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The Burden of Systemic Adiposity on Pancreatic Disease: Acute Pancreatitis, Non-Alcoholic Fatty Pancreas Disease, and Pancreatic Cancer

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Abstract

Obesity is a global epidemic as recognized by the World Health Organization. Obesity and its related comorbid conditions were recognized to have an important role in a multitude of acute, chronic, and critical illnesses including acute pancreatitis, nonalcoholic fatty pancreas disease, and pancreatic cancer. This review summarizes the impact of adiposity on a spectrum of pancreatic diseases.

Keywords

Obesity; Obesity; Morbid; Pancreatic Neoplasms; Pancreatitis

INTRODUCTION

Obesity is a global epidemic as recognized by the World Health Organization [1]. One third of the world's population is either overweight or obese, and it has doubled over the past two decades with an alarming 70% increase in the prevalence of morbid obesity from year 2000 to 2010 [2, 3, 4]. Obesity and its related comorbid conditions were recognized to have an important role in a multitude of acute, chronic, and critical pancreatic illnesses including acute pancreatitis, non-alcoholic fatty pancreas disease, and pancreatic cancer.

Obesity and Acute Pancreatitis

Acute Pancreatitis (AP) is one of the most common gastrointestinal-related causes of inpatient hospitalizations and health care expenditure (annual cost of 2.6 billion dollars), with a sizeable mortality rate of 3–5% [5]. There continues to be a steady increase in the prevalence of inpatient admissions for AP overtime and this attracted attention to better understanding of this disease process [4, 6]. AP typically resolves in the majority of patients without further complications; however, 20% of patients progress into severe AP (local and

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systemic complications), and sustain a very high mortality rate up to 30% in the setting of persistent multi-organ failure [7]. Obesity is associated with the development of multiple complications, worse outcomes, and even higher mortality in the setting of AP based on multiple reports [8, 9, 10, 11, 12]. Despite the rising incidence of AP over the past two decades, there has been a decrease in its overall mortality rate without any obvious decrement in the mortality rate among patients with concomitant AP and morbid obesity [12, 13]. Several prediction models and risk scores were proposed to anticipate the severity and prognosis of patient with AP; however, their clinical utility is variable, not completely understood, and didn't take obesity as a major contributor into consideration despite the aforementioned association [14].

Obesity was initially reported as an independent predictor of respiratory failure in patients with severe AP based on two reports in the early 1990's [15, 16]. More recent data also confirmed and substantiated the previous reports [17]. Published data prior to year 2000 didn't demonstrate an independent association between obesity and mortality from AP; however, multiple large prospective studies and meta-analyses over the past two decades showed that obesity (Body Mass Index [BMI]) is an independent predictor of severity and mortality from AP based on multiple risk score assessments [17, 18, 19]. This was also supported by population-based studies [12, 20]. Obesity in the form of excess subcutaneous tissue was also reported as an important predictor of post-ERCP pancreatitis based on a recent large retrospective study [21].

Multiple theories were proposed to understand the link between obesity and AP. Those include 1) toxic effects of the intra-pancreatic fat content, 2) toxic effect of the peripancreatic (visceral) fat content, and 3) the overall burden of obesity on other organ systems.

The intra-pancreatic fat content was shown to be proportional to BMI with specific predilection to unsaturated fat content [22, 23, 24]. This intra-pancreatic fat, and more so, the abdominal visceral fat are both metabolically active and produce multiple adipokines and cytokines (Adiponectin, Leptin, TNF a, Interleukin-6, monocyte chemotactic protein-1, macrophage IL-1b, and myeloperoxidase); which through adipocytokine imbalance could initiate and maintain a low pro-inflammatory state [25, 26], act as a substrate for lipolysis with further necrosis in the setting of necrotizing pancreatitis spectrum through the release of unsaturated fatty acids, [27] help spread the inflammation in AP across visceral fat to surrounding organs, and cause a direct toxic effect on the pancreatic parenchyma [23, 28]. Peri-pancreatic fat lipolysis can also result in multisystem injury independent of the development of pancreatic necrosis via the role of unsaturated fatty acids [29]. Overall, visceral obesity is positively correlated with morbidity and mortality among multiple studies [30, 31, 32].

Although most previous reports have focused on central obesity as the main predictor, a recent retrospective study found that excess subcutaneous fat (rather than visceral obesity) is an important predictor of post ERCP pancreatitis [21]. In addition to the inflammatory hypothesis driven by the intra-pancreatic and para-pancreatic fat; obesity could also predispose to severe AP by reducing the pancreatic microcirculation and causing subsequent

ischemic injury. Abdominal visceral obesity also decreases the inspiratory capacity due to the restriction of diaphragmatic movement. This leads to increased physiologic pulmonary arteriovenous shunting and further hypoxemia with oxygen deficits, further cellular damage, hyperactive inflammatory response, and ultimately increases the rate of multi-organ failure and death [8]. Overall, the precise mechanisms are still unclear and this is a material for further investigation.

Obesity and Non-Alcoholic Fatty Pancreas Disease

Non-Alcoholic Fatty Pancreas Disease (NAFPD) was first described in 1933. It is associated with aging and obesity among other less common predisposing factors with a variable prevalence among different studies due to differences in nomenclature and absence of unifying diagnostic criteria. NAFPD has a reported prevalence of 16–35% among an adult Asian population [33, 34, 35].

It is usually detected incidentally by cross sectional abdominal imaging. Believed to develop due to obesity and subsequent pancreatic fat accumulation in the setting of metabolic syndrome, and it has been reported to a much lesser extent among non-obese individuals.

The proposed mechanism of pancreatic fat accumulation is fatty replacement by death of acinar cells and replacement by adipocytes and fatty infiltration by fat accumulation within adipocytes due to obesity and type 2 diabetes [36]. NAFPD was shown to exacerbate the severity of acute pancreatitis, possibly impact the pancreatic endocrine and exocrine function, predispose to pancreatic cancer, increase intra-op and post-op morbidity after pancreatic surgery, and also increase mortality from pancreatic cancer [37, 38, 39].

Pancreatic steatosis with superimposed acute pancreatitis has also been shown to intensify the inflammatory cascade and cause more severe parenchymal damage in the setting of obesity [23, 28]; however, there is insufficient evidence to suggest an association of NAFPD with the development of chronic inflammation or chronic pancreatitis.

Obesity and Pancreatic Cancer

Obesity and high BMI have been proposed as risk factors for pancreatic cancer. Despite earlier conflicting data about the strength of the association between BMI and pancreatic cancer risk; more recent robust prospective and case-control studies highlighted and strengthened this association [40, 41, 42]. Obesity is now recognized as a significant risk factor for pancreatic ductal adenocarcinoma. Obesity was shown to increase the incidence of pancreatic cancer by 10–14% for each 5 kg/m^2 incremental increase in BMI based on a systematic analysis of prospective observational studies [40, 41]. Obese individuals were also shown to have an approximately 20% greater risk of developing pancreatic adenocarcinoma compared to normal weight controls based on a pooled analysis from the pancreatic cancer cohort consortium [42]. Obesity increases the odds of surgical complications and development of pancreatic fistulas among pancreatic cancer surgical candidates, and ultimately increases mortality from pancreatic cancer surgery [43, 44].

Obesity as an inflammatory trigger, is believed to increase the activity of KRas oncogene [45], increase insulin levels and insulin-like growth factor-1 with subsequent increase in cellular proliferation, and increase the burden of systemic oxidative stress in mice [43].

5-lipooxygenase (5-LO) and 5-LO activating protein is preferentially and abundantly more present in adipocytes and adipose tissue of obese rats compared to their lean counterparts [46] with accumulating evidence about the role of 5-LO in the growth of pancreatic tumors. Other theories include the role of immune dysfunction from the excessive production of pro-inflammatory cytokines and dysregulation of lipid-regulating proteins in obese individuals. Leptin, which is fairly more abundant in peripheral tissues of obese individuals, has also been implicated in the facilitation of pancreatic cancer invasion through increasing the matrix metalloproteinase (MMP-13) activity [47].

Extra- and intra lobular pancreatic fat was also correlated with pancreatic intraepithelial neoplasia, and NAFPD in the setting of obesity was shown to promote dissemination and lethality of pancreatic cancer by altering the tumor microenvironment [48, 49].

The Role of Bariatric Surgery

Patients with prior bariatric surgery had fewer incidents of respiratory failure and mechanical ventilation in the setting of AP [8]. A recent meta-analysis showed decreased interleukins and inflammatory markers (IL-6, C-reactive protein, and TNF-A) after bariatric surgery in addition to concomitant increase in anti-inflammatory mediators independent of the extent of the weight loss [50, 51, 52]. In addition, bariatric surgery was shown to markedly alter the pancreatic blood flow and pancreatic lipid metabolism based on a longitudinal study [53]. Acute pancreatitis in patients with prior bariatric surgery was not adversely associated with in-hospital mortality, development of multi-organ failure, or healthcare resource utilization in acute pancreatitis based on a large population study [54]. This explains the biologic plausibility of decreased mortality and improved clinical outcomes due to fewer incidents of respiratory failure, improved inspiratory capacity, and eventually reduced hypoxemia and cellular damage [8, 43].

CONCLUSION

The anticipated progression of the obesity pandemic will continue to fuel adiposity related complications. The existing body of evidence suggests that all patterns of adiposity (visceral, subcutaneous, and even pancreatic) have been associated with various adverse outcomes involving pancreatic diseases through multiple proposed mechanisms. However, the evidence for some of these associations, although demonstrated in a number of studies is not robust. There is a need for continued research in obesity-related mechanisms of acute pancreatic injury, the role of the emerging non-alcoholic fatty pancreatic disease, and the underlying mechanisms associating obesity and pancreatic cancer. Moreover, the impact of weight loss strategies (endoscopic or surgical) on outcomes of patients with obesity and pancreatic disease needs to be profoundly explored. In the meantime, we should spread awareness about the existing associations in an effort to alleviate pancreatic disease related morbidity and mortality.

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Abbreviations

NAFPD non-alcoholic fatty pancreas disease

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