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REVIEW

Obesity, Pancreatitis, and Pancreatic Cancer

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Abstract The only universally accepted risk factors for the development of pancreatic cancer are a positive family history or a history of smoking. Although the contribution of pancreatitis to pancreatic carcinogenesis has been debated for decades in the epidemiology literature, the actual mechanism is still unclear. With the rising epidemic of obesity, scientists have begun to focus on the contribution of chronic inflammatory state of morbidly obese patients in an effort to better understand the contribution of inflammation to the comorbidities of obesity. Notably, population studies are beginning to show that one of the most serious potential comorbidities of obesity is an increased lifetime risk of developing cancer. In this article, the current literature that exists supporting this Chronic Inflammatory Hypothesis as it pertains to obesity and pancreatic carcinogenesis is reviewed. To date, studies have focused on interleukin-6, a cytokine known to play a role in obesity, chronic pancreatitis and pancreatic cancer. The anti-inflammatory adipocytokine, adiponectin, has also shown promise as a key player in this mechanism and has recently been found to be more specific than standard tumor markers in differentiating pancreatic cancer from chronic pancreatitis. If the pathogenesis of pancreatic cancer is related to hormone levels associated with obesity, such as adipocytokines, and cytokines associated with chronic inflammation, this could potentially lead to the development of new pancreatic cancer tumor markers and ultimately new therapies and methods of prevention.

Keywords Pancreatic carcinogenesis · Cytokines · Adipocytokines · Adiponectin · Leptin

Introduction

With the rising epidemic of obesity, researchers have theorized that the chronic inflammatory changes associated with obesity may explain some comorbidities in obese patients and even the increased incidence of cancer in this patient population [1]. The association with chronic inflammatory states and carcinogenesis has been referred to as the chronic inflammatory hypothesis [1–5]. This theory as it pertains to obese patients has been supported by the observation that decreased cancer mortality rates have been found in morbidly obese patients that have undergone bariatric surgery [6]. Cytokine and chemokines and their receptors have been analyzed in cancer patients and animal models to attempt to elucidate this link. These molecules of inflammation have multiple functions ranging from mediation of inflammation, immune function, angiogenesis, and ultimately metastasis [7–9]. Because of these observations, studies of inflammatory mediators in pancreatic carcinogenesis have become more prevalent [10–12].

In a recently published review, it was noted that the increased understanding of hormonal alterations of obesity, specifically changes in the adipo-insular and entero-insular axes, are beginning to clarify the link between obesity and pancreatic cancer that has long been debated in the epidemiology literature [13]. In this article, the cytokines and adipocytokines involved in pancreatitis will be

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reviewed to see what evidence currently exists to support the chronic inflammatory hypothesis as it pertains to obesity and pancreatic cancer.

Adipocytokines and Pancreatic Cancer

Adipocytokines or adipokines are bioactive peptides that modulate insulin metabolism and fat catabolism through an intricate mechanism that is referred to as the adipo-insular axis [14]. The most studied adipocytokines are leptin, and adiponectin, which are secreted by white and mature adipocytes of the visceral fat, respectively. A third adipocytokine, resistin, is formed in the bone marrow and in monocytes. Adiponectin has anti-inflammatory properties, as opposed to leptin and resistin, which are pro-inflammatory [15]. Notably, adiponectin levels are decreased in obesity and resistin and leptin serum levels are increased [14, 15].

The anti-inflammatory effects of adiponectin include a downregulation of pro-inflammatory cytokines and an upregulation of anti-inflammatory cytokines, specifically, decreased secretion of IL-6 and TNF-alpha by monocytes. Interleukin-6 (IL-6) is an acute phase molecule that has activities in host defence and glucose and lipid metabolism and is overexpressed in obese patients [1]. Elevated TNF-alpha levels in turn cause feedback inhibition of adiponectin. Conversely, leptin's pro-inflammatory action is highlighted by its ability to cause macrophage release of IL-6 and TNF-alpha. This inverse relationship may explain why adiponectin levels are decreased in several cancers (breast, uterine, prostate, and colon) and leptin levels increased [15].

In the 2006 Presidential address at the 7th World Congress of the International Hepato-Pancreato Biliary Association in Scotland, Professor Henry Pitt hypothesized that nonalcoholic fatty pancreatic disease may lead to nonalcoholic steatopancreatits, worsened pancreatitis and ultimately pancreatic cancer in a similar model believed to lead to hepatocellular carcinoma [15]. Several animal models support his hypothesis. His group reported that obese mice have higher levels of the cytokine TNF-alpha and that leptin-deficient obese mice have more intrapancreatic fat than their lean controls [15, 16]. Obese mice were also found to have a more severe pancreatitis when injected with intraperitoneal saline or caerulin, in used to cause edematous pancreatitis [15]. Serum adiponectin levels are also found to be inversely related to the degree of pancreatitis in this model [15]. This lead the author to theorize that adiponectin levels may be more important then leptin in the pathogenesis of pancreatitis [15].

This theory has been supported by a recently published human study from Taiwan where adiponectin was found to be able to differentiate pancreatic cancer from chronic pancreatitis [17]. Researchers studied 72 patients with pancreatic cancer and compared them to 39 with chronic pancreatitis. They compared the utility of adiponectin to CA 19-9 in differentiating these two disease states and found that adiponectin had superior specificity [17]. Fourteen patients with pancreatic cancer were found to have an adiponectin level greater than or equal to 28 ng/ml compared to only one patient with chronic pancreatitis. Specificity was found to be greater than 97% when this cut-off level was used compared to 90% for CA 19-9 when a cut-off level of 240 U/ml was used [17]. The authors appropriately point out that adiponectin levels can be elevated in cholestatic states. However, when a multivariate analysis was done, bilirubin was found to be an independent factor when associated with elevated adiponectin levels, which was not the case for CA 19-9 levels [17].

Interestingly, two human studies analyzing severity of acute pancreatitis have argued that obese patients develop a more severe form of the disease [18, 19]. Papachristou et al. studied 102 patients with acute pancreatitis prospectively. They found that obese patients with a BMI>30 k/m^2 had higher APACHE scores than their lean counterparts. They also found that Il-6 levels tended to be higher in obese patients; however, this trend was not found to be statistically significant [18]. The authors theorized that obesity augmented the immune systems response to injury and resultant inflammation. Martinez et al. [19] did a meta-analysis of five studies analyzing a total of 739 patients and corroborated the finding of worsened acute pancreatitis in obese patients.

Proinflammatory Conditions and Pancreatic Cancer

Chronic tobacco abuse is the only consistently accepted environmental risk factor for pancreatic carcinogenesis. The possible link between pancreatitis and pancreatic cancer, however, remains controversial. One of the reasons for this may be the fact that a chronic inflammatory state is induced in the pancreas by smoking tobacco, thus complicating studies. An additional complicating factor is that most patient develop chronic pancreatitis as a sequela of alcohol abuse and long-term follow-up is often not possible because these patients often die as complications of their dependence before they develop cancer [20].

In a population-based case-control study of pancreatic cancer in America, researchers studied polymorphisms of several pro-inflammatory genes in patients with chronic inflammatory conditions (pancreatitis, obesity, and a history of smoking) to see if a link showing an increased risk of pancreatic cancer formation could be found [7]. Polymorphisms of the chemokine TNF-alpha and RANTES

(regulated upon activation, normally T-cell expressed and presumably secreted) were chosen because they are thought to play a role in antitumor immunity [7]. CC chemokine receptor 5C (CCR5) is one of the receptors of RANTES and was also studied.

In addition to finding a sevenfold increase in relative risk for the development of pancreatic cancer in patients with a history of pancreatitis, these authors found that pancreatic cancer development was specifically associated with two genetic polymorphisms of proinflammatory genes, TNF-α-308 and RANTES-403, in patients with a history of pancreatitis. Furthermore, they found a potential link to a genetic polymorphism of CCR5, CCR5-32*del*, and a current history of smoking [7]. These findings lend credence to the hypothesis that chronic proinflammatory conditions in people with proinflammatory genetic polymorphisms may increase their risk of pancreatic carcinogenesis [7].

However, when patients were stratified by body mass index (BMI), no correlation was found in different BMIs. This highlights the difficulty in studying chronic pancreatitis, pancreatic cancer and obesity. Most patients with chronic pancreatitis or pancreatic cancer are no longer (if ever) obese by the time they present. This is highlighted by the fact that no group was exclusively obese (BMI>30 kg/m^2) in this study. Because of this studies should probably focus on serum levels of hormones of obesity and not actual BMI.

Cytokines Elevated in Pancreatic Cancer

Because of studies revealing serum cytokine elevations that occur in both obesity and pancreatic cancer, many groups have begun trying to delineate the importance of cytokines in carcinogenesis [21, 22]. In an in vitro study of preneoplastic epithelial colonocytes treated with leptin, IL-6 levels were found to increase resulting in increased cell proliferation, a phenomenon not observed in normal epithelial colonic cells [23]. This is one of the first studies to offer a potential mechanism linking leptin-induced cytokine secretion and resultant cell proliferation to obesity-associated carcinogenesis, in this case colonic [23]. IL-6 induced tumor cell proliferation has also been found to occur in plasma cell neoplasms [24].

Okada et al. studied cytokine levels in 55 patients with pancreatic cancer. Serum IL-6 levels were found to correlate with the degree of disease, specifically, presence or absence of weight loss [25]. Detectable levels of IL-6 were found in only 5% of healthy controls and in 8% of controls with chronic pancreatitis. The authors theorized that anti-IL-6 medications could eventually ameliorate and treat symptoms of cachexia in patients with pancreatic cancer [25]. It is still not known if the IL-6 that is secreted comes from the cancer cells themselves or from the tumor associated host cells, specifically, macrophages and fibroblasts. Nonetheless, these findings raise the possibility that increased serum expression of IL-6 may also influence the rate of pancreatic cancer progression and metastasis [25].

Several studies have attempted to analyze the role of inflammatory modulators on pancreatic cancer cell lines. In a study of sodium salicylate on the human pancreatic cancer cell lines PANC-1 and BxPC-3, sodium salicylate was found to enhance TNF-alpha induced apoptosis in BxPC-3, but not in PANC-1. Population studies in over 28,000 postmenopausal women found that women who use the anti-inflammatory medication aspirin regularly had a decreased risk of developing pancreatic cancer when compared to controls [26]. These studies highlight the complexity of the role of cytokines involved in inflammation and the possibilities for future therapies [11].

Pancreatic Cancer and Cachexia

The development of cachexia in pancreatic cancer patients is not completely understood. Multiple theories exist to explain this occurrence in this patient population. The presentation of cachexia is highly variable depending on the type of cancer and not even consistent within the same cancer. One method used to study the effects of cachexia has been the resting energy expenditure (REE), researchers have found that although patients with esophageal or colorectal cancer are often hypermetabolic, some cancer such as hepato-pancreato-biliary malignancies are hypometabolic [27]. In an effort to explain this variability, a group from England studied REE, TNF and IL-6 levels in patients with pancreatic cancer. They found that although the serum levels of TNF and IL-6 do not correlate with an acute phase response, cytokine levels secreted by peripheral blood mononuclear cells did correlate [27]. This led the authors to theorize that local cytokine production may have more of a role in the degree of cachexia than systemic secretion [27].

With the identification of anorexigenic and orexigenic hormones such as leptin and ghrelin, studies began to attempt to link serum levels of these hormones with derangements in cytokines known to have an influence on cachexia. They studied seven patients with pancreatic cancer and a negative energy balance, patients were found to have decreased levels of leptin and increased insulin resistance and serum levels of IL-6 [28]. They point out that euglycemic hyperinsulinemic glucose clamp trials in patients with cancer have revealed that the degree of insulin resistance increases with rising levels of IL-6, which correlates with the findings that pancreatic cancer cell lines secrete elevated levels of IL-6 [28–30].

This led to the development of two main theories to explain the phenomena of cachexia pancreatic cancer patients. The first theory involves a dysregulation of the neuropeptide pathway of neurotensin and leptin and a second theory involves a disturbance of a protein and a lipid-mobilizing factor [31]. Notably, both of these theories involve alterations of cytokine regulation, specifically, TNF-alpha, IL-1 and IL-6 [31, 32]. Unfortunately, as alluded to in the study from England, it is not clear whether the dysregulation of these cytokines is due to alterations of the tumor itself or due to the host's response to the presence of the tumor [31].

Conclusion

To date studies evaluating the chronic inflammatory hypothesis for the increased rate of carcinogenesis in morbidly obese patients have focused on IL-6, a cytokine known to play a role in obesity, pancreatitis and pancreatic cancer. To properly ascertain the role of cytokines of inflammation on pancreatic carcinogenesis, future studies may need to also focus on the contribution of adipocytokines to the inflammatory process. If the pathogenesis of pancreatic cancer is related to hormone levels associated with obesity and cytokines associated with chronic inflammation, further investigation in this domain could potentially lead to the development of new pancreatic cancer tumor markers and ultimately new therapies. Adiponectin has recently shown promise in this domain by demonstrating superior specificity in differentiating chronic pancreatitis from pancreatic cancer when compared to more traditional tumor markers. Ultimately, future studies should help in the development of more specific microarrays to better delineate the genes linking obesity, inflammation and cancer.

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