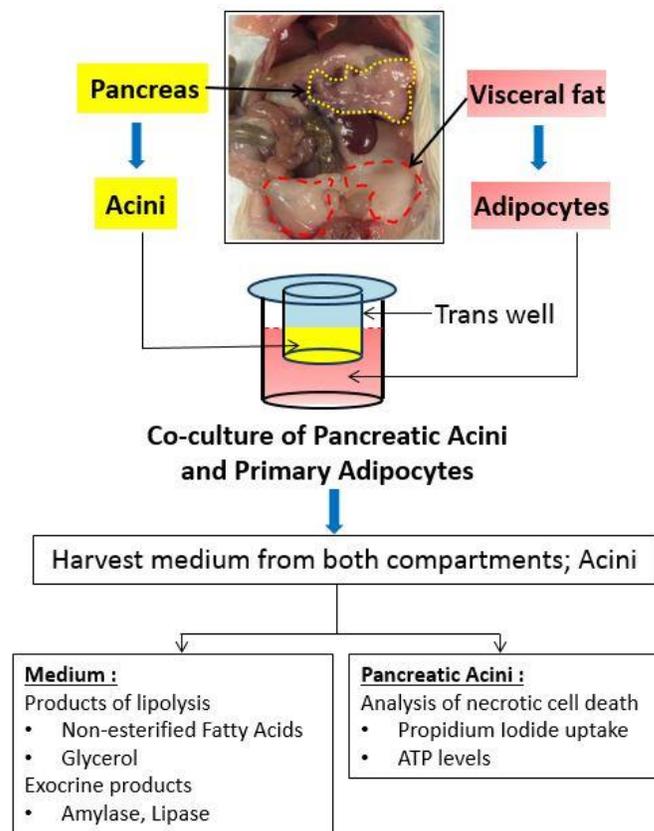


Figure 1: Schematic showing the setup to study *In Vitro* Lipolytic Fluxes. After harvesting, primary acinar cells are added to the upper compartment of the Transwell (with a 3 micron sieve at bottom of insert; Yellow) and primary adipocytes to the lower compartment of the well (Red). Medium from the individual compartments is analyzed for lipolytic and exocrine products, and the acinar cells are harvested for measuring parameters of necrotic cell death.

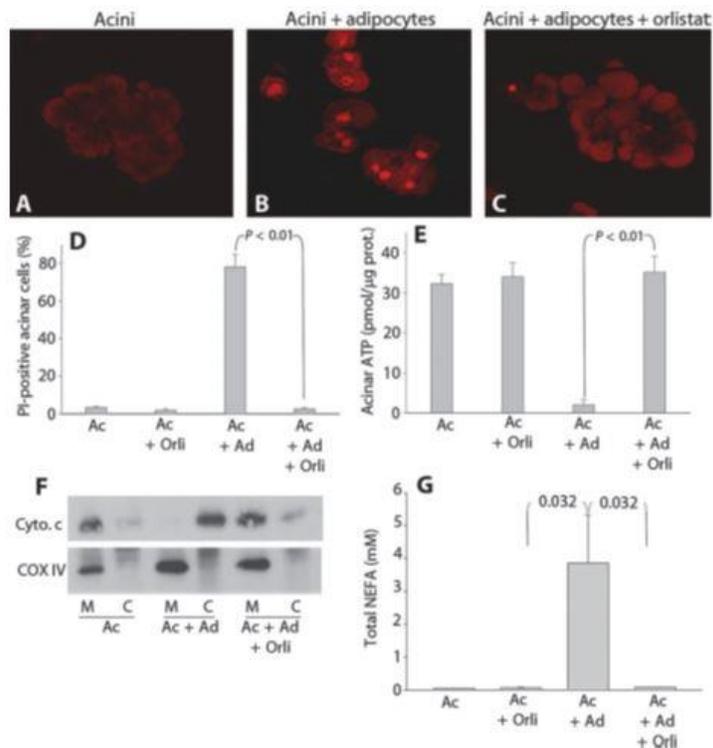


Figure 2: *In Vitro* Co-Culture of Acini and Adipocytes results in acinar necrosis. A to C show propidium iodide (PI) uptake in control acini (A), acini cocultured with adipocytes (B) or with adipocytes along with 50 μM orlistat (C). (D) Percentage of acinar cells which are positive for PI uptake in co-culture with adipocytes (Ac+Ad) are higher compared to acini cultured alone (Ac), with 50 μM orlistat (Ac+Orli), or 50 μM orlistat (Ac+Ad+Orli) in co-culture. (E) ATP levels in acinar cells treated as in (D) show a reduction in ATP level in the co-culture. (F) Cytochrome C (upper panel) in mitochondrial (M) and cytoplasmic (C) fractions of Ac, Ac+Ad, and Ac+Ad+Orli, show a migration from the mitochondrial compartment to the cytosolic compartment only in the Ac+Ad group. Mitochondrial marker COX IV (lower Panel) is similar in all groups. (G) Total NEFA concentrations in the medium of acini cells treated as in (D), show increased NEFA in Ac+Ad only. Republished with permission from (62).

The pancreatic lipases released from the acinar compartment diffuse through the transwell into the adipocyte compartment causing an increase in free fatty acids, which in turn diffuse into the acinar cell compartment resulting in acinar cell necrosis (4), seen as increased propidium iodide uptake, a drop in ATP levels, cytochrome C leakage and an increase in NEFA levels (**Figure 2**) (62). The lipase inhibitor orlistat prevents all these changes in the co-culture system.

Mossner et. al in 1992 showed the direct deleterious effect of long chain unsaturated fatty acids on pancreatic acini (60). Recently, Navina et. al showed that linoleic acid, oleic acid and linolenic acid were particularly toxic to acinar cells, while the saturated fatty acids palmitic acid and stearic acid were not (62). Incubation of

acinar cells with VLDL also results in an increase in free fatty acids, resulting in necrotic injury. (92) When acinar cells are stimulated with individual fatty acids, cytosolic calcium concentrations, released from an intracellular pool, are increased only with unsaturated fatty acids (**Figure 3**) (62).

Unsaturated fatty acids also cause leakage of lactate dehydrogenase, leakage of cytochrome C into the cytoplasmic fraction and inhibition of mitochondrial complexes I and V, causing a drop in ATP levels to induce necrotic cell death (**Figure 3**) (62, 71). Unsaturated fatty acids at sublethal concentrations also up-regulate mRNA levels of inflammatory mediators and thus are pro-inflammatory (62).

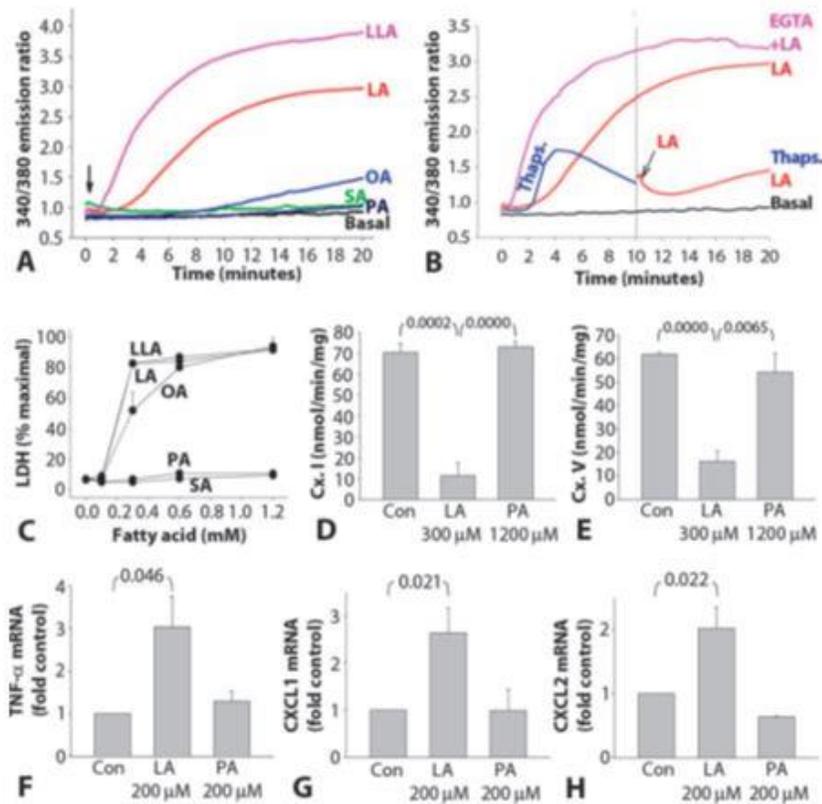


Figure 3: Unsaturated fatty acids induce acinar necrosis and inflammatory mediator generation. (A) Intracellular calcium concentrations (expressed as 340/380 emission ratio) in response to addition (arrow) of 600 μ M fatty acids (LLA, linolenic acid; LA, linoleic acid; OA, oleic acid; SA, stearic acid; PA, palmitic acid), showing release of intracellular calcium only with unsaturated fatty acids – LLA, LA and OA (B) Effect of depletion of endoplasmic reticulum calcium with thapsigargin (1 μ M) (blue line) and depletion of extracellular calcium by chelation with EGTA (1 mM added 10 min before adding linoleic acid, pink) on 600 μ M linoleic acid– induced intracellular calcium increase. (C) Leakage of Lactate Dehydrogenase (LDH) from acinar cells 5 hours after treatment with fatty acids as in (A). Unsaturated fatty acids cause releases of LDH, while saturated do not. (D and E) Effect of linoleic and palmitic acids on mitochondrial complex (Cx.) I and V activity in acini. Linoleic acid paralyzes Cx. I and V, while palmitic does not. (F) Effect of linoleic and palmitic acids on TNF- α mRNA in acini. (G) Effect of linoleic and palmitic acids on CXCL1 mRNA in acini. (H) Effect of linoleic and palmitic acid CXCL2 mRNA. Linoleic acid but not palmitic acid causes an increase in all three. Republished with permission from (62).

Exposure of peripheral blood mononuclear cells to unsaturated fatty acids at concentrations lower than those in the serum during SAP, results in their necro-apoptotic cell death (71).

In Vivo Models of Obesity Associated Severe Acute Pancreatitis

Role of Intra Pancreatic Fat (IPF) in Pancreatic Necrosis

Histologically, several studies show pancreatic acinar necrosis to border fat necrosis (48, 62, 66, 76, 87). Those studies analyzing intrapancreatic fat

in human autopsy samples (4, 48, 62, 69, 86, 87), surgically resected samples (83) and radiological appearance of pancreas (58, 86) show intrapancreatic fat to be increased with BMI. Intrapaneatic fat amounts in obese individuals are on an average, two fold higher than non-obese individuals (86). Analysis of pancreatic adipocyte triglyceride composition in humans showed increasing amounts of unsaturated triglycerides with higher amounts of fat. (80) Pancreatic necrosis fluid collected from obese patients with necrotizing pancreatitis had higher nonesterified fatty acid concentrations compared to patients with

pseudocysts and cystic neoplasms, who had a lower BMI (28, 62, 71, 73).

Several *in vivo* models have contributed to our understanding of the role of intrapancreatic fat in severe acute pancreatitis outcomes (28, 62). Obese mice have increased intrapancreatic fat (about 30% of total pancreatic area) resulting in lethal severe acute pancreatitis in response to IL-12, IL-18 that is associated with increased acinar necrosis (62). In these mice, a significant amount of pancreatic acinar necrosis (60-70% area) occurs in areas surrounding the fat necrosis, which is termed peri-fat acinar necrosis (PFAN). This PFAN contributes to about half the total acinar necrosis in these obese mice (62). In contrast, lean mice have less intrapancreatic fat, PFAN and have non-lethal SAP (62). Grossly obese mice have chalky white deposits of saponification, consistent with fat necrosis histologically (62). Evaluation of the triglyceride composition of adipose tissue in these obese mice show unsaturated fatty acids to be significantly increased in obese mice compared to lean mice, with a corresponding relative decrease in saturated fatty acids (62, 76). Normally, visceral fat pads of obese mice have about 70-80% unsaturated fatty acids which is significantly more than in lean mice which have about 50-60% unsaturated fatty acid content (62, 76).

The role of acute lipolytic generation of fatty acids on local pancreatic severity has been studied recently by Durgampudi et. al by injecting unsaturated triglyceride into the pancreato-biliary duct to increase intra pancreatic fat (28). Intraductal triglyceride injection followed by duct ligation, allows for triglyceride to be mixed with pancreatic lipases as would occur with basolateral leakage during acute pancreatitis, causing subsequent lipolysis of glyceryl trilinoleate mimicking intrapancreatic fat necrosis seen in obese patients with SAP (4, 62). Ligation of common bilio-pancreatic duct results in elevated amylase, lipase, bilirubin and ALT, fulfilling all the criteria of mild biliary AP. Intraductal injection of the triglyceride glyceryl trilinoleate (GTL), in amounts equivalent to about 10% of intrapancreatic fat,

along with duct ligation, results in severe hemorrhagic pancreatic necrosis with about 70% necrosis of the pancreatic acinar tissue, multisystem organ failure and mortality (28). This acinar parenchymal damage is prevented by inhibition of GTL lipolysis to linoleic acid by Orlistat (28). This inhibition does not affect the increase in serum amylase, bilirubin or ALT which mark biliary AP. Thus, in an animal model simulating biliary AP (classically regarded as a severe AP model), it was shown that outcomes are unrelated to the etiology of AP and intrapancreatic fat is a modifier of outcomes, converting mild AP to SAP (28). Hence, in obesity associated SAP, extracellular basolateral unregulated release of pancreatic lipase consequent to an initial insult may cause lipolysis of intrapancreatic fat, resulting in an increase in free fatty acids, which directly damage the acinar cells, causing necrosis.

A surge in systemic unsaturated fatty acids also results in significant mortality in these experimental models (28, 62, 76), similar to the trend of a rise in free fatty acids, particularly unsaturated fatty acids in the sera of patients with SAP (96). Prevention of lipolysis results in reduction in free fatty acids and systemic inflammatory markers (28, 62, 76). As noted in the spectrum of human SAP, obese animals or animals with higher unsaturated fatty acids generated by the lipolytic surge are more prone to multisystem organ failure in the form of renal failure and lung injury. Renal injury manifests as fat containing tubular vacuoles, tubular apoptosis and necrosis, along with mitochondrial swelling, expression of kidney injury molecule-1 (KIM-1) with associated functional renal injury in the form of high blood urea nitrogen (BUN) levels (28, 62, 76). Lung injury is manifested as increased apoptotic cells and lung myeloperoxidase levels (62, 76). Several isolated studies have previously shown intravenous oleic acid to cause acute respiratory distress syndrome with lung myeloperoxidase increase and apoptosis (39, 40, 49, 108). Unsaturated fatty acids are also known to cause elevation in the serum creatinine and cause renal tubular toxicity (108). This is also associated with release of pro inflammatory cytokines, which

have been reported to be increased in human SAP (8, 11, 23, 24, 37, 59, 102, 107). Recent studies from Closa et. al in rats showed unsaturated free fatty acids generated in peritoneal adipose tissue during pancreatitis to accumulate in ascitic fluid, and cause the release of inflammatory mediators that contribute to the progression of the systemic inflammatory response seen in severe acute pancreatitis (35).

In contrast to the intrapancreatic fat of obesity, the pancreatic fat present in chronic pancreatitis patients is rarely associated with severity during pancreatitis (17, 51, 53, 64, 70, 93, 104). A common feature of patients with chronic pancreatitis is fatty replacement of the pancreas after recurrent attacks of acute pancreatitis (82). Secondary fat replacement in chronic pancreatitis is independent of BMI and is associated with fibrosis which causes a protective walling off effect from the adipocyte-acinar lipolytic flux generated during acute pancreatitis (4, 62). This is supported by observations that chronic pancreatitis patients rarely die from acute pancreatitis or its related complications (51, 65, 70). Acharya et. al have showed that unlike obesity associated intrapancreatic fat which worsens acute pancreatitis outcomes, intrapancreatic fat accumulation in chronic pancreatitis is less prone to fat necrosis or surrounding parenchymal damage (4). In reference to fatty acid ethyl esters (FAEEs), it is noteworthy that the landmark study documenting high FAEE amounts in the pancreas of humans at autopsy clearly states that they had no pancreatitis. The study was done on alcoholics who had died from unrelated causes such as motor vehicle accidents (52). Criddle et. al have also shown that it is the conversion of FAEEs to FFAs which results in cell injury (22). This is supported by our studies in which we note the parent fatty acids to be much more toxic than FAEEs (unpublished data). Thus while the role and relevance of FAEEs to AP outcomes is unproven, and the human and experimental data mentioned above strongly support the lipolytic generation of UFAs to convert AP to SAP in obesity.

Role of Peri Pancreatic Fat in Severe Acute Pancreatitis

Visceral adipose tissue, such as surrounding the pancreas, contributes to about 10 to 30 % of the intra-abdominal area (15). This adipocyte mass can provide a potentially hydrolyzable pool of triglycerides during acute pancreatitis. Adipocytes normally consist of more than 80% fat, stored in the triglyceride form (99). Unregulated release of pancreatic lipases during an acute attack of pancreatitis can result in the breakdown of these triglycerides causing release of very high amounts of free fatty acids, resulting in adverse outcomes.

Obesity is considered as a proinflammatory state. A recently published study by Patel et. al has shown a traditionally mild model of caerulein acute pancreatitis to have severe outcomes in obese but not lean mice (76). Mortality in obese mice is associated with fat necrosis and peritoneal saponification, hypocalcemia, an intense cytokine response, lung injury and renal failure which are all commonly used markers in known severity scoring/predicting systems of acute pancreatitis (10, 76). Visceral fat pads of obese mice with AP showed the presence of active pancreatic lipases (76). The amount of pancreatic necrosis was not significantly different in the lean vs. obese vs. orlistat treated groups. However both the lean and orlistat treated groups had reduced fat necrosis, lack of sustained organ failure, a transient cytokine response and improved survival. Histologically, the areas of fat necrosis were surrounded by intense accumulation of polymorphonuclear neutrophils and macrophages (35, 76) suggesting that these necrotic areas of adipose tissue generate and release inflammatory mediators that contribute to the progression of the inflammation during SAP (76).

A recent study by Noel et. al (71) helped distinguish between the acute unsaturated fatty acid mediated lipotoxicity during SAP from the chronic inflammatory state of obesity. For this the amount of peri-pancreatic triglyceride was acutely changed by administration of triolein (the triglyceride of oleic acid, which is the most abundant UFA in visceral

fat) in lean rats with caerulein pancreatitis. This resulted in acute lung and renal injury with minimal pancreatic necrosis and an intense cytokine response, all of which were prevented by inhibiting lipolysis. Conversely, while the co-administration of the cytokines IL8 and IL-1 β , which are also increased in pancreatic necrosis collections, did cause pyrexia, they did not lead to any adverse outcomes. Thus peri-pancreatic fat necrosis may worsen inflammation and AP outcomes independent of the baseline proinflammatory state of obesity (71).

In summary we have learnt that obesity worsens the outcomes of acute pancreatitis due to the acute lipolytic generation of unsaturated fatty acids. This is unrelated to the baseline pro-inflammatory state of obesity and unrelated to the etiology of AP.

While the hydrolysis of intrapancreatic fat by pancreatic lipases contributes to pancreatic necrosis in obesity, in chronic pancreatitis fibrosis reduces this lipolytic flux and resulting severity of recurrent AP attacks. Necrosis of the large amounts of peripancreatic fat can worsen AP outcomes independent of pancreatic necrosis. These observations mimic human disease, support obesity as modifier of outcomes, and also suggest a different way to design and interpret models of AP which are not directly linked to the etiology.

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