Chapter

Islet Inflammation: The Link between Type 2 Diabetes and Pancreatic Cancer

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Abstract

The role of islet inflammation in type 2 diabetes (T2DM) and pancreatic ductal adenocarcinoma (PDAC) is complex. About 80% of pancreatic cancer patients have glucose intolerance or T2D. Chronic type 2 diabetes increases risk for pancreatic cancer, but the mechanisms are unknown. In this context two hypotheses exist: (i) pancreatic cancer causes diabetes and (ii) diabetes promotes the development of pancreatic cancer. Pancreatic ductal adenocarcinoma is the most common and deadly form of pancreatic cancer that is associated with diabetes. There are many possibilities by which obesity links to pancreatic cancer. These possibilities include insulin resistance, hyperinsulinemia and inflammation. Adipose tissue deposition near pancreas (peri-pancreatic depot) increase proinflammatory response to a high fat or high calorie containing diet. Inflammatory processes in the islets act as main mediators during the development and progression of pancreatic cancer. Recently, studies have been carried out to investigate the underlying mechanisms that contribute to tumorigenesis induced by inflammation. Tumor-elicited inflammation, secretion of pro-inflammatory cytokines and migration of immune cells play the key roles in initiation, promotion and progression of malignant metastasis in pancreatic cancer. Initiation and progression of islet inflammation in diabetes and pancreatic cancer occurs as a result of various protein–protein interactions and genetic events. The increase in pancreatic cancer cases may be attributed to the obesity endemic and obesity mediated Type 2 diabetes. The existence of link between islet inflammation in chronic diabetes and pancreatic cancer cannot be ignored, although the details about the underlying mechanisms are not clear, and must be studied in detail.

Keywords: Islet inflammation, type 2 diabetes, pancreatic cancer, obesity, insulin resistance

1. Introduction

Type 2 diabetes (T2D) is characterized by hyperglycemia which occurs due to impaired insulin production and reduced pancreatic beta cell population during insulin resistance. Most diabetes patients are able to compensate increasing insulin resistance by increasing insulin production. Now the decrease in insulin secretion occurs due to increased beta cell apoptosis, and the reason behind apoptosis remains endoplasmic reticulum stress, mitochondrial dysfunction and inflammation. Since a long time T2D and pancreatic cancer have been associated and

development of diabetes is related to occurrence of pancreatic cancer. The causes behind association of T2D with pancreatic cancer may be chronic inflammation and common progenitor cells for endocrine and exocrine pancreas, however still more research is needed in this field, and every detail about diabetes and pancreatic cancer must be studied [1].

Firstly, Type 2 diabetes is the third most possible risk factor for pancreatic cancer after obesity and cigarette smoking. Studies have shown that chronic type 2 diabetes increases risk of pancreatic cancer by 1.5- to 2.0-fold. Prediagnostic assessment of glucose and insulin levels may help in early diagnosis. The reasons behind development of diabetes-associated pancreatic cancer remain insulin resistance, hyperglycemia, hyperinsulinemia, and inflammation. On the other hand, people diagnosed with Type 2 diabetes may be part of a population of pancreatic cancer patients who have been detected earlier. There are several signaling pathways regulating metabolic processes which dictate cell proliferation and tumor growth. Better insight on the different mechanisms common in Type 2 diabetes and pancreatic cancer can be helpful in the development of new biomarkers and potent preventive or therapeutic strategies [1].

Ductal adenocarcinoma of pancreas is the fifth major cause of death in cancer in developed countries after lung, stomach, colorectal and breast cancer. 23% of the patients can live for 1 year after diagnosis and 6% of the patients have a 5-year survival rate due to advanced stage of cancer at the time of the diagnosis. Ductal adenocarcinoma of pancreas is also the thirteenth most common type of cancer and eight most common cause of cancer-related deaths. Here it must be mentioned that 80% of pancreatic cancer patients have been ailing with Type 2 diabetes or compromised glucose tolerance at the time of diagnosis [2–4].

Patients with ductal adenocarcinoma of pancreas and also Type 2 diabetes, have a record of diagnosis of diabetes less than 24 months before the diagnosis of ductal adenocarcinoma of pancreas in 74–88% of cases [5]. It means that Type 2 diabetes and ductal adenocarcinoma of pancreas show "dual causality," while chronic Type 2 diabetes remains a risk factor for the development of ductal adenocarcinoma of pancreas and, on the other hand, ductal adenocarcinoma of pancreas is also presumed to be a cause for Type 2 diabetes in many cases.

The Centre for Disease Control and Prevention recorded that ~29 million people in the U.S. suffered from Type 2 diabetes in 2014, while about 8 million of these patients have not yet been diagnosed. Also, ~86 million adults in the U.S. are known to be prediabetic, having a fasting plasma glucose level of 100–125 mg/dL, a 2-h plasma glucose level of 140–199 mg/dL, or a glycohemoglobin (HbA1c) level of 5.7–6.4% [6]. The global increase of ductal adenocarcinoma of pancreas further escalates the need to understand the pathophysiology of Type 2 diabetes. Chronic Type 2 diabetes is established to be a risk factor for ductal adenocarcinoma of pancreas [7]. Type 2 diabetes is also linked with obesity, and obesity also increases the risk for developing ductal adenocarcinoma of pancreas [8]. Type 2 diabetes is also associated with defective insulin function since insulin fails to suppress hepatic glucose release. As a result, peripheral glucose utilization mainly by skeletal muscle, is compromised, with initial increase in insulin levels since the beta cells try to overcome insulin resistance by producing more insulin [9]. With chronic Type 2 diabetes, beta cells undergo failure leading to apoptosis and decreased beta cell mass [10]. Patients with obesity and Type 2 diabetes are likely to suffer for long time periods with high intrapancreatic insulin levels due to beta cell compensation to overcome the increasing insulin demand and to maintain glucose homeostasis. Insulin is released into the circulation by beta cells through intrapancreatic portal circulation that also supplies blood to acinar and ductal cells near the islets. Acinar and ductal cells neighboring the islets may also get blood supply from intrapancreatic

portal circulation [11]. This close association allows high levels of islet hormones to directly get supplied to acinar and ductal cells, resulting in proxicrine effects on insulin receptors present on acinar cells and also on insulin like growth factor-I receptors in any differentiated cells in the region, enhancing survival and proliferation of the cells. Hence, intrapancreatic hyperinsulinemia, arising due to obesity and insulin resistance in prediabetic patients or in early diabetic patients contribute to increased risk in ductal adenocarcinoma of pancreas.

Compromised glycemic control is also associated with increased levels of advanced glycation end products (AGE) which activate RAGE, a receptor for AGE [12]. RAGE receptor belongs to the immunoglobulin super family and can bind to several ligands apart from AGE, including some proinflammatory cytokines that have role in inflammation and ductal adenocarcinoma of pancreas [12]. Also, activation of RAGE contributes to obesity and inflammation [13]. Excess of activation of RAGE also contribute to the higher prognosis of ductal adenocarcinoma of pancreas in Type 2 diabetes.

2. Mechanisms between type 2 diabetes and pancreatic cancer

The mechanism behind the association of Type 2 diabetes and pancreatic cancer is elaborate and include metabolic, hormonal, and immunological modifications that regulate tumor growth (**Figure 1**). The most presumed mechanisms behind the association between Type 2 diabetes and pancreatic cancer are insulin resistance, compensatory hyperinsulinemia and increased levels of circulating insulin-like growth factors (IGFs). In-vivo studies showed that islet cell turnover, linked with insulin resistance, is important for pancreatic cancer. Like, in hamsters, islet cell proliferation increase pancreatic ductal cancer [14], while destruction of islet cells by streptozotocin or alloxan impede pancreatic cancer prevalence [15, 16]. Also, biguanide metformin treatment inhibit the creation of pancreatic tumors by N-nitrosobis-(2-oxopropyl) amine, a potent pancreatic carcinogen. High-fat containing diet in hamsters normalize the islet cell turnover rate [17].

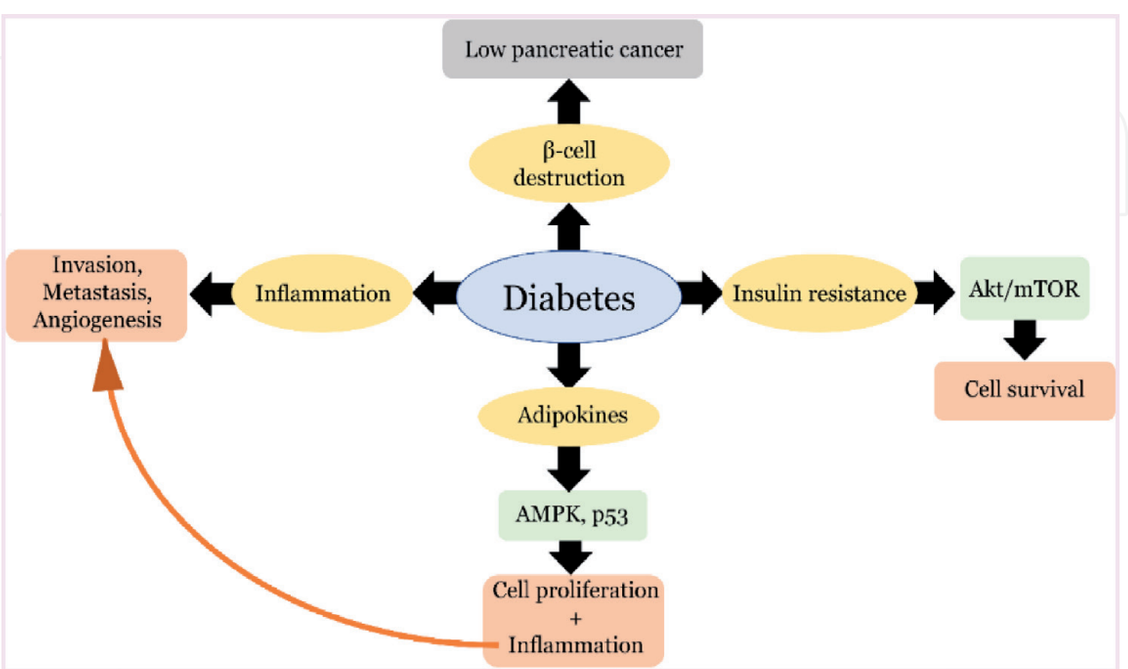

Figure 1.
Association between diabetes and pancreatic cancer [1].

Pancreatic β-cells become hyperactive, their mass increase which together led to insulin over secretion to combat insulin resistance. The exocrine part of pancreatic tissue is exposed to much higher level of local insulin concentrations than the amount of insulin in the circulation of hyperinsulinemic patients. Insulin also acts as a growth-promoting hormone which increases cell proliferation. Hence, insulin not only promotes cell proliferation but also increases uptake of glucose [18], and both of these processes are important for development and progression of tumor. Moreover, insulin increases the availability of insulin like growth factors by decreasing hepatic production of binding proteins for insulin like growth factors [19, 20]. The two main properties of insulin like growth factor-1 (IGF-1) are mitogenic and antiapoptotic activities which increase growth of cells expressing insulin as well as IGF-1 receptor (IGF1R). Here it must be noted that IGF-1 and IGF1R are overexpressed in pancreatic cancer cells [21]. Also, IGF-1 regulated signal transduction elevates proliferation, invasion, and expression of different mediators of angiogenesis and decrease apoptosis of pancreatic cancer cells as well [22–24]. IGF1R-induced signal transduction also activates several intracellular signal pathways, like Ras/Raf/mitogen-activated protein kinase and phosphoinositide-3 kinase/Akt/mammalian target of rapamycin (mTOR) pathways [25]. Decreased levels of IGF binding protein 1 can predict increased risk of pancreatic cancer [26]. Unusual glucose metabolism can also predict presence of tumor cells, since most tumors have upregulated insulin-independent glucose uptake mechanisms while, diabetic animals with β-cell destruction induced by alloxan show reduced tumor growth [27]. This suggests that hyperglycemia has no role in increasing neoplastic growth in insulin deficiency. High dietary glycemic index increases the risk of pancreatic cancer due to deleterious effects of high postprandial glucose and increasing insulin demands [28]. Type 2 diabetes and diabetes associated obesity increase the risk of pancreatic cancer due to increased oxidative stress and inflammation during type 2 diabetes and also due to the link between oxidative stress and insulin resistance [29–32]. Antioxidant supplementation with vitamin E or α-lipoic acid can be preventive or curative in insulin resistance [33, 34]. Moreover, postprandial hyperglycemia directly increases oxidative stress leading to overproduction of superoxide by the mitochondrial electron-transport chain [35]. Impairment of the cellular redox state reduces tyrosine phosphorylation and elevates serine phosphorylation of insulin receptor substrate 1, which leads to impaired insulin-signaling pathway [35]. Moreover, obesity and macronutrient intake activate inflammatory signaling pathways [36, 37], and glucose and fat intake stimulate inflammation by increasing oxidative stress and the activating transcriptional factors such as nuclear factor-κB, activating protein-1 and early growth response-1 [38–40]. Also, adipose tissues may act as an endocrine organs to regulate the release of fatty acids, hormones, and cytokines like tumor necrosis factor-α, interleukin-6, and resistin [41].

Adipocytokines, which are secreted from adipocytes, are mainly involved in apoptosis, development, metabolism, innate immunity and inflammation. Proinflammatory cytokines are known to stimulate angiogenesis, tumor progression, and metastasis. During obesity or Typ2 2 diabetes altered levels or dysfunctions of many molecules like leptin [42], IGF-1 [43], and peroxisome proliferator-activated receptor-γ [44], lead to development of pancreatic cancer by impeding immune system.

Several genome-wide studies have shown new genetic variants that increase the risk of diabetes, and some of the susceptible loci already established in Type 2 diabetes are known to be involved in differentiation and development [45]. NR5A2 (or LRH1) is one such pancreatic cancer susceptibility gene identified in genome-wide association studies [46]. NR5A2 is a direct target of pancreatic duodenal homeobox (PDX-1) gene in pancreatic development and differentiation [47]. It regulates the

expression of developmental genes, like transcription factors hepatocyte nuclear factor (HNF)-3β, HNF-4α, and HNF-1β. On the other hand, NR5A2 expression is regulated by HNF-3β and HNF-1, so the case is regulated both ways. PDX-1 is necessary for pancreatic development and also for casual function of β-cell and secretion of insulin [48]. Mutations in HNF-1β gene is associated with maturity-onset diabetes in the young people [49]. Better insight about the function of NR5A2 gene in the progression and development of pancreatic cancer can be helpful in curbing the risk of diabetes-linked pancreatic cancer and also decipher the genetic mechanisms behind Type 2 diabetes and pancreatic cancer.

2.1 Genomic associations between type 2 diabetes, chronic pancreatitis and pancreatic ductal adenocarcinoma

Several clinical and epidemiological studies associate the risk of ductal adenocarcinoma of pancreas to chronic Type 2 diabetes and chronic pancreatitis (CP). The genetic reasons of susceptibility among all these three diseases are quite variant however, some reasons are common. The mechanism behind the function of these genes and how they influence susceptibility is not common because of the difference in methodology of identification of the genes. Interestingly, all three diseases share these characteristics: 1) all patients have a report of family history or familial clustering, which indicate shared genetic or environmental influence, 2) difference in age of patients at the time diagnosis is due to familial risk, and 3) analyzing Mendelian segregation prove that in some families there are some hereditary components which demonstrate the common features of the gene [11]. Apart from genetics factors, there are epidemiological factors like obesity in diabetes, alcohol intake in chronic pancreatitis, and smoking in ductal adenocarcinoma of pancreas that may work with genetic factors to increase the risk. Several approaches have been evolved to discover these susceptibility genes, from family-based case control studies and cohort studies, from where a list of candidate genes is identified, and large-scale genome-wide association studies (GWAS) are conducted to search for single nucleotide polymorphisms (SNPs) or next-generation sequencing. The genetic basis of Type 2 diabetes is characterized as polygenic, having implication of over 50 genes [50]. Any single major gene cannot explain the genetic risk of Type 2 diabetes except in some rare cases [51]. However, chronic pancreatitis and ductal adenocarcinoma of pancreas can be explained by mutations in some major genes. Genome-wide association studies (GWAS) have identified many low-penetrance common SNPs which are associated with risk of ductal adenocarcinoma of pancreas. Among all these three diseases, Type 2 diabetes has been studied in detail, which depict that Type 2 diabetes is a multifactorial disease and is genetically complex. Variants of more than 50 genes have been studied which increase genetic risk. These genes are divided into some having modest effect like PPARG and KDNJ11, and others having strong association like TCF7L2, WFS1, HDF1B, FTO, CDKN2A, and SLC20A8. New strategies have been developed which have characterized the genetic basis of the disease through subclinical or related phenotypes by predisposition of the genes [52]. Since Type 2 diabetes is a polygenic risk model, each genetic variant has a small effect. These genetic variants improve risk assessment from common risk factors like age, sex, family history and BMI (Body Mass Index) [53]. Family-based studies and data on pathophysiology of chronic pancreatitis facilitate success in explaining the genetic heterogeneity [54]. Most of the variations in susceptibility are due to acute and chronic pancreatitis being related to genetic variations among patients. Alcohol was considered to be the primary reason behind genetic contributions but after the discovery of PRSS1, CFTR, and SPINK1 variants which associated with pancreatitis the reasons have been resolved [55]. Hence, no

single factor can cause pancreatitis, and majority of cases having acute and chronic pancreatitis have multiple variants of a gene, or multiple genes having epistatic interactions, or genetic factors coupled with environmental cues.

The genetic predisposition to ductal adenocarcinoma of pancreas is difficult due to the poor collection and analysis of biospecimens from patients owing to their low survival rate. Alike Type 2 diabetes and chronic pancreatitis, ductal adenocarcinoma of pancreas is also genetically heterogeneous. The identification of susceptibility genes has led to discovery of some rare gene mutations which are associated with cancer syndromes linked with common single nucleotide polymorphisms (SNPs). Study designs on family hierarchy and case-controls have led to discovery of mutations in known syndrome-associated genes, like BRCA1, BRCA2, CDKN2A, and CFTR. Moreover, next-generation sequencing has led to identification of additional mutations like PALB2 [56] and ATM [57]. Patients with sporadic ductal adenocarcinoma of pancreas carry germline mutations in major genes [58] and it changes the present knowledge for risk assessment. Large numbers of sporadic cases of ductal adenocarcinoma of pancreas and healthy subjects have exposed SNPs in chromosomal regions containing ABO, TERT, and CLPTM1L and other genes. Nevertheless, risk modeling using GWAS SNPs cannot provide sufficient genetic information that can improve prediction of pancreatic cancer [59].

2.2 Role of obesity and pancreatitis mediated inflammation in pancreatic ductal adenocarcinoma

Obesity is linked with an elevated risk of cancer, including pancreatic cancer [60]. The observed increase in pancreatic cancer epidemiology and deaths can be partially attributed to obesity taking the form of an endemic disease. Obesity can lead to pancreatic cancer, insulin resistance, hyperinsulinemia and inflammation by many possible ways [61]. Pancreatic cancer development can be attenuated in genetically engineered mouse model by using nonsteroidal anti-inflammatory drugs, which indicate that tissue inflammation plays an important role in this disease [62]. Tissue inflammation during obesity creates a perfect microenvironment for tumor initiation and promotion. Besides obesity, increase in BMI and visceral adiposity bears a strong link with metabolic diseases and gastrointestinal cancers, together with pancreatic cancer [63]. The accumulation of adipose tissue near the pancreas (peri-pancreatic depot) lead to an enhanced proinflammatory reaction in response to high-fat or high-calorie containing diet compared to peri-gonadal depot [64]. The association between adipose tissue depot-specific reactions to diet-induced obesity and the effect of these adipose tissue depots on cancer development is very crucial to understand the connection between body condition and risk of cancer. Moreover, high-fat or high-calorie containing diet increases the progression of pancreatic intraepithelial neoplasia, which is a known precursor of ductal adenocarcinoma of pancreas, and this accelerates the incidence of pancreatic cancer in an invasive and metastatic manner in conditional KrasG12D mouse model [65, 66].

2.3 Mechanisms behind type 2 diabetes in pancreatic ductal adenocarcinoma

To be specific, prevalence of Type 2 diabetes among ductal adenocarcinoma of pancreas patients is really very high. Type 2 diabetes is found in 47% of ductal adenocarcinoma of pancreas patients compared with only 7% of healthy subjects, and a normal fasting glucose occurs in 59% of healthy subjects, while it is found only in 14% of ductal adenocarcinoma of pancreas patients [5] (**Figure 2**). In 74% of ductal adenocarcinoma of pancreas patients with diabetes, diabetes is diagnosed within 24 months before the diagnosis of ductal adenocarcinoma of pancreas [67].

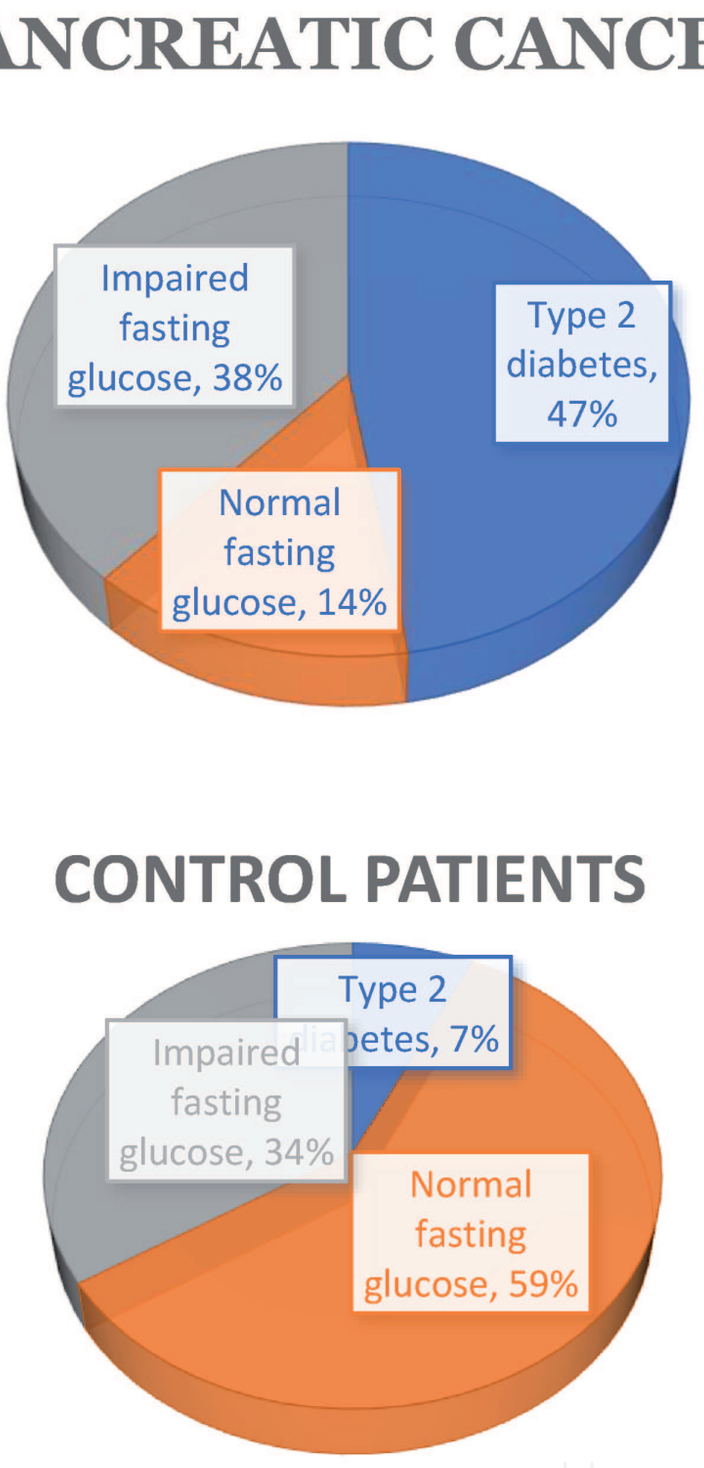

Figure 2.
Prevalence of type 2 diabetes in ductal pancreatic adenocarcinoma [5, 11].

This remarks that in most of the patients, new-onset diabetes is due to the tumor and this diagnosis of diabetes may be a useful "biomarker" for the diagnosis of ductal adenocarcinoma of pancreas. Although known risk factors for Type 2 diabetes like obesity, age and family history of diabetes are also the common risk factors in case of risk factors for ductal adenocarcinoma of pancreas, the occurrence of Type 2 diabetes in ductal adenocarcinoma of pancreas is pretty higher than the occurrence of Type 2 diabetes among all other common types of cancer. Type 2 diabetes is found in 68% of patients with ductal adenocarcinoma of pancreas while it occurs in 14.8–23.5% of patients with breast, colon, lung, and prostate cancers [68]. Also, insulin resistance is common in patients with both ductal adenocarcinoma of

pancreas and Type 2 diabetes, while many patients with ductal adenocarcinoma of pancreas undergo weight loss. Deteriorating glycemic control along with weight loss occurs in ductal adenocarcinoma of pancreas along with its incidence in Type 2 diabetes. These common characteristics give alert to the clinicians for the possibility of ductal adenocarcinoma of pancreas -associated diabetes. New-onset diabetes associated with ductal adenocarcinoma of pancreas can be cured after tumor resection, if there are enough islets left in the pancreatic tissue. Several reports show that Type 2 diabetes improves after resection of pancreatic tumors [69]. 57% of the patients with new-onset diabetes get cured of diabetes post operation of pancreatic tumors, while all of ductal adenocarcinoma of pancreas patients with long-standing diabetes cannot be cured of diabetes even after pancreatic resection [5] (**Figure 3**). These data strongly support that new-onset diabetes is associated with ductal adenocarcinoma of pancreas and it can be a paraneoplastic phenomenon, where malignancy interferes with insulin secretion or insulin function, finally leading to Type 2 diabetes. Numerous studies have tried to identify the mechanisms behind Type 2 diabetes caused by ductal adenocarcinoma of pancreas or the genomic and protein markers of Type 2 diabetes caused by ductal adenocarcinoma of pancreas. Connexin 26, a gap junction protein, is highly overexpressed in islets of ductal adenocarcinoma of pancreas patients with Type 2 diabetes [70], and a pancreatic ductal adenocarcinoma -derived S-100A8 N-terminal peptide is a diabetogenic agent [71, 72] which is also upregulated patients with ductal adenocarcinoma of pancreas associated with new-onset diabetes. Vanin-1 and matrix metalloproteinase 9 can also act as predictors of ductal adenocarcinoma of pancreas associated diabetes [73]. Vanin-1, is also overexpressed during inflammation, which means that mediators of inflammation play an important role in damaged islet function and insulin function in ductal adenocarcinoma of pancreas. Pancreatic Polypeptide (PP) release increases in Type 2 diabetes, and a deficit in PP response due to nutrient ingestion can transform into new-onset diabetes caused by pancreatic exocrine

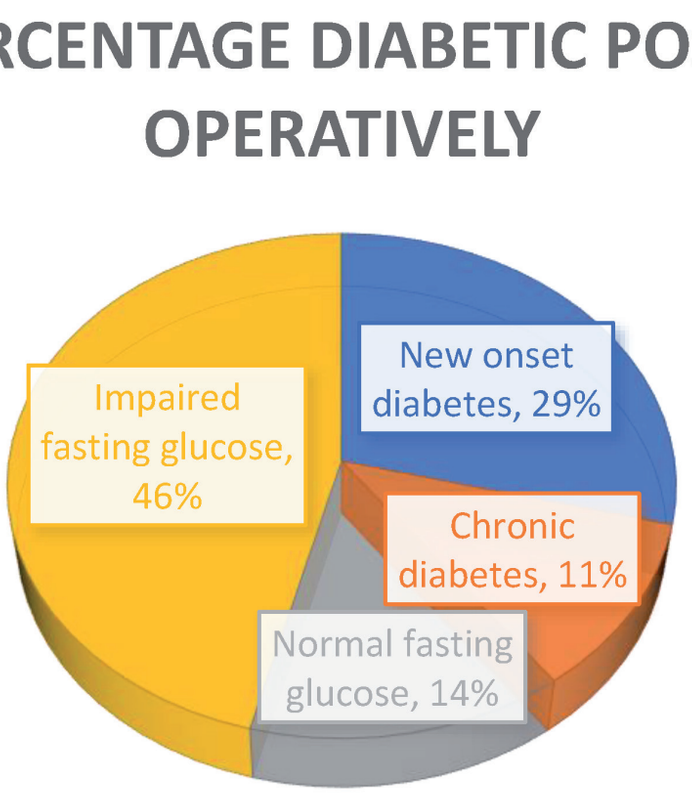

Figure 3.
Prevalence of type 2 diabetes after pancreaticoduodenectomy for ductal pancreatic adenocarcinoma [5, 11].

disease. Basal and meal-stimulated PP release significantly decreases in patients with diabetes associated with ductal adenocarcinoma of pancreas localized in the head of pancreas in comparison to patients with Type 2 diabetes [11].

2.4 Significance of type 2 diabetes in pancreatic ductal adenocarcinoma

Some researchers say that diabetes does not contribute to earlier diagnosis or clinical features or tumor size or prognosis of pancreatic cancer [74], although, previous studies had established that diabetes can predict pancreatic cancer [75]. A study compared diabetic and non-diabetic patients and observed a worse overall mortality and median survival in diabetic patients [76]. In another study, patients with diabetes had a better overall survival [77]. On the other hand, Type 2 diabetes is known to confer a poor survival in ductal adenocarcinoma of pancreas patients [78]. Actually, gender and mean age of the patients in these two studies regulated the number of comorbidities, time of diabetes and also time for development of complications in diabetes [75]. Use of preventive medicine, frequent clinical follow-up and earlier diagnosis of ductal pancreatic adenocarcinoma can generate a better median survival.

3. Future perspectives of dealing with pancreatic ductal adenocarcinoma

The explanation of hormonal [79], paracrine [21] and autocrine [22, 23] mediators of pancreatic cancer and its association with new-onset diabetes can be helpful in pathogenesis and showing new therapeutic targets. A better explanation of the epidemiology of pancreatic cancer, is poorly controlled diabetes or it can be an intrinsically genetic [8] or epigenetic [80–82] or immunologic [83, 84] or gastrointestinal microbiota [85, 86] or tissue microenvironment which are characteristic of Type 2 diabetes [87–89] patients progressing towards pancreatic cancer.

The various techniques like gene sequencing, lymphocyte flow cytometry, mRNA profiling, PCR studies and microbe identification microarray from Type 2 diabetes patients in different stages of progression can help in early diagnosis and prevent diabetic complications in pancreatic cancer and diabetes. Molecular biomarkers can be very crucial to diagnose patients with new-onset diabetes who should be tested with endoscopic ultrasound for identifying pancreatic cancer [75]. Hyperinsulinemia can negatively predict value development of new-onset diabetes associated with pancreatic cancer if all other hormonal, paracrine or autocrine factors play against development of insulin resistance [75].

Metformin, a well-known medication for Type 2 diabetes, improves survival in pancreatic cancer patients and has prognostic effects [90]. The knowledge available on the mechanism of action of metformin helps in the understanding of the ductal adenocarcinoma of the pancreas cancer pathways [75].

4. Altered intracellular metabolism in pancreatic ductal adenocarcinoma

Deregulated systemic physiology is the effect of disruption of energy homeostasis, and metabolic processes within the cells of a pancreatic tumor can also be knowledgeable [91]. Malignant cells of a pancreatic tumor, have alterations that are mediated by both oncogene-driven programs and also by the rare physiology of tumor. Pancreatic tumors have a dense, fibrotic stroma which inhibits vascular function and also disrupts delivery of nutrients and oxygen [92]. Mutant Kras

expression regulates metabolic networks facilitating redox balance, bioenergetics, and anabolic metabolism for better survival and cell proliferation under these poor circumstances [93–95]. Nutrients recycled by autophagy fuel these pathways [96, 97] and also the nutrients scavenged by nonspecific bulk extracellular space engulfment or by micropinocytosis [98] as well as overexpressed nutrient importers help in regulating these pathways [93, 99]. Together, the regulation of metabolism of pancreatic cancer cells are controlled by oncogene-driven pathways, and they engage nutrient scavenging mechanisms as well as improve nutrient utilization to overcome the problems of insufficient vascularization [91].

Malignant cells constitute 10% of the total cellular content of a pancreatic tumor [92]. As a result, the non-malignant cells help in shaping the metabolic condition and facilitate tumor growth [91]. These processes can be divided into 2 types: First, the cooperative reactions between non-malignant cells and malignant cells support the metabolism in cancer cells, and second, the reaction between malignant and non-malignant cells is competitive and it happens between tumor cells and the antitumor immune reaction [100].

One main cooperative reaction is the nutrient exchange pathway that occurs between pancreatic cancer cells and activated pancreatic stellate cells (PSCs) [101]. Pancreatic cancer cells are known to induce autophagy in the PSCs. As a result, protein breakdown occurs through autophagy and nonessential amino acids are released. Now, the pancreatic cancer cells engulf alanine and utilize it to in mitochondrial metabolism and also in the biosynthesis of cellular building blocks. Here it must be mentioned that alanine can be used in metabolism in replacement of glucose and glutamine, and the biosynthetic substrates also aid in cancer cell metabolism. If this metabolic crosstalk pathway is blocked or inhibited by suppressing autophagy particularly in the PSCs then it can lead to a dramatic decrease in tumor growth. Interestingly, pancreatic tumors can suppress immune responses and are highly resistant to immunotherapies [102]. Local nutrient depletion and waste accumulation indeed play important roles in aiding tumor immune suppression [100]. Moreover, Cytotoxic T-cells, are intrinsically less apt at obtaining nutrients than oncogene-driven cells, and they are compelled to compete for the limited nutrients like carbohydrates and amino acids, in a tumor microenvironment, and later result in defective antitumor immune response. The compromised antitumor T-cell response in melanoma and sarcoma is directly connected with glucose deprivation [103, 104], while high titres of lactate aid in the polarization of anti-inflammatory macrophages [105]. Mutant Kras-expressing pancreatic cancer cells vigorously consume glucose and then release lactate (so-called, Warburg metabolism) [93], and all of these mechanisms result in suppressed immune function in pancreatic cancer. Moreover, M2 type anti-inflammatory macrophages and cancer cells can exhaust tumors of amino acids such as arginine and tryptophan [106]. These processes also restrict antitumor T-cell responses and aids the differentiation of T-cells into anti-inflammatory T-regulatory cells.

5. Role of bariatric surgery in obesity and pancreatic ductal adenocarcinoma

Premorbid obesity unpleasantly influences ductal adenocarcinoma of pancreas associated mortality in a dose-dependent manner [107, 108]. A high BMI is also linked with an increased risk of ductal adenocarcinoma of pancreas [107, 108]. The etiology of obesity-linked diseases starts with excess energy and deposition of triglyceride in the adipose tissue. This excess of triglyceride cannot be completely deposited in the adipose tissue, hence ectopic fat deposition occurs in various

organs like liver and pancreas. Triglyceride deposition in the liver leads to oxidative stress and inflammation, resulting in cirrhosis, steatohepatitis and hepatocellular carcinoma. Similar mechanisms occur in the pancreas. Free fatty acids and inflammatory mediators remain in high amounts in the pancreas of obese high fat fed mice [109], and this accelerates tumor growth [110]. Fat depots in liver and pancreas increase in obese individuals. After bariatric surgery, weight loss occurs, and hepatic and pancreatic fats rapidly disappear [111]. After weight loss, insulin resistance and circulatory levels of inflammatory factors also rapidly normalize [112]. Weight loss occurring after bariatric surgery decreases cancer mortality by 40–60% [113, 114]. Also, the risk of ductal adenocarcinoma of pancreas is significantly lower among the patients who have undergone bariatric surgery [115]. Nevertheless, bariatric surgery is restricted to individuals with high obesity (mean BMI >40 kg/m2). Substantial weight loss (mean > 30% total body weight) occurs in these individuals after bariatric surgery. Moreover, intentional weight loss by bariatric surgery or changes in lifestyle or pharmacotherapy or less invasive surgical or endoscopic procedures also helps in reducing the risk of cancer in obese patients [115].

6. Role of visceral and Peripancreatic fat in pancreatic ductal adenocarcinoma

BMI is a well-known marker for adiposity, and can also be linked with insulin resistance, metabolic syndrome and gastrointestinal malignancies, like ductal adenocarcinoma of pancreas [116]. Highly inflamed visceral adipose tissue (VAT) in obese patients remains the main reason behind metabolic dysfunction and gastrointestinal cancer due to the close proximity of the visceral organs with the portal system. VAT has a high correlation with occurrence of ductal adenocarcinoma of pancreas. Interestingly, conditional KRasG12D (KC) mice fed high-fat and high calorie containing diet gained more weight than the standard diet fed mice and ended up developing hyperinsulinemia and hyperleptinemia with extensive VAT expansion and high inflammation [64, 65, 117]. These obese KC mice had highly inflamed pancreas and were more prone to develop ductal adenocarcinoma of pancreas than the control mice fed on standard diet and this occurred in the male mice, which meant that the sex hormones had a role in it [117]. Interestingly, the increased incidence of pancreatic ductal adenocarcinoma in obese KC mice was largely seen in male mice, suggesting a role for sex hormones in this process, since the female mice gained more adipose tissue subcutaneously [64, 65, 117].

7. Role of gut microbiome in pancreatic ductal adenocarcinoma

Human microbiome has gained a lot of popularity recently to tackle prevention, as well as early diagnosis, and treatment of ductal adenocarcinoma of pancreas, since many diseases have now started to be linked with composition of microbiome [118–120]. The composition of microbiome also interferes with development of ductal adenocarcinoma of pancreas and its relation with diabetes, obesity, and inflammation [121]. Ductal adenocarcinoma of pancreas is an inflammation-mediated cancer and gut microbiome can stimulate chronic inflammation via changes in molecular pattern recognition receptors. These pattern recognition receptors and their downstream signaling cascade leads to the incidence of inflammation-mediated cancers. These bacteria regulate the efficiency of calorie absorption in the intestines and hence lead to obesity. Many diseases like Type 2 diabetes, obesity, and chronic pancreatitis are linked with chronic inflammation, which also result in

ductal adenocarcinoma of pancreas [122]. Moreover, alteration of oral microbiome increases risk of ductal adenocarcinoma of pancreas, and it can be a useful biomarker of the disease. Specific abundance in certain oral bacteria and gut microbiome in pancreatic secretions or fecal matter may be associated with risk of ductal adenocarcinoma of pancreas, hence these knowledges can help in preventing or in early diagnosis of ductal adenocarcinoma of pancreas [122].

8. Role of inflammation in pancreatic ductal adenocarcinoma

As already mentioned above, chronic inflammation in pancreas or chronic pancreatitis is a major reason behind ductal adenocarcinoma of pancreas. Activated PSCs play a key role in progression of chronic pancreatitis. Activation of PSCs is also increased by cytokines secreted from injured acinar and immune cells. The mechanisms underlying triggering of macrophages and survive the fibrotic processes by reacting with PSCs, if interfered end in suppression of inflammation and fibrosis in chronic pancreatitis [123]. Alcohol and smoking are also potent risk factors for chronic pancreatitis and ductal adenocarcinoma of pancreas. IL-22 signaling during inflammation and cross talk between immune cells and PSCs is one of the signaling involved in smoking-induced progression of chronic pancreatitis [124]. The other pathways that are behind progression of ductal adenocarcinoma of pancreas are IL-6 and histone deacetylases in immune and cancer cell interactions, which together mean that immune signals are key factors in promoting pancreatitis and pancreatic cancer progression [125]. However, most cases of ductal adenocarcinoma of pancreas are resistant to immunotherapies treatment with immune checkpoint antibodies because inflammatory processes are important in promoting the malignant transformation, growth, and metastasis of pancreatic cancer. For example, Kras mutations stimulate profuse cytokine and chemokine secretion in tumor epithelial cells and recruit immune cells like macrophages, dendritic cells (DCs), and myeloid-derived suppressive cells, all of which stimulate tumor growth and progression. So, all these cells need to be reprogrammed in ductal adenocarcinoma of pancreas to create a favorable immunostimulatory environment for efficient immunotherapy. Since, ductal adenocarcinoma of pancreas is often followed by metastatic relapse even after complete surgical pancreatic resection, the newly developed cancer cells fail in immunotherapy, which means that a better knowledge about the factors affecting metastasis is important for the development of more effective immunotherapies and treatments [126]. Early metastases are linked with dense networks of CD11b + CD11c + MHC-II + CD24 + CD64 and low F4/80 cells, and all of these cells develop from monocytes and aid in promoting metastasis by increasing regulatory T-cells and suppressing the development of cytotoxic T-cells. Phenotypically similar dendritic cells are seen to accumulate at primary and secondary sites in pancreatic portions of ductal adenocarcinoma of pancreas patients [127]. Dendritic cells can be reprogrammed into immunostimulatory antigen-presenting cells in tumor metastasis, which is one of the most popular immunotherapeutic strategies at present. Another strategy is based on the availability of tumor-binding immunoglobulin G antibodies along with some dendritic cell-stimulating molecules which help the enable tumor-associated dendritic cells to uptake, process, and present a variety of tumor antigens to T-cells. Then the T-cells proliferate and attack the tumors throughout the host. This technique can eradicate metastases, and also primary tumors in many types of cancers, including ductal adenocarcinoma of pancreas by overcoming tumor-mediated immunosuppression [128]. But the tumor cells tend to enter into the circulation and metastasize and end up colonizing distant organs [129]. Metastatic ductal adenocarcinoma of

pancreas has many epigenetic modifications in the primary tumor. While the cancer cells circulate in clusters and colonize different organs, the establishment of a new premetastatic niche in a new organ includes proinflammatory processes, exosomes and immune cells [130]. All of this information can help in developing new therapeutic approaches targeting different agents for primary ductal adenocarcinoma of pancreas and also in its metastasis.

9. Conclusion

Ductal adenocarcinoma of pancreas is a very challenging malignancy with a high incidence and high lethality. Moreover, the disease has intricate relationships with diabetes and obesity. Type 2 diabetes has its own risks and can be both a risk factor for ductal adenocarcinoma of pancreas as well as an early manifestation of the disease. Obesity is also strongly associated with increasing risk of ductal adenocarcinoma of pancreas. However, every detail about all these diseases and their association is not fully understood, particularly the specific mechanisms that contribute to ductal adenocarcinoma of pancreas are not clear, which makes the diagnosis and treatment of ductal adenocarcinoma of pancreas very difficult. Hence present research is targeted in bringing out all the minute details and the mechanisms to tame this malignancy and preferably find a cure or a preventive mechanism or at least a better biomarker in near future.

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Conflict of interest

The author declares no conflict of interest.

Notes/thanks/other declarations

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