Relationship between obesity and pancreatitis

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Acute pancreatitis (AP) has several etiologies and diverse outcomes. The outcomes may range from spontaneous resolution of an acute attack which may never recur again, to a disease which over a few days may progress to severe acute pancreatitis (SAP) resulting in prolonged hospitalization for local or systemic complications, and sometimes mortality. Several studies have reported obese patients, who have increased visceral fat depots, including pancreatic fat, as being at risk of SAP (1, 22, 37, 42, 89, 95, 100, 109, 117, 119, 149). Repeated attacks of AP may result in a clinical picture of recurrent acute pancreatitis which may progress to chronic pancreatitis (CP) with an associated increased in pancreatic fat (70, 86, 146). However, while being potentially debilitating due to pain, exocrine insufficiency, diabetes or quality of life issues, recurrent acute or chronic pancreatitis rarely result in SAP (70, 87, 92).

SAP typically occurs during the first or second AP attack (2, 70). The disease spectrum of SAP includes local complications, primarily pancreatic necrosis (PN) and peripancreatic necrosis (PPN) which sometimes get infected, and systemic complications including organ failure involving the respiratory, renal systems and a shock like state. Local complications from extensive PN or PPN, or systemic complications lasting > 48 hours (sustained organ failure) or involving more than one organ system (multisystem organ failure) can result in prolonged hospitalization or mortality. While obese patients are prone to both local and systemic compilations in AP, no consistent relationship has been reported between the etiology of AP and SAP (21, 116, 137, 143) with the exception of hypertriglyceridemic pancreatitis (31, 33, 72). This association and reports that obese patients may have worse outcomes in AP suggest a common lipid related modifier to alter the course of acute pancreatitis for the worse. Over the last 150 years, investigators have repeatedly broached the role of fat and the cells that contain it i.e. adipocytes in pancreatitis. The reports have ranged from gross descriptions of the appearance of the peritoneal cavity in patients dying from severe pancreatitis to the molecular mechanisms by which fatty acids may mediate these outcomes. Within this spectrum are studies of the influence of adipocytes on the histological appearance of pancreatitis, animal models of obesity and pancreatitis and cell culture models of lipotoxicity. In this chapter we will systematically explore the role that fat may play in the outcomes of pancreatitis especially in the context of obesity.

1. Historical Perspective

The relevance of obesity to acute pancreatitis was first documented in the 19th century. Balser in 1882 first indicated the presence of fat necrosis in acute pancreatitis (7). In 1889, while writing on acute pancreatitis in the *Medical Monographs,* Dr. Reginald Fitz quotes Zenker as stating "An excessive growth of the fat cells near the pancreas occurs in many men. It may become so excessive, in very fat people, that a large part of the abdominal

fat dies, and if this proves fatal, whether on account of the quantity destroyed or the associated hemorrhage" (39). Simon Flexner is 1896 was the first to suggest the role of lipases in pancreatitis associated fat damage (94). While Fitz mentions that Hans Chiari also noted the association between fat and pancreatitis (39), Chiari, widely known for the hypothesis of the pancreas auto digesting itself during pancreatitis (thus pioneering the proteolytic hypothesis of pancreatitis), published only later on this topic (23) as did others (53). More details of the early observations of fat in pancreatitis are mentioned in the work by Dr. Fitz (39) and are well summarized in more recent reviews (94).

Chemical analysis of pancreatic fat necrosis was initially performed in the early part of the 20th century (50) and revealed this to be predominantly free fatty acids with some saponification and calcium soaps. In the 1970s several independent investigators systematically explored the association between fat and pancreatitis. There were several elegant studies on the lipolytic pathogenesis (126), morphology (122) hypocalcemic complications (126) and therapeutic interventions (125) in animal models of fat necrosis. Quantification of fat cells in the pancreata of humans at autopsy showed the adipocyte amount to increase with body weight (90, 113). Studies in the 1980's by Schmitz-Moormann on pancreatic tissue from patients with acute pancreatitis showed pancreatic parenchymal and vascular damage to be in close proximity to fat cell necrosis (112). Kloppel made similar observations (67) in the peripancreatic fat of patients with acute pancreatitis, and both investigators hypothesized fat necrosis to be the initiating factor in human pancreatitis. This topic was debated and contrasted to the ubiquitous nature of active proteases in all models of pancreatitis, while the earlier use of pharmacologic protease inhibitors like trasylol and gabexate focused attention on proteases (129-131) preceding the focus on lipases. However as we have learnt over time, targeting proteases has provided no clinically

relevant improvement in outcomes (4, 16, 118). The discovery of the lipase inhibitor tetra-hydrolipistatin (THL) in the 1980s, from which orlistat is derived renewed interest in understanding the role of lipolysis in pancreatitis. *In vitro* studies by Mossner et al in the 1990s showed a protective effect of lipase inhibition on pancreatic acinar cells *in vitro* (81) but not when pancreatitis was induced by infusing bile salts such as sodium taurocholate into the pancreatic ducts of rats (65). Subsequent to this, there was a gap in the pursuit of systematic studies on the role of fat in pancreatitis, however the steady stream of clinical reports repeatedly mentioning intrabdominal fat/ viseral fat/obesity as being risk factor for SAP over this time has revived interest in this topic as we will discuss below.

2. Epidemiology of Obesity and Pancreatitis

Several studies have associated obesity or increased intra-abdominal fat with SAP (1, 22, 37, 42, 89, 95, 100, 109, 117, 119, 149). Body mass index (BMI) is commonly used as a measure of body fat amount. Apart from BMI, visceral adipose tissue, as measured by waist-to-hip ratio and waist circumference above ideal cut-off value have been proposed as risk factor for worse outcomes in AP (73, 76). Waist circumference has been shown to correlate with intra-abdominal fat volume (17) and is reported as being a risk factor for SAP (109).

Obesity is defined as a BMI of >30 kg/m^2 in the western hemisphere or >25 kg/m^2 in the East including countries such as Japan, Korea, China and India. Studies exploring the association of BMI with SAP from these regions commonly correlate severity of AP to these BMI cut offs. BMIs >30kg/m^2 are mentioned as being associated with SAP in reports from north America and Europe (15, 49, 62, 63, 100, 117) while reports from Asia mention BMIs > 23-25 kg/m^2 (119, 124, 148, 149) to be associated with SAP. The reason for this association is unclear. Previous studies have shown that fat composition in humans is related to

the fat composition of their diets. This observation may link the eastern diets and the visceral adipose tissue of the populations that consume these diets to be richer in unsaturated fatty acids particularly poly unsaturated fatty acids (PUFA) (58, 108, 115, 134) compared to the west (57, 58, 115). An example is that the high PUFA diets of Korean monks was associated with higher PUFA in visceral fat than in American soldiers whose diet was lower in PUFA (115). The relevance of this to AP outcomes is supported by the correlation between dietary fatty acid composition and adipose tissue fatty acid composition(52, 115) and the findings that unsaturated fatty acids (85, 97), especially PUFAs (34, 83) are relatively more toxic than saturated fatty acids during pancreatitis.

Characteristics of Visceral Fat in Obesity Associated SAP

Total body fat may comprise more than 30% of the body weight in obesity (36). Fat accumulation can occur in the subcutaneous and viseral compartments, and while there are case reports of fat necrosis distant from the pancreas during pancreatitis, including osseous (45, 84) and subcutaneous fat (11, 18, 114) associated with detectable pancreatic lipases (18, 138); the principal fat depots commonly affected in pancreatitis are the intra-abdominal or visceral ones which are in close proximity to the pancreas. The sites of visceral fat deposition include the mesentery, omentum, liver (55, 96), the pancreas and peripancreatic space (8, 90, 107, 110, 113). Visceral fat averages more than 3% body weight in obese humans (24, 30), and thus contributes a large potentially hydrolysable pool for fat necrosis in SAP.

Supporting the human pathologic findings from the 1980's (67, 112), recent studies have noted that both extrapancreatic (6) and intrapancreatic fat necrosis (2, 83) are associated with an increase in severity of pancreatitis. The evidence comes from both radiologic studies (6, 78) and ones using histology of post mortem pancreata (2, 83) to systematically compare pancreatic parenchymal and fat necrosis with the severity of pancreatitis.

Extrapancreatic fat necrosis is a part of necrotizing pancreatitis (9, 40), the revised Atlanta criteria (9), radiographic scoring systems for SAP (e.g. Schroeder and Balthazar) (8, 111), and correlates with worse outcomes during AP (12, 78, 120).

Fat within the pancreas, that is intrapancreatic fat (IPF) has been shown to increase with BMI in studies analyzing autopsy samples (90, 110, 113), surgically resected samples(107), and radiological appearance of the pancreas (74, 110). The distribution of fat is fairly uniform in the dorsal pancreas and is reduced in the ventral pancreas (113). Uneven fatty replacement in the pancreas is infrequent (3.2%), and the pattern of fat distribution is not influenced by obesity (74).

White adipocytes, which are the major cell type comprising visceral fat in obesity, are predominantly composed of triglyceride, which in a pure form has an extremely high concentration of about 1 molar, and forms 80-90% of adipocyte mass (43, 103, 127). As we shall note in the section of pathophysiology, the generation of unsaturated fatty acids from the lipolysis of this triglyceride has been mechanistically associated with adverse outcomes in SAP. Recent studies systematically quantifying the amount of IPF in control pancreata and patients with pancreatitis noted the percentage area occupied by adipocytes correlated with, and significantly increase with BMI (2, 83). Patients with a BMI >30 had significantly higher IPF (18.3 ± 2.3%) compared to those with a BMI <30 (10.2± 1.9%). These values were similar to AP patients in the respective BMI categories suggesting that the amount of IPF does not influence the risk of developing AP. Patients who had SAP associated with pancreatic necrosis however had higher IPF (23.4±4.3%) and BMIs (40.0±2.8 Kg/m^2) compared to those with mild disease (7.8±1.9% and 30.3±2.5 kg/m^2 respectively). As we shall see later, the higher amount of IPF may modify of AP outcomes for the worse.

Interestingly, in contrast to obesity associated IPF, the IPF increase noted in chronic pancreatitis (CP)

(20, 71, 121, 135), is rarely associated with SAP (70, 87, 92). Fatty replacement is commonly known to occur in chronic pancreatic diseases over the course of several years, which in some cases may start in utero (60, 106). These diseases include Shwachman-Diamond syndrome (128), cystic fibrosis (106) and Johannson-Blizzard syndrome (106). While AP may result in mortality over days (6, 91, 136), mortality in CP is rarely attributed to AP (70, 87, 92) over the several years duration of the disease. A recent detailed morphometric analysis comparing AP to CP noted that unlike the IPF associated with obesity which worsens AP, IPF accumulation in CP is independent of BMI (2, 3). Moreover, a large proportion of CP associated fat is walled off by fibrosis from the rest of the pancreatic parenchyma resulting in a reduction of the "lipolytic flux" between adipocytes and acinar cells (discussed in more detail in the pathophysiology section), which during AP causes peri-fat acinar necrosis, contributing to about half of the parenchymal necrosis in obese patients (2, 83).

Chemical analysis of pancreatic fat in normal pancreata has shown an enrichment of unsaturated fatty acids in the pancreatic triglyceride from individuals with higher amounts of pancreatic fat (99) compared to those with lesser amounts. Pancreatic necrosis debridement fluid has a higher concentration of unsaturated fatty acids (34, 83, 85, 93). These observations along with the predisposition of obese patients to have a severe AP attack (1, 22, 37, 42, 89, 95, 100, 109, 117, 119, 149), the higher serum levels of UFAs reported in patients with SAP (123), SAP being reported at lower BMIs from countries with higher UFAs or PUFA in their diets and visceral fat (119, 124, 148, 149) support an association between lipolysis of viseral triglyceride enriched in UFAs with SAP. The mechanisms of this phenomenon are discussed in the section on pathophysiology below.

3. Pathophysiologic Role of Obesity Related Fat in SAP

Adverse outcomes early in the course of the SAP are typically related to distant organ complications such sustained respiratory, renal failure or shock (61, 75, 79). Those later in the disease course are typically associated with complications of severe pancreatic necrosis (19, 41, 44, 82) including infection and the organ failure associated with it. Here we will systematically explore each of these in the context of obesity.
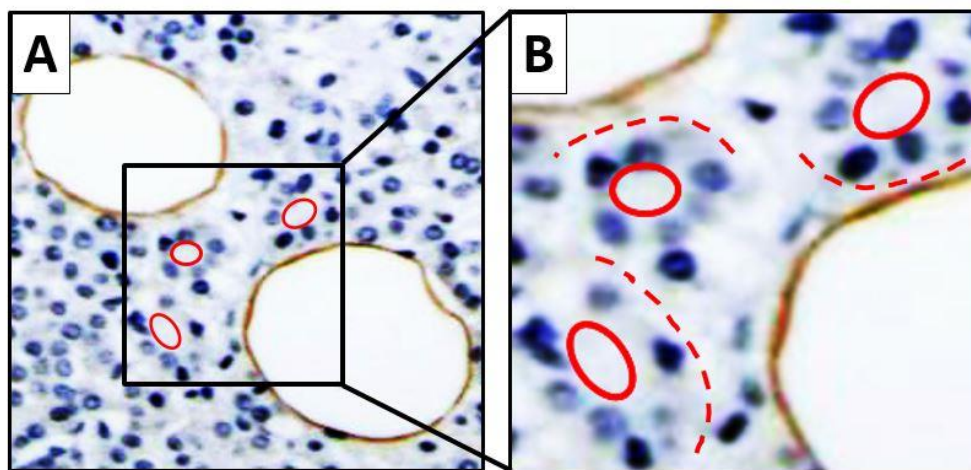

Figure 1: Immunohistochemistry for Perilipin1, showing brown staining adipocytes in the human pancreas. A: The apical lumen of the exocrine pancreatic cells (red ovals) into which pancreatic enzymes are secreted face away from the adipocytes. It is the basal surfaces of the exocrine acinar cells (red dashes) that abut the adjacent adipocytes.

Role of Pancreatic Fat in Exacerbating Pancreatic Necrosis

As detailed in the section above, both histologic and radiologic quantification show Intrapancreatic adipocyte mass to increase with BMI in the human pancreas (2, 83, 110). Unsaturated triglyceride is higher in human pancreata with a larger number of adipocytes (99), and pancreatic necrosis collections from obese patients have higher UFA concentrations than pancreatic fluid from pseudocysts and pancreatic cystic neoplasms (85), which are typically from patients with lower BMIs compared to patients with necrotic collections. These observations along with the epidemiologic data mentioned above associating obesity with SAP supports the need for further mechanistic exploration of this area.

The first question these observations bring is how do pancreatic fat and the exocrine pancreas interact in health and disease? Most obese persons will live life without experiencing an episode of pancreatitis. While adipocytes which accumulate in obesity are adjacent to cells of the exocrine pancreas **(Figure 1A)**, it is the basal surface of the exocrine cells which abuts the adipocytes (red dashed arcs in **Figure 1B**), and the apical lumen into which the exocrine cells pour their secretions (red ovals) is not in contact with the adipocytes. Thus the two compartments do not communicate normally. Paraffin embedded sections show adipocytes in the pancreas to have a clear cytoplasm consistent with the wash out of triglycerides from these cells during processing **(Figure2A)**. In contrast, during AP some adipocytes take on an amorphous blue appearance on Hematoxylin and Eosin staining consistent with fat necrosis **(Figure 2C)** and there is loss of cellular detail of the surrounding exocrine parenchyma, with a morphological appearance of parenchymal necrosis termed peri-fat acinar necrosis (PFAN) (2, 83). Consistent with the observations from the early 20th century of fatty acids generated in fat necrosis being saponified (50), staining of serial sections of these areas for calcium (e.g. using the Von Kossa method) shows intense brown staining of the fat necrosis.
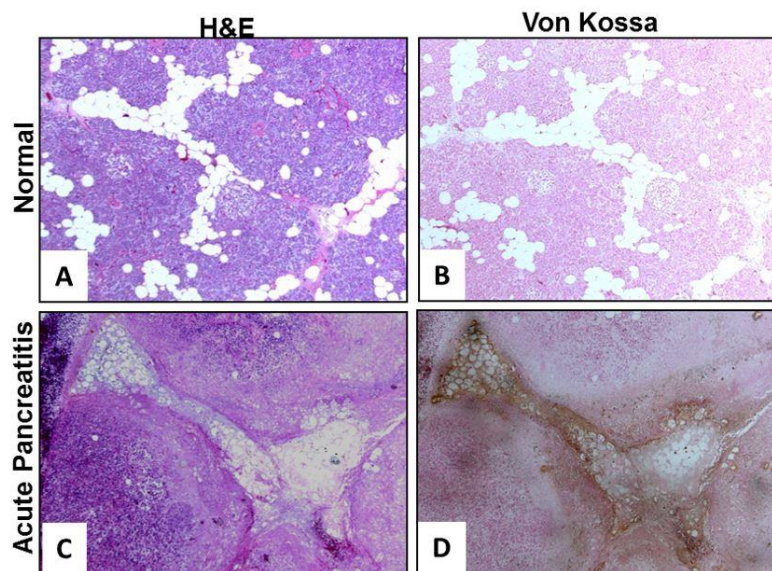

Figure 2: Serial sections of human pancreas stained with Hematoxylin and Eosin (H&E) and calcium (von Kossa). Normally the adipocytes stain as clear empty round areas and the exocrine parenchyma adjacent to the adipocytes retains its morphological detail (A) and is von Kossa negative (B). In pancreatitis fat necrosis of the adipocytes appears amorphous blue (C), with the adjacent parenchyma losing its morphological detail and appearing diffusely pink consistent with necrosis. This is termed peri-fat acinar necrosis (PFAN). Von Kossa staining (D) is intensely positive in the necrotic fat, and adjacent PFAN, with the staining progressively becoming weaker with increasing distance from the fat necrosis. Modified from (2).
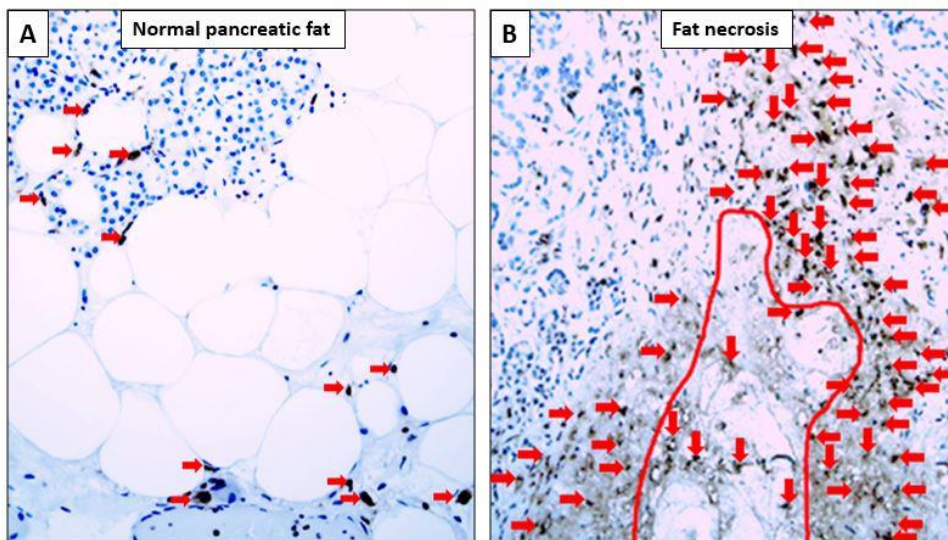
Figure 3: Human pancreas staining for macrophage marker CD68. While there are a few CD68 positive cells (red arrows) around the adipocytes in a normal pancreas (A), sections from pancreatitis patients (B) show areas of fat necrosis (red polygon) and surrounding PFAN to have a large increase in CD68 positive cells supporting the pro-inflammatory and ante-mortem nature of fat necrosis.

Interestingly, this brown staining is not restricted to the fat necrosis and is also positive in the necrotic parenchyma in close proximity to the necrosed fat. The staining becomes less intense with increasing distance from the fat necrosis suggestive of spillage of the products of fat necrosis, i.e. free fatty acids (FFAs) into this PFAN (2, 83). The pathophysiologic relevance of this observation is supported by the intense inflammatory reaction and accumulation of CD68 positive macrophages in and around the PFAN, compared to what is normally seen in pancreatic fat **(Figure 3)**. This inflammatory response also supports the ante-mortem nature of pancreatic fat necrosis in humans. Previous immuno-histochemical studies have shown the presence of pancreatic lipases in fat necrosis (38), suggestive of their mechanistic role in fat necrosis. Basolateral leakage of pancreatic enzymes has been mechanistically studied in detail, and while the polarized acinar cells normally pour their exocrine secretions into the lumen, during pancreatitis there is loss of this polarity with basolateral release of digestive enzymes (25, 26). This phenomenon potentially explains the basolateral leakage of lipases into fat during pancreatitis resulting in the ensuing lipolysis of fat, with consequent fat necrosis, generation of

a high concentration of FFAs locally, eventually culminating in PFAN.

Proof of this "lipolytic flux" between acinar cells and adipocytes being relevant to pancreatic injury during AP is provided by studies using a co-culture system of these two cell types. In this system suspension cultures of acinar cells and adipocytes are physically separated into two different compartments by a 3 micron grid, which allows macromolecular diffusion (2, 83) without contamination of one compartment by the other cell type. This system simulating basolateral release, allows for pancreatic lipases to increase in the adipocyte compartment and lipolytic products including FFAs and glycerol generated by hydrolysis of adipocyte triglyceride, to thereby increase in not only the adipocyte compartment, but also to diffuse into the acinar compartment. The increase in FAAs in the acinar compartment causes necrosis of these cells, as evidenced by prevention of FFA increase and necrosis by the lipase inhibitor orlistat. The pathophysiologic relevance of this *in vitro* system is supported by the Von-Kossa positive areas in PFAN noted in histologic sections of human AP [**Figure 2C, D**, (2, 83)], and is proven further by induction of acinar

necrosis by direct exposure to UFAs at concentrations present in human pancreatic necrosis collections (2, 34, 83, 85). Further proof is provided by *in vivo* models in which intraductal injection of the unsaturated triglyceride glyceryl trilinoleate (GTL) results in severe pancreatic necrosis, which is prevented by inhibition of its lipolysis to linoleic acid (34) by orlistat. The mechanism of UFA induced acinar cell necrosis has been shown to be the inhibition of mitochondrial complexes I and V, resulting in a drop in ATP levels (83). While the intermediary signaling involved in this lipolytic flux and fatty acid induced acinar injury described above is yet to be determined, the existing level of evidence regarding the detrimental role of obesity associated fat necrosis in worsening pancreatic necrosis, some of which is cited above is extremely strong. Thus the increase in pancreatic fat during obesity worsens pancreatic necrosis via fat necrosis in those of whom develop AP.

Role of Peri-Pancreatic Fat in Exacerbating Systemic Complications during SAP

Early mortality in SAP, i.e. within the first week, may occur from multisystem organ failure (MSOF) (61, 75, 79) with minimal or no evidence of pancreatic necrosis. Recent clinical reports (6, 12, 111, 120) and the revised Atlanta criteria (9) mention peripancreatic necrosis as a risk factor for SAP. Early severe peri-pancreatic fat stranding is associated with SAP (35, 66) including organ failure, mortality and longer duration of hospital stay (78). While AP associated mortality is currently quoted at 1-3% (98, 139, 145), recent studies show isolated extrapancreatic necrosis with no radiologic evidence of pancreatic necrosis to have mortality rates of 9-13% (6, 78).

Extrapancreatic or peripancreatic necrosis is predominantly fat necrosis around the pancreas (67, 68, 88). Gross and microscopic pathologic studies of surgically resected human pancreata early in the course of pancreatitis were systematically done in the 1980s by different groups including Nordback et al in Finland (88), Kloppel et al (67, 68), and separately by Schmitz-Moormann (112) from the Federal Republic of Germany. Conclusions from these studies supported fat necrosis, especially peri-pancreatic fat necrosis as the earliest lesion in acute pancreatitis. Nordback et al (88) categorically state, "The most vulnerable areas seemed to be the peripancreatic adipose tissue, from where the necrosis spread through the septa towards the pancreatic parenchyma". In their series of 78 patients with acute necrotizing pancreatitis they note that while all patients had peripancreatic necrosis, 10% had peripancreatic necrosis without acinar necrosis. Peripancreatic necrosis involved >50% of the peri-pancreatic fat in 23 of the 30 patients operated within 4 days of presentation, while only 8 of these had >50% of parenchymal necrosis. Supporting the role of systemic injury in SAP associated early mortality (61, 75, 79), autopsy studies showed patients dying within the first week of AP to have lung injury with moderate amount of fat necrosis around the pancreas (104). Overall, this information suggests peri-pancreatic fat necrosis to be a distinct player in the pathogenesis of multisystem organ failure during the initial few days of AP.

Visceral fat, which is the major hydrolyzable pool of triglyceride surrounding the pancreas has been quantified by various groups. It is estimated that this may average more than 3 Kg in persons with a body weight averaging 84 Kg (24, 30). Calculations from imaging studies estimate visceral fat to occupy 10-30% of the intra-abdominal abdominal area (17), and with intra-abdominal volumes of obese individuals estimated to be between 23-30 liters (46), the volume occupied by visceral fat can range from 2-9 liters. Since triglyceride comprises 80-90% of adipocyte volume (43, 103, 127), and each triglyceride molecule can generate three FFA molecules after lipolysis, unregulated leakage of lipases from the pancreas during pancreatitis can potentially generate large amounts of lipotoxic FFAs from these peripancreatic visceral fat depots in a short time and result in adverse outcomes.

Recently mechanistic studies have explored the role of peri-pancreatic fat necrosis in multisystem organ failure. Patel et al noted a classically self-limited model of pancreatitis in mice, i.e. caerulein pancreatitis, to be lethal in obese mice but not lean mice (97). Interestingly they noted that pancreatic acinar necrosis was no different in the groups that survived compared to non-survivors. In contrast, fat necrosis was absent in lean mice, significantly more in obese mice which died, and reduced by treating these mice with the lipase inhibitor orlistat. The most impressive changes at necropsy were noted in the abdominal fat surrounding the pancreas, with fat necrosis and saponification being noted in the mice which died; which resembles human disease. This was associated with hypocalcemia [a SAP marker/predictor included in the Ranson's (101), Glasgow criteria(10) and the Japanese severity score(132)] , lung injury and renal failure (evidenced by elevated BUNs), all of which are commonly used markers or predictors for SAP (10, 48, 101, 141). Further proof of the role of peri-pancreatic fat necrosis in worsening AP outcomes independent of pancreatic necrosis comes from a recent study where triolein [the triglyceride form of the most abundant UFA in humans i.e. oleic acid] when co-administred during the induction of caerulein pancreatitis in lean rats resulted in multisystem organ failure with 97% mortality (85). This was evidenced by hypoxemic respiratory failure (PaO2 < 89%) associated with acute lung injury, renal tubular injury along with elevated serum BUNs; all in the absence of significant pancreatic necrosis. Serum cytokines including IL-1ß and IL-8 in the rats with organ failure were more than 10x elevated than those with caerulein pancreatitis alone. All of the parameters described above are a part of SAP markers (5, 14, 28, 29, 51, 77, 102, 133) or prediction systems (10, 48, 101, 132, 141). To explore this further, the authors exposed peripheral blood mononuclear cells to UFAs IL-1ß +IL-8 (85, 97) and noted that while UFAs at concentrations below those noted in the serum resulted in necro-apoptotic cell death, cytokines at concentrations above those in the serum did not do so. This is consistent with findings that while UFAs can increase mRNA levels of cytokines and induce cell death (2, 83), cytokines do not induce cell injury and in some cases are hypothesized to have a protective role in acute pancreatitis (27, 47) and may do so by reducing systemic injury (13, 64, 105, 144, 147).

It is worth noting that in the studies mentioned above triolein was administered to lean rats and its hydrolysis resulted in high serum levels of its lipolytic product oleic acid (350±294 micromolar), similar to SAP patients with complications (614±146 micromolar) (123). These patients also had serum FFA >1400micromolar (123) which were in the same range as the rats dying with multisystem organ failure (1421 ± 851 micromolar). Thus it is the acute lipotoxicity from UFAs and not the chronic inflammatory state associated with obesity those results in adverse AP outcomes. Further proof of the role of UFAs in SAP comes from studies in which UFAs were administered to rodents in pure form. These showed UFAs to cause acute lung injury (54, 56, 69, 142), renal tubular toxicity (59, 80)renal failure (32, 142), and hypocalcaemia,(32); which is a spectrum of endpoints highly relevant to multisystem organ failure associated with SAP and parameters of which are used in grading AP severity (10, 48, 101, 132, 140, 141). Thus the acute release of large amounts of UFA by lipolysis of the large pools of peri-pancreatic visceral fat can worsen the course of the disease even in cases where there is minimal pancreatic necrosis, such as early in the course of the disease.

4. Summary

In summary we have studied the mechanisms resulting in excessive pancreatic or visceral fat necrosis during AP in obese patients, and how this may change the course of the disease for the worse. This occurs due to lipolysis of the viseral triglyceride by the leaked pancreatic lipases, resulting in a large and acute release of UFAs locally or systemically. The local release results in

inhibition of mitochondrial complexes I and V and pancreatic necrosis, while the systemic UFA release can result lung and renal injury culminating in multisystem organ failure. Thus unregulated lipolysis of visceral fat in obesity can convert acute pancreatitis to SAP.

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