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ROLE OF PANCREATIC FAT IN THE OUTCOMES OF PANCREATITIS

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Abstract

The role of obesity in relation to various disease processes is being increasingly studied, with reports over the last several years increasingly mentioning its association with worse outcomes in acute disease. Obesity has also gained recognition as a risk factor for severe acute pancreatitis (SAP) [1–8]. The mortality in SAP may be as high as 30% and is usually attributable to multi system organ failure (MSOF) earlier in the disease, and complications of necrotizing pancreatitis later [9–11]. To date there is no specific treatment for acute pancreatitis (AP) and the management is largely expectant and supportive. Obesity in general has also been associated with poor outcomes in sepsis and other pathological states including trauma and burns [12–14]. With the role of unsaturated fatty acids (UFA) as propagators in SAP having recently come to light [15] and with the recognition of acute lipotoxicity, there is now an opportunity to explore different strategies to reduce the mortality and morbidity in SAP and potentially other disease states associated with such a pathophysiology. In this review we will discuss the role of fat and implications of the consequent acute lipotoxicity on the outcomes of acute pancreatitis in lean and obese states and during acute on chronic pancreatitis.

INTRODUCTION

In the past decade the role of obesity and fats in relation to various disease processes has been studied. According to recent estimates, more than 1/3rd of US adults are obese (37.5%) [16, 17]. The annual medical costs associated with obesity were estimated at \$147 billion for 2008[18], and are projected to reach \$ 960 billion by 2030 [19].

Obesity has long been labelled an epidemic, with clinicians and scientists recognizing the deleterious effects of fats, be it the cardiovascular, gastrointestinal or renal system [20].

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Apart from its role in hypertension and atherosclerosis, in recent years scientists are understanding the role of free fatty acids (FFA) in nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), acute pancreatitis (AP) and also in various cancers [21–23].

Certain studies suggest the risk of SAP is 2–3 fold higher in obese than non-obese individuals [24]. Obesity is known to worsen AP outcomes [1–8], and the mortality associated with MSOF complicating SAP may be as high as 46% [25]. In obesity, it is the visceral and android fat distribution that has been known to predict severity of acute pancreatitis [26] and several recent articles emphasize the association of visceral fat with worse outcomes [5, 27–29]. Over recent years there has also been more recognition of fat within the pancreas (Intrapancreatic fat or nonalcoholic fatty pancreas), which has been investigated further [15, 30–34]. The temporal relationship between obesity and visceral fat, in particular pancreatic fat has been documented [34, 35], but the implications of pancreatic fat with reference to its proximity to pancreatic acinar cells and its toxic effects on acinar cells has only recently come to light [15, 32]. We know that fat is also increased within the pancreas in chronic pancreatitis (CP) [32, 36, 37], however no relationship has been recognized between obesity and CP.

In this article we will summarize our understanding on the recent advances on this subject (Table 1), discuss the implications of obesity and fatty pancreas on AP, the probable mechanism by which obesity effects outcomes in AP, is the role of systemic lipotoxicity with reference to SAP, and how fat in CP is different from fat in AP (Table 2).

PANCREATIC FAT AND ACUTE PANCREATITIS

The fat in adipocytes is composed of triglycerides, which are free fatty acids hinged to a glycerol backbone, forming >80% of adipocyte mass [38–40]. As one gets more obese (BMI>30), more fat accumulates in various areas in our body including within the abdominal viscera such as the pancreas [15, 34, 35] and also around the viscera. Saisho et al have shown that pancreatic fat increases with increasing BMI [34]. We have studied human pancreas autopsy samples of obese and non-obese controls and compared them with obese and non-obese patients with AP, and noted that the amount of intrapancreatic fat increased with increasing BMI in both controls and patients with AP [15, 32].

The mechanism by which obesity may influence AP is being explored. Fat adjacent to acinar tissue has been shown to be associated with parenchymal damage in AP [15, 32, 41, 42], and it has been shown that fat in the pancreas during acute pancreatitis, has a direct toxic effect on the pancreatic parenchyma [15, 32]. On human pancreatic samples we noted that necrosed adipocytes were surrounded by a zone of necrosed parenchyma, and the worst damage was immediately around the fat (peri-fat acinar necrosis; PFAN), with progressively less necrosis noted with increasing distance from the necrosed fat. PFAN is an ante-mortem phenomenon since it is surrounded by CD68 positive macrophages and was significantly more in patients with pancreatitis compared to controls. This PFAN was significantly higher in SAP and was the predominant form of necrosis noted on the autopsy samples [15]. The other form of necrosis noted, was isolated acinar necrosis i.e. necrosis in pancreatic

parenchyma not adjacent to the necrosed fat. This was found to be significantly lesser than PFAN in SAP. The sum of both forms, i.e. total necrosis, was also noted to be significantly higher in obese individuals who had SAP.

On a molecular level it is important to recognize the predominant free fatty acids (FFA) contained in visceral fat impact the severity of AP. It has been shown on fluid analysis of necrosectomy samples, which were from obese patients, that the predominant long chain fatty acids (up to 73%) were unsaturated fatty acids (UFA), comprising primarily of oleic acid and linoleic acid. This is similar to what other investigators have noted where UFA's accumulate in the pancreas adipocytes and can be 6–11 fold higher in necrosed pancreas samples as compared to a normal pancreas [33, 43]. Similarly, in obese patients with NAFLD the quantities of UFA's were noted to be significantly increased in abdominal fat [44]. Hence, there is sufficient evidence that the predominant fatty acids that accumulate in abdominal and visceral fat in obesity are UFA's, which ties in well with our current dietary trends and recommended daily allowance according to which the saturated fat should be <30% with correspondingly more unsaturated fat (<http://www.health.gov/dietaryguidelines/dga2000/document/choose.htm>).

The direct deleterious effects of UFA's on pancreatic acinar tissue have also been well documented [45]. Co-culturing mice acinar tissue with adipocytes [15] or activated pancreatic homogenates along with triglyceride [45], resulted in a significant amount of acinar necrosis, increased levels of lipase in the medium and resultant increase in FFA's. These were prevented by lipase inhibition. Addition of long chain unsaturated fatty acids alone caused acinar necrosis.[15, 45] Co-incubation of VLDL with acinar cells and cholecystokinin also resulted in an increase of FFA's [46]. More significantly, similar trends of increased FFA's in particular UFA's have been documented in sera of patients with severe acute pancreatitis [47, 48].

In studying the toxic effects of FFA's on mice pancreatic acini in more detail, we noted a rise in cytosolic calcium which was released from an intracellular calcium pool, fall in ATP levels with leakage of cytochrome c and inhibition of mitochondrial complexes I and V, confirming necrosis as the form of cell death induced by the FFA's[15]. The UFA's linoleic acid, oleic acid and linolenic acid were found to be toxic to acinar cells and not the SFA's palmitic and stearic acid[15, 45]. Of note, in these studies the levels of resistin were increased in response to lipolytic generation of FFAs, and mRNA levels of TNF- α and chemokines CXCL1 and CXCL2 were also up-regulated in response to linoleic acid and not palmitic acid.

Hence in SAP, after the initial insult, the extracellular release of lipase may cause lipolysis of IPF, with a consequent increase in FFA's, and resultant direct toxicity to the acinar cells causing necrosis (lipolytic flux). The localized spread of UFA's in the surrounding tissues (as evidenced by the presence of saponified fatty acids seen as positive von-Kossa staining in the exocrine parenchyma) results in the phenomenon of PFAN. Thus higher IPF in obesity is associated with more PFAN and worse pancreatic necrosis. The potential interaction between the adipocyte and acinar compartment in different disease states is summarized in the schematics shown in figure 1.

It would be worthwhile to mention that in the case of Hypertriglyceridemic pancreatitis where there is an abundance of substrate, different studies have shown worse outcomes in AP [32, 49–52]. This suggests the possible role of lipases, in influencing the outcomes of acute pancreatitis. Of the four different lipases in the pancreas [namely PTL (pancreatic triglyceride lipase), CEL (carboxyester lipase) and pancreatic lipase related proteins 1 and 2 (PLRP-1, 2)] [53], the exact lipase that contributes to lipotoxicity is yet to be determined. The mechanism by which the triglycerides are released from adipocytes is also yet to be determined exactly. In our previous studies of adipocyte and acinar cell co-culture, addition of a serine protease-specific trypsin inhibitor resulted in a 20% drop in the generation of glycerol. Hence trypsin apart from its traditional known role in acinar injury [54–59] could also be playing a role in adipocyte injury, and further studies to validate this are required.

PANCREATIC FAT AND CHRONIC PANCREATITIS

On studying the natural history of CP, it has been suggested to be a continuum of AP leading to recurrent acute pancreatitis (RAP) that eventually progresses to CP [60–63]. Progression from RAP to CP involves a change in the morphology of the pancreas with reduction in the pancreatic parenchymal mass, and its replacement with adipose tissue and fibrosis [64–66].

The differential roles of intrapancreatic fat in AP vs. CP are summarized in Table 2, and how fibrosis may influence the course of an acute exacerbation of CP is schematically shown in figure 1. A comparison of non-obese controls and non-obese CP showed that IPF was higher in CP [32]. The linear relationship that exists between IPF and BMI in obesity and AP is lost during progression to CP and for the same BMI patients suffering from CP may have a higher amount of IPF compared to their control counterparts. However, despite having a large amount of IPF the severity of acute attacks in CP are milder as compared to obese patients with AP, with mortality rarely being attributed to AP [62, 67, 68]. Interestingly, there have been case reports of AP and CP possibly being associated with the metabolic syndrome in children as no other etiology was observed [69]. Whether this remains true in adults remains to be determined.

Studies in the past have noted that fibrosis in CP can be 10 fold more than that of controls [70] with estimates suggesting that fibrous tissue may be up to 66% of the pancreatic area in CP [32, 70]. It is known that during CP, there is an induction of genes that transcribe TGF- β and other fibrogenic growth factors, which in turn stimulate pancreatic stellate cells (PSC) to produce extracellular matrix (ECM) and fibrous tissue [71, 72]. Several noxious stimuli may initiate fibrogenesis and the role of ethanol has been extensively studied in this phenomenon [73, 74]. There is also evidence that on cessation of alcohol, fibrogenesis could be partly reversed by induction of PSC apoptosis [75]. Apart from alcohol, animal models have shown that chronic high fat diets in rats induce fibrogenesis too [76, 77]. *In vitro* studies [78], rodent models using high fat diets [76, 79] and studies on tissue from patients with chronic pancreatitis support lipid peroxidation products to play a role in stellate cell activation and fibrogenesis. The predominant collagen present in fibrous tissue, produced by the PSC is type I collagen [80–82], with other components of the ECM being mainly proteoglycans. It has been shown that the arrangement of Type I collagen in the interstitial

matrix affects the diffusion of macromolecules across it [83]. Additionally, apart from being a physical barrier to macromolecular diffusion, electrostatic repulsive forces from collagen and proteoglycans may play a role in limiting diffusion [83].

In contrast to CP, there is minimal fibrosis in AP. Apart from the aforementioned changes, CP pathology is distinct in the relationship between fibrosis, fat and parenchymal tissue. During CP, large islands of adipose tissue are walled off from the acinar parenchyma by fibrous tissue, limiting interaction between the two compartments in contrast to AP, where lipolysis of unsaturated adipose tissue triglyceride releases UFA's that leach into the surrounding tissue and cause necrosis, as there is no fibrous tissue to limit the interaction.

While all these studies were performed on alcoholic or non-congenital etiologies of CP, Singhi et al recently studied the histopathology of PRSS1 hereditary pancreatitis [84] and noted that while children and young adults had predominant inter and interlobular fibrosis (Figure 1C in the referred manuscript), with increasing age there was a progressive loss of acinar mass and an increase in fatty replacement of the pancreas. While the amount of fibrosis was not quantified biochemically or histologically, it was localized at the periphery of the fat and surrounded the pancreatic ducts (Figure 2 of the referenced manuscript). Fatty replacement of the pancreas has also been noted to occur in rodent models of hereditary pancreatitis [85]. The fatty acid composition of the fat stored in these adipocytes and those in chronic pancreatitis remains unknown (Table 2). To conclude, with recurrent attacks of AP, and with increasing fibrosis, there is gradual walling off of the fat and parenchyma, and eventually the lipolytic flux between the two compartments gets limited and attacks of AP are attenuated (Figure 1). As mentioned earlier, in CP there is a reduction in acinar mass. There has been some thought that the lower acinar mass may be contributing to a muted response. However, it is also known that serum levels of lipase and amylase do not correlate well with the severity of AP [86] and children and adolescents with lower pancreatic acinar masses have been found to have similar severity of AP attacks [87–91]. It has also been noted that the severity of attacks reduces sharply after the initial attack in AP [62]. This suggests that apart from a lower exocrine acinar mass possibly contributing to milder attacks, fibrosis is very likely to have a role in dampening the severity of attacks.

SYSTEMIC LIPOTOXICITY IN SAP AND MSOF

Early mortality in SAP usually involves sustained failure of one or more organ systems manifesting as respiratory failure and/or acute kidney failure. We know that in SAP the levels of cytokines in the serum particularly TNF- α , IL-6 and adipokines (resistin and visfatin) are significantly elevated [92–95]. Low adiponectin levels have been associated with worse outcomes in AP [96].

In SAP associated with obesity, cytokines and adipokines have so far been noted as markers of SAP [92–94, 97]. It is unknown whether cytokines and adipokines contribute to the progression of AP. While IL-6 and TNF- α are increased in mice with oleic acid induced acute lung injury [98, 99] and in obese mice with SAP [15, 100], mortality and SAP in obese mice did not improve by neutralization of IL-6 or in IL-6 knock outs[101], and IL-6 may have a protective role in acute lung injury[102]. Similarly TNF- α mimetics have been

shown to improve lung injury and [103] case reports on anti-TNF therapy [104–108] have shown mixed outcomes in AP.

We have shown that SAP and mortality were induced in obese mice that were administered IL12, 18 [15] or in rats with intraductal infusion of the unsaturated triglyceride glyceryltrilinoleate [109]. In these models the levels of cytokines including of TNF- α , IL-6 and MCP-1 in obese mice (and IL-1 β and KC/GRO in rats) increased along with serum unsaturated fatty acid, but treatment with the lipase inhibitor orlistat reduced the levels of these cytokines and UFAs significantly, suggesting that the increase in cytokines was a response to UFAs generated by the lipolysis resulting in necrosis and an inflammatory response. Our recent *in-vitro* studies have also shown that when pancreatic acini were incubated with adipocytes, the levels of adipokines (resistin) and FFA's increased, which was prevented by inhibiting fatty acid generation using a lipase inhibitor. Adipokines (resistin and visfatin) were tested for inciting necrosis in acinar cells and were found to have no such effect [32]. Hence, apart from lipolysis being directly responsible for necrosis, it is also a likely contributor to the milieu of exaggerated inflammation that characterizes SAP.

Obesity has also been associated with increased mortality in burns and severe trauma patients apart from acute pancreatitis [12–14]. The average length of stay is prolonged for these patients and recoveries are complicated by multisystem organ failure and mortality can be 2 fold higher in obese trauma patients [110]. With higher adipokines and other cytokines in obesity, the inflammation initiated by burns and trauma may get amplified, leading to MSOF. On looking at the data available for obesity, critical illness and trauma, various studies have shown an elevated serum lipase [111–113] to be associated with worse outcomes. In our studies with *ob/ob* mice with SAP, we noted acute renal failure with elevation in BUN and creatinine levels. On pathology we found oil red O stained in renal tubular vacuoles. Additionally, there was an increase in serum UFAs in mice with SAP. The infusion of oleic acid in rodents to induce acute lung injury/acute respiratory distress syndrome is a commonly practiced model [99, 114, 115], which confirms the toxicity of UFAs generated by the lipolysis of visceral fat. Our studies also noted similar patterns of lung injury with an increase in apoptotic cells and lung myeloperoxidase levels. All the above changes were reversed with orlistat- a lipase inhibitor, which also normalized the increase in serum UFAs. These studies suggest that the UFA's may have a direct toxic effect to the renal tubular epithelium and may be a mechanism by which lipotoxicity contributes to MSOF. Further studies to validate this in humans are needed.

SUMMARY

With lipotoxicity now being recognized as a strong contributor to increased morbidity and mortality in SAP, sepsis, trauma and burns, it presents us with an opportunity to intervene. There have been no studies done to demonstrate the effectiveness of lipase inhibition in reducing severity of AP in humans. Further studies need to be directed towards studying lipolytic fluxes in AP and the effects of blocking these on the local and the systemic effects postulated above.

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Figure 1. Schematics describe the influence of adipocyte mass and fibrosis on the progression of an acute pancreatitis attack

An attack induced by an insult in lean (A), obese (B) and chronic pancreatitis (CP, C) patients progresses differently. The lipases released by the insult increase UFA formation when the increased adipocyte mass, such as in obesity is adjacent to the acinar cells. This UFA formation is reduced by fibrosis walling-off the adipocytes in CP.

Table 1

Summary of the recent advances involving the role of fat in pancreatitis

Previously known information:	
1	Obese patients are at increased risk of severe acute pancreatitis.
2	The initial AP attacks may be severe, while subsequent recurrent acute or chronic pancreatitis attacks are milder.
3	Cytokines are markers of severe acute pancreatitis.
New information:	
1	There is an increase in intrapancreatic fat with obesity.
2	The fat composition in obesity is predominantly unsaturated.
3	Lipolysis of unsaturated adipocyte triglycerides in obesity worsens local and systemic injury.
4	Fat amount in chronic pancreatitis is unrelated to BMI and is walled off by fibrosis, which reduces the lipolytic flux between adipocytes and acinar cells, thus limiting injury.
5	Cytokine increase in SAP may be secondary to lipotoxicity.

Table 2

Comparison of intrapancreatic fat in acute and chronic pancreatitis.

	Acute Pancreatitis	Chronic Pancreatitis
Relative amount in non-obese individuals	Lower	higher
Relationship to BMI	Positive correlation	No Correlation
Composition of fat	Predominantly UFA's in obesity	Unknown
Presence of Surrounding Fibrosis	Minimal	Significant, with "walling off" of fat
Macromolecular diffusion between fat and parenchyma	significant	reduced
Amount of Fat necrosis	Present, increases with obesity, IPF	reduced
Amount of PFAN	Significant	Minimal
Role of IPF in acute Exacerbation	Significant	Minimal