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Review article

Role of pancreatic fat in the outcomes of pancreatitis

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A B S T R A C T

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).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. With the role of unsaturated fatty acids (UFA) as propagators in SAP having recently come to light 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.

1. 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 labeled an epidemic, with clinicians and scientists recognizing the deleterious effects of fats, be it the cardiovascular, gastrointestinal or renal system [20]. 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

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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.

lipotoxicity with reference to SAP, and how fat in CP is different from fat in AP (Table 2).

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 Fig. 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

Table 2
Comparison of intrapancreatic fat in acute and chronic pancreatitis. Q4

	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

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