HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2019 July 19.

Published in final edited form as:

Curr Opin Gastroenterol. 2017 September ; 33(5): 374–382. doi:10.1097/MOG.0000000000000386.

Obesity and pancreatitis

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Abstract

Purpose of review—The obesity pandemic poses a unique set of problems for acute pancreatitis – both by increasing acute pancreatitis incidence, and worsening acute pancreatitis severity. This review explores these associations, underlying mechanisms, and potential therapies.

Recent findings—We review how the obesity associated increase in gallstones, surgical, and endoscopic interventions for obesity management, diabetes, and related medications such as incretin-based therapies and hypertriglyceridemia may increase the incidence of acute pancreatitis. The mechanism of how obesity may increase acute pancreatitis severity are discussed with a focus on cytokines, adipokines, damage-associated molecular patterns and unsaturated fatty acid-mediated lipotoxicity. The role of obesity in exacerbating pancreatic necrosis is discussed; focusing on obesity-associated pancreatic steatosis. We also discuss how peripancreatic fat necrosis worsens organ failure independent of pancreatic necrosis. Last, we discuss emerging therapies including choice of intravenous fluids and the use of lipase inhibitors which have shown promise during severe acute pancreatitis.

Summary—We discuss how obesity may contribute to increasing acute pancreatitis incidence, the role of lipolytic unsaturated fatty acid release in worsening acute pancreatitis, and potential approaches, including appropriate fluid management and lipase inhibition in improving acute pancreatitis outcomes.

Keywords

lipase inhibition; obesity; pancreatitis; unsaturated fatty acids

INTRODUCTION

Obesity is a growing pandemic [1] with increasing healthcare costs, and acute pancreatitis is one of the most common gastroenterological causes for hospitalization in the United States affecting 275 000 patients annually [2]. Obesity has likely contributed to increasing the incidence [2,3] and severity [4–11] of acute pancreatitis. Here we discuss the underlying mechanisms, and emerging acute pancreatitis management options based on clinically relevant studies.

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Conflicts of interest

There are no conflicts of interest.

DISCUSSION

Obesity describes excessive adiposity, and currently afflicts humans in pandemic proportions. Visceral abdominal adiposity has the biggest impact on acute pancreatitis [12,13■■,14]. Although the definition of obesity varies, on a global scale more than 35% of adults are overweight (BMI > 25 kg/m^2) and more than 10% are obese (BMI > 30 kg/m^2) [15]. Interestingly, when defined by criteria accepted by national organizations, the proportion with obesity increases. For example, although only about 4% of men in China or Japan, and 34% in the United States have a BMI of more than 30 [15]; based on waist circumference cutoffs relevant to these countries, more than 35% of adult men in all three countries are obese [16]. Therefore, despite the varying definitions of obesity, the rates of abdominal adiposity are similarly high across the globe. This is important as over the last 3 decades, both the prevalence of obesity [1] and incidence of pancreatitis [3,17] have increased. Moreover, as we discuss below, obese patients have a higher risk of severe acute pancreatitis (SAP). In the following section, we will separately discuss the pathophysiology of how obesity may increase the incidence, and also worsen the severity of acute pancreatitis.

Contribution of obesity to the development of acute pancreatitis

The several ways by which obesity increases the risk of acute pancreatitis are summarized in Table 1 and are discussed below:

1. Cholelithiasis: Overweight and obese patients have higher incidence of biliary disease [18■,19■] and pancreatitis [19■]. Biliary disease causes acute pancreatitis by stones, sludge, or micro-lithiasis in the biliopancreatic passages either causing bile reflux or increasing pancreatic duct pressure [20]. Obesity may impact gallstone formation by multiple mechanisms. A high-fat western diet may predispose to cholesterol-rich crystals or stones in the bile [21] by increasing cholesterol crystal number [22] or growth [23]. This is supported by obese children with biliary pancreatitis having a higher likelihood of stones than sludge [24]. Additional factors may include the decrease in circulating bile acids, and gall bladder stasis from increasing intervals between meals in an attempt to lose weight or prevent obesity [25,26]. Obesity may also affect diagnosis of gallstones, as one study reports a decreased sensitivity of magnetic resonance cholangio-pancreatography in detecting gallstone in obese and overweight patients [27].

2. Hypertriglyceridemia (HTG): HTG is associated with obesity and pancreatitis [28,29]. Obesity can unmask primary HTG from genetic causes [30■], and is a risk factor for secondary HTG [31■]. Weight loss, a treatment modality for HTG [32], is an additional risk factor pancreatitis. Among the potential mechanisms of HTG-induced pancreatitis is the insolubility of the lipid triglycerides in the aqueous environment of blood resulting in microthrombi in the pancreatic vasculature causing ischemia and pancreatic infarction. Interestingly, hypertriglyceridemic pancreatitis tends to be severe [33–35] more often than other causes. This may be because of the lipolysis of circulating triglycerides,

and the resulting unsaturated fatty acids (UFAs) generated causing SAP, as discussed below.

3. Diabetes: Diabetes mellitus type-2 and obesity are intimately associated. Although diabetes may occur as an acute pancreatitis complication from loss of pancreatic mass or function, diabetes mellitus type-2 may increase acute pancreatitis risk via HTG [36■], cholelithiasis [37■] because of a high-fat diet, and incretin-based treatments – perhaps via β-cell hypertrophy[38]. Although the exact mechanisms are unknown, islet cell hypertrophy such as in nesidioblastosis can result in duct obstruction and pancreatitis [39■–41■,42]. Some studies and metaanalyses support the increased acute pancreatitis risk [43■–45■,46] with either, for example, glucagon-like peptide-1 receptor agonists[47] or dipeptideyl peptidase-4 inhibitors [48]; however, others refute this [49■–51■,52]. The data on acute pancreatitis outcomes in diabetic patients are inconsistent, with some reporting worse [53] and others showing better outcomes [54] and need further studies.

4. Therapeutic interventions for obesity: The morbidity associated with obesity has resulted in several interventions to prevent or reverse it. Although strong proof that medical therapies for obesity are associated with pancreatitis is lacking, the body of literature associating surgical or minimally invasive interventions with pancreatitis is fairly strong and is discussed below:

    a. Bariatric surgery: Surgical weight loss options include Roux-en-Y gastric bypass (RYGB) surgery, laparoscopic gastric banding, and sleeve gastrectomy. Pancreatitis may occur during the extended postoperative period in 0.2–1% cases of laparoscopic RYGB surgery without cholelithiasis noted at operation [55,56]. Gallstones and pancreatitis amount to 5 and 10% of all complications in the first 3 years after surgery [57■]. Although the risk of pancreatitis is higher than the general population (0.02–0.04%), it is too low to warrant a cholecystectomy without concomitant gallstones or cholecystitis. The main mechanisms attributed to the increased risk of gallstones and pancreatitis are postoperative rapid weight loss [56] and gallbladder stasis. Other mechanisms hypothesized to cause pancreatitis include ampullary stenosis, sphincter of oddi dysfunction, and closed-loop obstruction [58■] and nesidioblastosis [59,60]. Hyperamylasemia and lipasemia are noted in a large proportion of patients with postoperative small bowel obstruction of the biliopancreatic limb [61] without a clinical diagnosis of pancreatitis.

    b. Duodeno-jejunal bypass liner (DJBL). Case report series show pancreatitis to occur in 2–3% of patients with a DJBL [62■,63]. The pathophysiology includes edema or physical blockage of the ampulla of Vater by food material accumulating between the duodenum and the liner of the DJBL, pressure from the device causing reflux of duodenal

contents or blocking flow from the pancreatic duct, or the DJBL's anchor migrating to obstruct the ampulla.

c. Gastric balloons: There are several reports of acute pancreatitis following placement of gastric balloons for weight loss [64,65,66■]. The largest series includes 301 patients followed for 6 months, two of whom developed pancreatitis [67]. Pancreatitis may occur from dislodgement or pressure on the pancreas. Interestingly, an emerging therapy for pancreatitis is a rapidly reversible cooling balloon placed in the stomach [68■], which cools the pancreas transgastrically and may slow the numerous mechanisms active in pancreatitis simultaneously.

Role of obesity in severity of acute pancreatitis

The severity of acute pancreatitis is typically unrelated to the acute pancreatitis cause [69–72]. Unlike subcutaneous fat, which rarely impacts the severity of acute pancreatitis [73■■] obesity associated increase in visceral fat in or around the pancreas can worsen acute pancreatitis outcomes [8,14,74,75] (Fig. 1A, B). This can present as hypocalcemia earlier, or as organ failure later in the disease course (Fig. 1C, D). The resulting damage to visceral fat, described as fat necrosis, is a part of radiographic criteria for pancreatitis severity [76,77] and the revised Atlanta criteria [78]. Additionally, obesity increases the risk of HTG both preceding and during an attack of pancreatitis [79■]. Therefore, obesity can worsen pancreatitis.

Patterns of severe pancreatitis noted in obesity:

1. Local pancreatic necrosis: About 95% of necrotizing pancreatitis involves fat necrosis and pancreatic necrosis [76–78,80,81], with isolated pancreatic parenchymal necrosis occurring in less than 5% of cases [81]. In obesity, adipocytes within the pancreas (i.e., intrapancreatic fat) increase with BMI [82,83] and are dispersed fairly uniformly [84] adjacent to the basolateral membranes of the lipase rich exocrine pancreatic acinar cells (Fig. 2). Although these triglyceride-rich adipocytes are normally not subject to lipolysis because of the apically polarized secretion from acinar cells, this homeostasis is disrupted during acute pancreatitis. The basolateral release of digestive enzymes including lipases into adipocytes damages them [85,86] and hydrolyzes their triglyceride which forms more than 80% of adipocyte mass [87–89]. The composition of this triglyceride is predominantly unsaturated in obesity [83,90■■]. This hydrolysis causes UFAs release from the damaged adipocytes, which in turn causes necrosis of acinar cells by inhibiting mitochondrial complexes I and V [83]. This vicious lipolytic flux causes further acinar damage; perpetuating necrotizing pancreatitis via lipase leak-mediated UFA release. In contrast, adipocyte mass in chronic pancreatitis is unrelated to BMI, and is surrounded by fibrosis, which prevents the lipolytic flux between the two compartments [86] and thereby SAP.

2. Systemic injury including organ failure: Although about 80% cases of pancreatic necrosis occurs with peripancreatic fat (PPF) necrosis [81,91], about 10–15% of cases of moderate-to-severe pancreatitis have PPF necrosis without pancreatic

parenchymal necrosis [81,91] (Fig. 1b–d). PPF close to the pancreas, such as perinephric, mesenteric, perisplenic is prone to lipolysis. When extensive, PPF necrosis alone can result in moderate acute pancreatitis to SAP [81,91–93] (Fig. 1b–d, Fig. 2) and sometimes mortality [94–96] via systemic injury including shock, renal, and respiratory failure from UFA toxicity [90■■].

Mechanisms by which obesity may exacerbate pancreatitis

In obesity, adipose tissue can exceed 30% of body weight [97] with visceral fat comprising more than 3% of body weight [98]. More than 80% of adipocyte mass is triglyceride [87–89], which when hydrolyzed by the leaked lipases can generate three fatty acids from each cleaved triglyceride molecule. Studies analyzing the composition of pancreatic necrosis collections, report these to be enriched in the UFAs oleic (C18 : 1) and linoleic acid (C18 : 2) [83,90■■,99]. Additionally, cytokines such as interleukin (IL)-1β and IL-8 have been shown to be increased in necrotic collections [90■■].

1. Lipid mediators: UFAs is the major class of lipid mediators in SAP. In-vitro UFA toxicity to pancreatic cells was shown by Mossner *et al.* [100] and the clinical, in-vivo relevance of these was shown recently by Navina *et al.* [83] [90■■, 101,102■■]. The concentration of UFAs generated in fat necrosis can be in the millimolar range [83,90■■,99] and high concentrations are noted in the sera of patients with SAP [103,104]. Being polar, UFAs are normally bound by calcium, resulting in their saponification and inactivation in fat necrosis. This can result in the hypocalcemia noted during SAP (Fig. 1c), which is part of Ranson *et al.*'s [105], Japanese severity score [106] and the recently validated [107] Glasgow criteria [108]. The remaining unbuffered nonesterified UFAs can increase inflammatory mediators such as tumor necrosis factor (TNF-α), CXC ligand 1 (CXCL1), and CXCL2, and cause necrosis by reducing ATP levels via inhibiting mitochondrial complexes I and V [83], thus worsening acute pancreatitis. This damage is noted within the pancreas as perifat acinar necrosis [83,102■■], forming half of all parenchymal necrosis, and systemically as renal tubular apoptosis associated with renal failure, and dead cells in lung alveoli [83,90■■, 101,102■■] similar to acute respiratory distress syndrome [109,110] (Fig. 2). Thus uncontrolled UFA release by being proinflammatory and causing cell death seems to be the orchestrator of the cytokine response and release of damage-associated molecular patterns (DAMPs) from dying cells. These are discussed below:

2. Proteins: The proteins whose concentrations are altered in the circulation of patients with SAP have been studied as therapeutic targets in SAP. Chief among these are activated protein C which is reduced, or cytokines like IL-6 [111–114], IL-1β [115], IL-8 [111,114,116], monocyte chemotactic protein-1 [117], TNF-α, [112] or adipokines, including resistin and visfatin [76,118] which are increased in SAP. The clinical trials replacing activated protein C, whereas showing its safety [119], have not shown a clear benefit of improving outcomes in SAP [120]. Similarly, although cytokines are markers of SAP, conclusive proof of them mediating acute pancreatitis severity is lacking. A recent study showed that

IL-1β and IL-8 cause fever and an increase in leukocyte infiltration into the pancreas and lungs; however, they did not worsen acute pancreatitis, as evidenced by the lack of pancreatic necrosis, systemic injury, or mortality [90■■]. Moreover inhibition of triglyceride lipolysis by orlistat reduced serum UFAs, IL-1β, and IL-8, and prevented organ failure and mortality [90■■]. Interestingly, some studies ascribe a protective role to IL-6, IL-8, and TNF-α [121–123]. These findings along with the inability of cytokines to induce outcomes relevant to SAP [122–126], and the unclear benefit of anti-TNF-α therapies in acute pancreatitis [127–131], make cytokines unfavorable therapeutic targets in obesity-associated SAP.

3. DAMPs: DAMPs are released when there is cell injury such as in necrosis. DAMPs include high-mobility group box 1 (HMGB1), the soluble receptor for advanced glycation end products, nuclear components (e.g., DNA, nucleosomes, histones), belonging to the S100 protein family, ATP, and extracellular matrix components such as hyaluronan fragments. Hoque *et al.* [132] first showed the requirement of the DAMP receptors TLR9 (agonist; nucleic acids) and P2X7 (agonist; ATP) in caerulein pancreatitis. Intracellular HMGB1 was later shown to be protective in L-arginine and caerulein pancreatitis [133]. Although serum HMGB1 [134], soluble receptor for advanced glycation end products [135], histone [136■], and nucleosome [137■] levels correlate with human acute pancreatitis severity; it remains unclear whether DAMPs are markers or mediators of SAP outcomes and conclusive studies on them inducing end points that are clinically relevant to SAP need to be done.

Potential therapies for obesity related severe acute pancreatitis

1. Choice of intravenous (IV) fluids: As the initial study by Wu *et al.* [138] reporting Lactated Ringer's reduces SIRS and C-reactive protein more than saline in acute pancreatitis patients, other studies have shown similar results [139,140■]. Potential beneficial mechanisms of Lactated Ringer's include 1) the 3 mEq/l calcium it contains, 2) Lactated Ringer's being buffered whereas saline is not, and 3) the lactate in Lactated Ringer's being a G-protein receptior (GPR81) agonist and thereby reducing inflammasome and nuclear factor kappa B activation [141]. It should be noted that the role of GPR81 has not been studied in obese mice or in the context of organ failure. Additionally, saline has no buffering capacity and is unlikely to influence blood pH. Hypocalcemia is a known complication of SAP [105,106,108] (Fig. 1c). A study comparing extracellular calcium replacement to pH 7.4 buffered lactate showed improved outcomes in the calcium group [142■]. Thus Lactated Ringer's benefit is most likely via replacing extracellular calcium which can bind and saponify UFAs.

2. Lipase inhibitors: Therapeutic use of lipase inhibitors improves outcomes in etiologically different lethal models of experimental acute pancreatitis in obesity [83,102■■,143]. This includes a reduction in mortality, severe pancreatic necrosis, renal, and respiratory failure. These benefits are also noted in lethal acute pancreatitis induced concurrently with administration of triglycerides

containing UFAs found in human pancreatic necrosis [90■■,101]. However, the only Food and Drug Administration-approved formulation of the lipase inhibitor, orlistat is oral, which is poorly absorbed (<1%) and is used worldwide as the counter drug for weight loss. For use in SAP, orlistat requires a special parenteral formulation [102■■], which would be off-label use of the drug. The few case reports of orlistat and pancreatitis [144–146] over the last decade show a latency period varying from 2 to 10 days and there is no rechallenging data. The evidence against orlistat is thus class III [147], and is likely coincidental given orlistat's widespread use and the fact that about 20% of acute pancreatitis is idiopathic. These points reinforce the urgent need to develop better agents for use in acute pancreatitis.

CONCLUSION

The growing pandemic of obesity has increased acute pancreatitis's incidence and severity. The increase in incidence is because of increased risk of gallstones, HTG, medications, and weight loss interventions. Obesity worsens acute pancreatitis severity by allowing unregulated lipolysis of visceral fat enriched in unsaturated triglyceride, thus releasing UFAs which inhibit mitochondrial complexes I and V, cause necrosis, and worsen acute pancreatitis. Lactated Ringer's benefit over saline as an IV fluid for managing acute pancreatitis because of the calcium it contains, and whereas definitive measures to prevent and neutralize UFA toxicity are needed, parenteral formulations of orlistat remain a potential option.

Acknowledgements

The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official view of DOA, NIDDK.

Financial support and sponsorship

Supported by Grant number PR151612 from the Department of Army (DOA) (VPS), award number R01DK092460, R01DK100358 (VPS) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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KEY POINTS

- Obesity increases acute pancreatitis via gallstones, HTG, drugs, and weight loss interventions.
- Obesity worsens acute pancreatitis via visceral fat lipolysis releasing UFAs that inhibit complexes I and V.
- Lactated Ringer's and parenteral pancreatic lipase inhibitors may decrease acute pancreatitis severity.
- Lactated Ringer's benefit is via calcium, whereas lipase inhibition decreases UFA release.

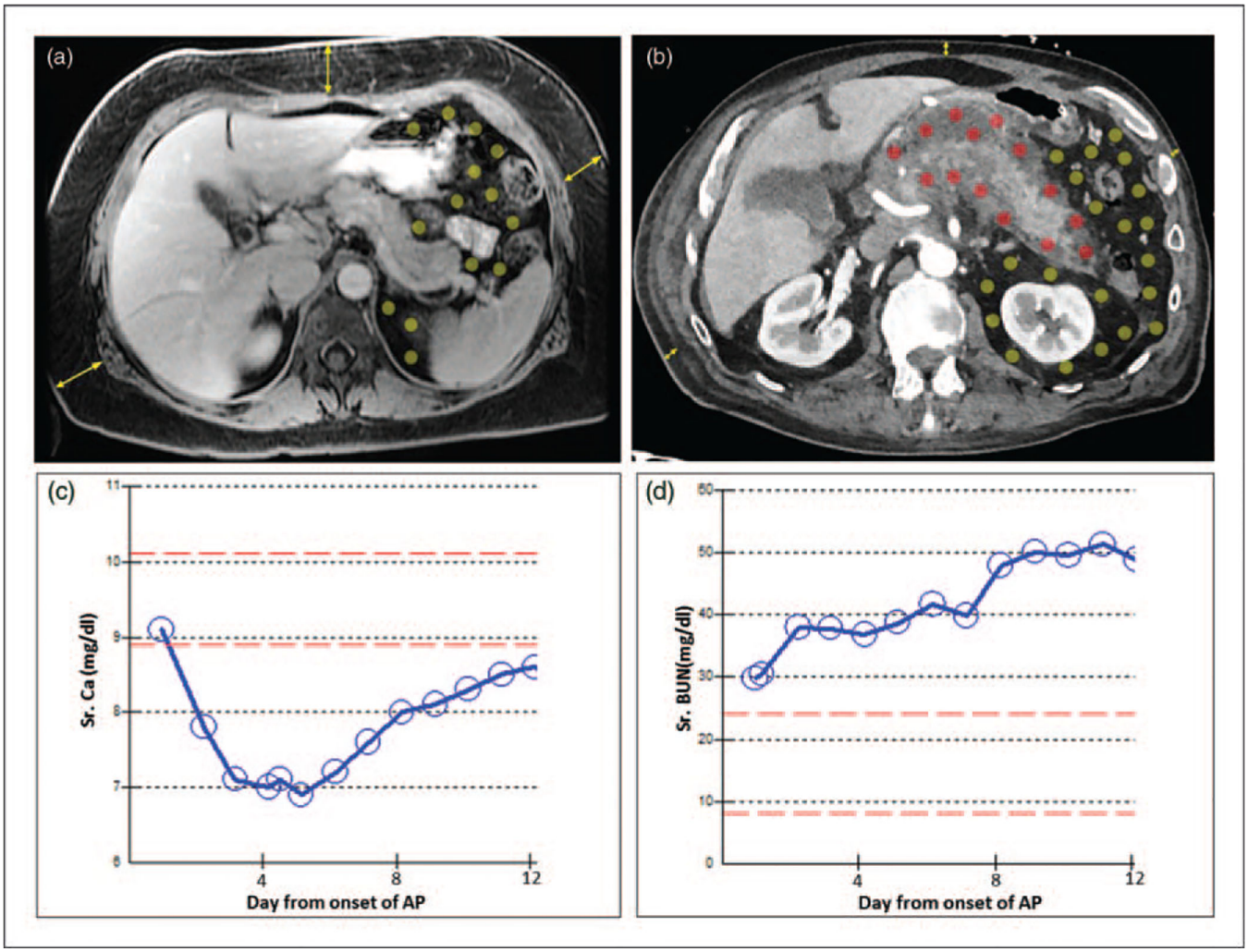

FIGURE 1.

Abdominal imaging showing how location of fat influences the severity of pancreatitis. (a) MRI of a 50-year-old female (weight 85 kg, BMI 34.4) on the second day of biliary pancreatitis showing predominantly subcutaneous fat (yellow arrows) compared with visceral fat (area with yellow dots) with no fat necrosis. The patient had a mild course and was symptom free after 3 days of conservative management. (b) CT scan of a 83-year-old male (weight 84 kg, BMI 26.6) 2 weeks into alcoholic pancreatitis showing little subcutaneous fat (yellow arrows), but a large amount of visceral fat (dots in the peritoneal cavity). The fat around the pancreas was involved in peripancreatic fat necrosis (red dots), whereas the more distant visceral fat remained uninvolved (yellow dots). The clinical course was associated with early hypocalcemia (c), renal failure of >48 h (d) and the patient requiring ventilator support. AP, acute pancreatitis; CT, computerized tomography.

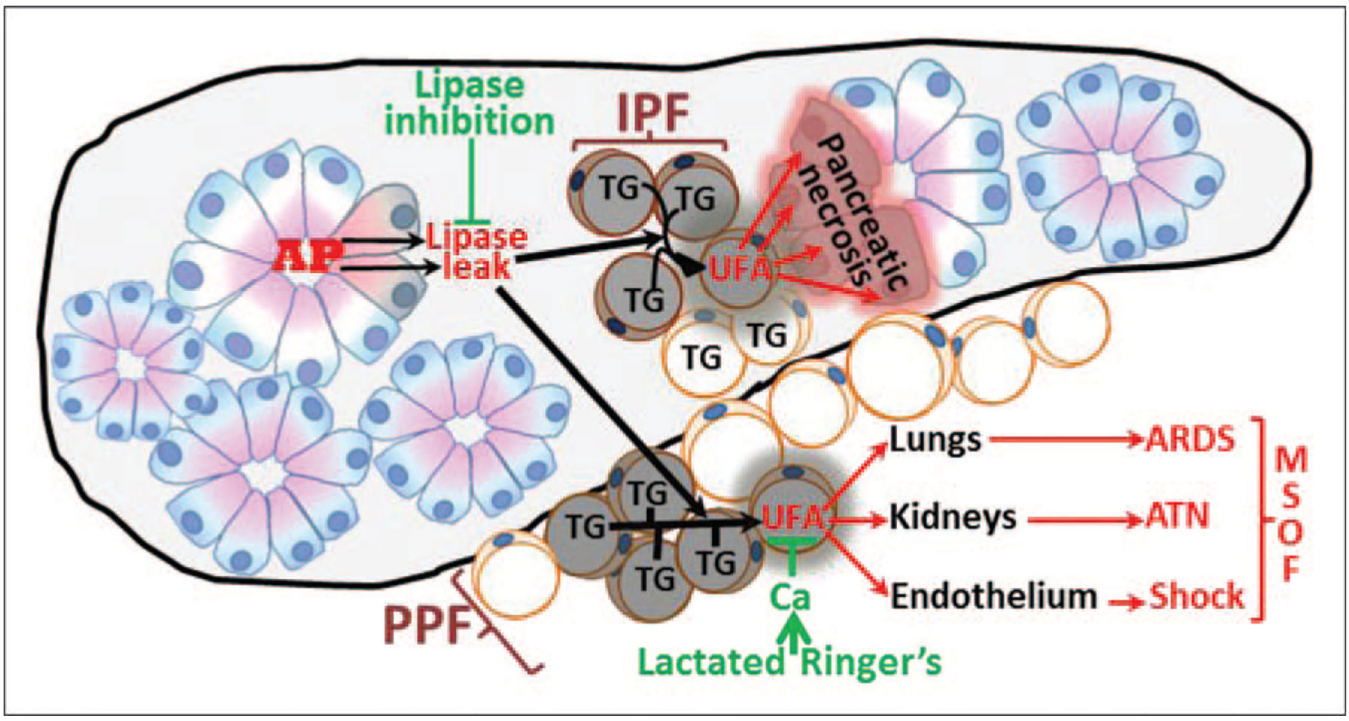

FIGURE 2.

Schematic showing how obesity associated IPF and PPF may, respectively, worsen pancreatic necrosis and lead to MSOF, along with therapeutic interventions (green) that may prevent this exacerbation. AP initiation results in lipase leakage from acinar cells (healthy acini shown in pink and blue, damaged ones orange). This lipase can hydrolyze the TG in IPF and PPF releasing UFAs. When released within the pancreas from IPF, UFAs can worsen pancreatic necrosis, or leak from visceral fat and cause systemic injury resulting in MSOF. AP, acute pancreatitis; IPF, intrapancreatic fat; MSOF, multisystem organ failure; PPF, peripancreatic fat; TG, triglyceride; UFA, unsaturated fatty acid.

Table 1.

Table summarizing the mechanisms by which obesity may contribute to initiating acute pancreatitis, thus increasing acute pancreatitis incidence, and also worsen acute pancreatitis outcome by increasing local and systemic injury

Role of obesity in initiating acute pancreatitis:
Increased cholelithiasis
high cholesterol: bile acid- crystal nucleation, number.
HTG
Unmasked primary HTG
Secondary HTG
Diabetes
associated HTG
increased cholelithiasis
Incretin based therapies
Therapeutic interventions for obesity
Weight loss (associated gallbladder stasis)
Bariatric surgery
Duodeno-jejunal bypass liner
Gastric balloons
Role of obesity in worsening acute pancreatitis outcomes:
Increased intrapancreatic fat: worse pancreatic necrosis
Increased peripancreatic fat: systemic unsaturated fatty acid toxicity resulting in respiratory, cardiovascular, renal failure

HTG, hypertriglyceridemia.