Diabetes and Pancreatic Cancer

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Abstract

Epidemiological studies clearly indicate that the risk of pancreatic cancer is increased in diabetic patients, but most studies focus on overall diabetes or type 2 diabetes (T2DM), and there are few studies on the risks of type 1 and type 3c (secondary) diabetes. Possible mechanisms for increased cancer risk in diabetes include cellular proliferative effects of hyperglycemia, hyperinsulinemia, and abnormalities in insulin/IGF receptor pathways. Recently, insulin and insulin secretagogues have been observed to increase the pancreatic cancer risk, while metformin treatment reduces the cancer risk in diabetic subjects. In addition, anti-cancer drugs used to treat pancreatic cancer may either cause diabetes or worsen coexisting diabetes. Type 3c diabetes (T3cDM) has emerged as a major subset of diabetes and may have the highest risk of pancreatic carcinoma especially in patients with chronic pancreatitis. T3cDM is also a consequence of pancreatic cancer in at least 30% of patients. Distinguishing T3cDM from the more prevalent T2DM among new-onset diabetic patients can be aided by an assessment of clinical features, and confirmed by finding a deficiency in post-prandial PP release. In conclusion, diabetes and pancreatic cancer have a complex relationship that requires more clinical attention. The risk of developing pancreatic cancer can be reduced by aggressive prevention and treatment of T2DM and obesity, and the prompt diagnosis of T3cDM may allow detection of a tumor at a potentially cureable stage.

Keywords

Diabetes, Pancreatic cancer, Obesity, Hyperinsulinemia, Insulin, Insulin-like Growth Factors, Sulfonylureas, Incretin therapy, Metformin, Pancreatic duodenal homeobox-1 (PDX-1), Glucagon-like peptide-1 (GLP-1), Pancreatic polypeptide (PP), Chronic pancreatitis
INTRODUCTION

Pancreatic cancer (PC) is one of the most lethal malignant diseases due to the high rate of advanced stage disease at diagnosis, and the lack of any effective medical therapy (Ko AH and Tempero MA 2009). The overall incidence of the disease has increased over the past few decades such that over 265,000 people worldwide are diagnosed annually (Jemal A et al. 2011). Five-year survival after surgical resection has slowly risen to about 20%, owing to better selection of surgical candidates and some modest improvements in adjuvant therapy, but only 10-15% of patients are candidates for resection, and more than 95% of all patients will succumb to their illness within 2 years of diagnosis (Edwards BK et al. 2005). This high mortality rate confers PC as the fourth leading cause of cancer-related deaths in the U.S. currently (Jemal A et al. 2010). With the continuing decline in mortality rates of cancers of the lung, colon, breast, and prostate due to the combined effects of widespread screening, smoking cessation and more effective therapy, it is projected that pancreas cancer will become the leading cause of cancer-related deaths in the U.S. by 2050 (Siegel et al. 2012).

The etiology of PC is complex and poorly understood. Therefore the identification of risk factors, especially those which are modifiable through medication or behavioral change, is important for preventing the development and progression of PC. Risk factors for pancreatic cancer include family history, smoking, obesity, chronic pancreatitis, and diabetes mellitus (DM). The recent increase in the prevalence of type 2 DM (T2DM) is thought to have contributed to a parallel rise in the incidence of PC. Roughly half of all PC patients are found to have DM at the time of diagnosis, and roughly half of the DM which is present at the time of PC diagnosis is of new onset having developed over the 2-3 years preceding the diagnosis of PC. This new-onset DM is therefore thought to be secondary, or type 3c, DM (T3cDM). The association between PC and DM has been investigated extensively, but the causal relationships have yet to be fully elucidated, in part due to difficulties in distinguishing T2DM from T3cDM.

In this review, we highlight important recent studies and discuss the available evidence concerning the possible mechanisms that are involved in the etiologic role of DM in the development of PC, the effects of anti-diabetic therapy on the risk of PC, and a strategy for distinguishing T3cDM from T2DM so as to identify the patient with early and indolent PC.

DIABETES (AND OBESITY) AS A CAUSE OF PANCREATIC CANCER
The Risk of Pancreatic Cancer is Increased in Type 1, Type 2 and Type 3c Diabetes

It has long been known that PC is associated with DM, and recent studies have revealed that about 85% of patients diagnosed with PC have impaired glucose tolerance or frank DM (Pannala 2008) (FIGURE 1). DM is a group of metabolic disorders characterized by hyperglycemia. The three most common subtypes of DM differ greatly in their metabolic and hormonal characteristics, however (Table1) (Cui YF & Andersen DK 2011). Type 1 DM (T1DM) is associated with a profound or absolute deficiency of endogenous insulin secretion and an absolute requirement for exogenous insulin administration. Hyperglycemia and hyperinsulinemia coexist in T2DM due to insulin resistance in peripheral tissues usually in association with obesity. T3cDM is associated with benign and malignant disease of the exocrine pancreas, including acute and chronic pancreatitis of any etiology, pancreatic neoplasms, pancreatic trauma, pancreatic resection, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, and pancreatic agenesis, and is characterized by a severe deficiency of all pancreatic glucoregulatory hormones (American Diabetes Association 2011, Cui Y & Andersen DK 2011).

Epidemiological studies have demonstrated that DM is a risk factor for multiple forms of malignancy including PC (Wideroff L et al. 1997, Calle EE et al. 2003, Huxley R et al. 2005). A recent meta-analysis of 35 cohort studies concluded that a two-fold risk of pancreatic malignancy exists in diabetic patients (Ben Q 2011). DM was associated with an increased relative risk (RR) of PC (RR=1.94; 95% confidence interval [CI]: 1.66-2.27), with significant evidence of heterogeneity among the studies surveyed (p<0.001, I²=93.6%). Subgroup analyses revealed that the increased risk of PC was independent of geographic location, sex, study design, alcohol consumption, body mass index (BMI) and/or smoking status. In addition, the risk of PC correlated negatively with the duration of DM, with the highest risk of PC found among patients with DM diagnosed within less than 1 year. This finding implies that many of the diabetic subjects had PC-induced DM (T3cDM), but the type of DM was not identified in most epidemiologic studies.

A meta-analysis of three recent studies in which 2192 PC patients were compared to 5113 controls revealed a 1.8-fold increase in risk of PC associated with T2DM, although many of the patients classified as T2DM likely harbored T3cDM which became evident close to the time of diagnosis of the cancer (Li D 2011). Finally, a recent cohort study comparing 110,919 DM subjects and 211,695 controls provides strong support for an etiologic role of T2DM and hyperinsulinemia in the pathogenesis of PC (Yacoub A et al. 2011). The DM cohort had 124 PCs develop during 0.558 million person-years (MPY) of follow-up (222 PCs/MPY), whereas the control cohort had 140 PCs develop during 1.299 MPY of follow-up (108 PCs/MPY). Stratified
Cox regression of PC incidence yielded a hazard ratio (HR) of 2.17 (95% CI: 1.70-2.77) for T2DM compared to controls. So the risk of developing PC is clearly although modestly increased (about 2 fold) in the presence of long-standing, mostly type 2, DM.

Genetic studies have also provided insights underlying the association of DM and PC. Pierce et al examined the 37 risk alleles of T2DM, and found two which showed nominally significant positive associations with PC risk (FTO rs8050136 per-allele OR = 1.12; 95% CI: 1.02-1.23; MTNR1B rs1387153 OR = 1.11; 95% CI: 1.00-1.23), and the glucose-raising allele of MADD rs11039149 was associated with increased risk of pancreatic cancer (OR = 1.14; 95% CI: 1.03-1.27) (Pierce BL et al. 2011). Prizment et al reported that GCKR rs780094, a single-nucleotide polymorphism related to T2DM, may be associated with PC risk. In a multivariate-adjusted model, a significant association was observed only for rs780094 in the glucokinase regulator (GCKR) gene: odds ratios for pancreatic cancer were 1.00 for the TT genotype, 1.35 (95% CI: 0.71-2.58) for the CT genotype, and 2.14 (95% CI: 1.12-4.08) for the CC genotype (P = 0.01), which did not change after the adjustment for the presence of DM (Prizment AE et al. 2012).

There are few studies which specifically address cancer incidence in T1DM patients. A cohort study evaluating cancer incidence in nearly 30,000 Swedish T1DM patients diagnosed in the period 1965–1999 identified 355 cases of cancer, which equated to a standardized incidence ratio (SIR) of 1.2 (95% CI: 1.0–1.30) compared with the general Swedish population (Zendehdel et al. 2003). In contrast to these modest findings, a meta-analysis including three cohort studies and six case-control studies has found that the RR for PC was doubled in T1DM patients and “young-onset” diabetics in comparison with non-diabetics (Stevens RJ et al. 2007).

T3cDM has emerged as a major subset of the total population of DM and harbors the highest risk of PC especially in patients with T3cDM secondary to chronic pancreatitis (Cui Y and Andersen DK 2011). Persons with any form of chronic pancreatitis are at increased risk of developing PC, and Lowenfels et al observed that the risk is cumulative over the course of chronic pancreatitis, such that 4-5% of patients develop pancreatic cancer over the course of 20 years, a risk which is 10-20 times greater than the general population (Lowenfels AB et al. 1993). In a case-control study in which 823 pancreatic cancer patients and 1,679 controls were surveyed from centers in Australia, Canada, the Netherlands, and Poland, the risk of PC was seen to be increased (RR 4.7) for subjects with a history of pancreatitis (not otherwise defined), although was increased only among alcohol drinkers (RR 7.5) and not among teetotalers (RR 0.57) (Maisonneuve P et al. 2010) (FIGURE 2). A recent cohort study in Taiwan showed that in addition to age, chronic pancreatitis (HR = 19.40), gallstones (HR = 2.56), and hepatitis C infection (HR = 3.08) were significant factors predicting PC; patients with concurrent DM and chronic pancreatitis had a dramatically elevated risk of developing PC (HR = 33.52), as compared with subjects without these co-morbidities (Liao KF et al. 2011).
Obesity as a Risk Factor for Pancreatic Cancer

In 2003, Calle et al examined the American Cancer Society database to assess the possible role of obesity on the risk of cancer. In their cohort of over 900,000 individuals, massive obesity (BMI > 40) was associated with a 50-60% increased death rate from cancers of the pancreas, liver, kidney, colon and rectum, esophagus, non-Hodgkins lymphoma, and multiple myeloma over a 16 year period (Calle EE et al. 2003). The greatest effects were seen in liver cancer (RR 4.52 for men and 1.68 for women), colorectal cancer (RR 1.84 for men and 1.46 for women), and PC (RR 1.49 for men and 2.76 for women). Over 80% of T2DM patients are obese and studies on the obesity–pancreatic cancer association are influenced by the high prevalence of obesity in T2DM patients, and by the high percentage of T2DM which is undiagnosed. Recent epidemiological studies have demonstrated that a high BMI is positively associated with an increased risk of many common cancers independent of the co-existence of T2DM (Teucher B et al. 2010), and a high BMI has been identified as an independent risk factor for PC (Silverman DT 2001, Michaud DS et al. 2001, Gumbs AA 2008, Arslan AA et al. 2010,). More recently, large prospective cohort studies with a long duration of follow-up have been conducted in the U.S. showing a positive association between high BMI and the risk of PC (adjusted RR, 1.13–1.54) (Jiao L et al. 2010, Johansen D et al. 2010), suggesting the role of obesity and overweight as conferring a higher risk for the development and eventual death due to PC. Among the many possible mechanisms involved, hyperinsulinemia, diet and nutritional factors, and other hormone abnormalities have been suggested as causal factors.

Reduced caloric intake and physical exercise have both been shown to reduce the risk of PC (Silverman DT 2001, Michaud DS et al. 2001), and studies on the effects of bariatric surgery are also consistent with a reduction in PC risk after weight loss. In 2007, the Swedish Bariatric Surgery Trial reported a 38% reduction in cancer-related deaths compared to non-operated controls of similar BMI (Sjostrom L et al 2007), and a significant reduction in cancer-related medical care was documented in a study of 1035 bariatric surgery patients compared to 5746 morbidity obese controls reported by Christou et al (Christou NV et al. 2008). In a similar but larger study, Adams et al found a lower incidence of obesity-related cancers, defined as esophageal, colorectal, pancreas, liver, gallbladder, breast, and uterine cancers, in addition to non-Hodgkin’s lymphoma, leukemia and multiple myeloma in 6596 gastric bypass patients compared to 9442 morbidity obese control subjects (Adams TD et al 2009). As with the studies by Sjostrom et al and Christou et al, the incidence of PC, per se, was too low for valid statistical analysis. Although the mechanisms of risk-reduction remain speculative, the successful
treatment of morbid obesity (and concomitant T2DM in about half the subjects) appears to clearly reduce the risk of malignancy, and may reduce the incidence of PC.

**Proliferation Rates of Pancreatic Ductal Endothelium in Diabetes and Obesity**

The effects of DM and obesity on pancreatic ductal pathology were recently studied by Butler et al, who examined the expression of the neoplastic markers cytokeratin and Ki67 in pancreatic ductal epithelia from 45 human autopsy and 9 surgical pathology specimens (Butler AE et al. 2010). In autopsy specimens obtained from obese non-diabetic individuals, pancreatic duct replication was seen to be increased 10-fold compared to lean non-diabetics. In lean diabetics, duct epithelial replication was increased four-fold compared to lean non-diabetic subjects. These results indicate the independent effects of obesity and long-standing diabetes on the replication rate in pancreatic ductal cells, and presumably therefore on the likelihood of the development of pancreatic exocrine neoplasia (FIGURE 3). Markers of pancreatic ductal replication were increased synergistically in obese diabetic subjects. When surgical specimens of chronic pancreatitis or non-tumor tissue adjacent to pancreatic cancer were examined, even higher rates of the expression of replication markers were seen. These findings support the epidemiologic studies which have identified chronic pancreatitis, DM, and obesity as contributory to oncogenesis in the pancreas.

**Proposed Mechanisms of Diabetes-Related Pancreatic Carcinogenesis**

Although epidemiologic studies clearly indicate that DM is positively associated with an increased risk of PC, the molecular mechanism(s) of diabetes-related oncogenesis have not been fully elucidated. Insulin resistance and induced compensatory hyperinsulinemia are widely considered to be likely mechanisms to explain the association of DM and PC (Magruder JT et al 2011, Li D 2012). Several epidemiological studies have shown that insulin resistance status, characterized by hyperinsulinemia, is associated with an increased risk for a number of malignancies, including carcinomas of the breast, prostate, colon and kidney. Hyperglycemia has also been shown to be a risk factor for PC. Batty and colleagues in England found evidence for a graded dose-response relationship between fasting glucose and the development of pancreatic or liver cancer resulting in mortality (Batty GD et al. 2004). Jee and colleagues similarly found a positive linear relationship between fasting glucose and the risk of developing PC across all categories of obesity in a cohort analysis of 1,298,385 Korean patients (Jee SH et
al. 2005). In a study of 29,133 Finnish smokers followed for over 10 years, Stolzenburg-Solomon et al found that hyperglycemia, hyperinsulinemia, and insulin resistance were each associated with an increased risk of PC (Stolzenburg-Solomon RZ et al. 2005). The HR for PC for each entity did not increase significantly until more than 10 years of follow-up, suggesting that long-standing impairments were necessary for the development of PC.

Detailed reviews of these insulin-related mechanisms are provided by Pollak (Pollak M 2008) and Rosengurt et al (Rozengurt E et al. 2010). The insulin-like growth factor receptor 1 (IGF-1R), a tyrosine kinase receptor for IGF-I and IGF-II, has been well documented in cell culture, animal studies, and humans to play a role in malignant transformation, progression, protection from apoptosis, and metastasis in a variety of malignancies. In addition, the hormone insulin and its tyrosine kinase receptor (IR) have been documented both in vitro and in vivo to play a key role in cancer biology (Frasca F et al. 2008). Chronic hyperinsulinemia is a possible factor favoring cancer initiation and/or progression in diabetic patients due to the mitogenic effect of insulin. Insulin/IGF-1 could activate the PI3K/Akt/mTOR signaling pathway by activation of insulin receptor substrates 1–4, which contribute to the development of cancers including PC (Kornmann M et al. 1998). Recent reports indicate that IR is over-expressed in several human malignancies and one of the two IR isoforms (IR-A) is especially over-expressed in pancreatic adenocarcinoma. The IRs expressed in malignant tissue also have the capacity to form a hybrid receptor with the IGF-1R (Belfiore A 2007). By binding to hybrid receptors, insulin may stimulate specific IGF-1R signaling pathways which mediate cell proliferation, inhibition of apoptosis, and growth (FIGURE 4). Furthermore, Han et al recently found that high glucose promotes PC cell proliferation via the induction of epithelial growth factor (EGF) expression and transactivation of the EGF receptor (EGFR) (Han L et al. 2011).

In addition to activation of receptors linked to proliferative and anti-apoptotic pathways, other possible mechanisms have also been suggested as important mediators of pancreatic carcinogenesis. The DM and obesity-related effects on PC development may be mediated by oxidative stress and induced inflammatory responses (Li D 2012). Inflammatory responses to external stimuli can accelerate proliferative and repair processes, and obesity itself may activate inflammatory signaling pathways (Greer JB & Whitcomb DC 2009, Gallagher EJ & LeRoith D 2010). Proinflammatory cytokines released from adipose tissue, known as adipokines, can promote angiogenesis, tumor progression, and metastasis (van Krijsdijk RC et al. 2009).

Evidence for Increased Risk of Pancreatic Cancer with Insulin, Insulin Secretagogues, and Incretin-based Treatment
Although the mortality attributable to cancer in DM is overshadowed by that due to cardiovascular disease, emerging data from basic and epidemiologic studies suggest that insulin therapy may confer an added risk for cancer, perhaps mediated by signaling through the IGF-1 receptor (Azar M & Lyons TJ 2010). In 2000, Ding et al found that physiologic concentrations of insulin increased PC cell proliferation as well as glucose utilization by activating MAP kinase, PI3 kinase, and GLUT1 expression (Ding XZ et al. 2000). In 2003, Bonelli and co-workers in Italy reported a case-control study in which the effect of type of treatment for DM on the subsequent development of PC was assessed (Bonelli L et al. 2003). 244 patients with documented pancreatic carcinoma and 459 controls were assessed to determine whether insulin therapy or non-insulin therapy affected the subsequent rate of PC development. These investigators found that although DM was associated with a 2.86-fold increase in the risk for PC, the risk increased to 6.49-fold for those treated with insulin, compared to 2.12-fold for those treated with oral hypoglycemic agents. Furthermore, although the duration of insulin treatment had no effect on the high risk ratio (RR), longer duration of oral hypoglycemic therapy was associated with a lower RR for the development of PC. These findings were corroborated in 2006 by Bowker et al who also found increased cancer-related mortality in T2DM patients treated with insulin or sulfonylureas (Bowker SL et al. 2006). In the 2010 multinational case-control study by Maisonneuve et al, a history of DM conveyed an increased RR for PC overall (2.16), which was 6.68 for those whose history of DM started within one year of the diagnosis of cancer, falling to 1.28 for those whose diabetic history had existed for more than 10 years (Maisonneuve P et al. 2010). In addition, the type of treatment for the DM was found to have a differential effect, with those who had been treated with insulin having an RR of 3.54, while those who had been treated only with oral agents having an RR of 1.78. These findings confirmed those of Bonelli et al who similarly found a higher risk associated with insulin treatment than with non-insulin therapy. The higher risk seen with insulin treatment in the case-control studies of Maisonneuve et al and Bonelli et al may reflect a direct effect of insulin on tumor cell proliferation as insulin therapy would also be expected to produce periods of hyperinsulinemia. In addition, however, other factors may have contributed to the results, including length of treatment and the degree of hyperglycemia present, both of which would be expected to be greater in insulin-requiring patients. Carstensen et al. recently analyzed the effect of diabetes and diabetic therapy on cancer incidence in the Danish health system over a 27 year period, and noted that the adverse effects of insulin treatment were quite modest (Carstensen B et al. 2012). Therefore, caution has been advised in the acceptance of a cancer-promoting effect of insulin until further data are available (Gerstein HC 2010, Giovannucci E et al. 2010, Hernandez-Diaz S & Adami HO 2010).

Insulin therapy has also been associated with a greater than expected incidence of breast cancer and other malignancies (Jonasson JM et al. 2009, Home PD & Lagarenne P 2009), however, and insulin secretagogues have similarly been implicated in an increased incidence of
PC. Case-control studies indicate an increased risk of cancer overall in T2DM patients treated with sulfonylureas (Bowker SL et al. 2006, Monami M et al. 2009), and studies of PC in particular indicate that sulfonylurea therapy confers an increased risk (Currie CJ et al 2009, Li D et al. 2009).

Incretin-based therapies (glucagon-like peptide-1 [GLP-1] analogues and inhibitors of dipeptidyl peptidase-IV [DPP-IV], the enzyme which metabolizes GLP-1) are the newest form of insulin secretagogue treatment of T2DM. No long-term epidemiologic studies have yet been reported of their effect on the incidence of PC due to the relatively short period of clinical availability of these agents. However, laboratory studies suggest an adverse effect of these agents on the development of pre-neoplastic or malignant lesions of the pancreas, possibly related to the growth-promoting effects of GLP-1 and its analog exendin-4. Matveyenko et al. described the effects of sitagliptin, a DDP-IV inhibitor, on pancreatic ductal cell proliferation and beta-cell mass in the human islet amyloid polypeptide (HIP) transgenic model of T2DM in rats (Matveyenko AV et al 2009). Sitagliptin was seen to induce beta-cell replication, beta-cell apoptosis, pancreatic ductal metaplasia, and a 4-fold increase in duct cell proliferation, all effects that were blocked by concurrent metformin administration (FIGURE 5).

Gier and colleagues recently reported that the GLP-1 analog exendin-4 increased duct cell replication and increased the development of dysplastic pancreatic intraepithelial neoplasia (PanIN) lesions in a rat model in which activated Kras\textsuperscript{G12D} was induced (Gier B et al. 2012). These investigators found that pancreatic duct glands (thought to be precursors of PanINs) in both rats and humans contain GLP-1 receptors, and are increased by treatment with exendin-4.

GLP-1 and its analogs have been shown to increase expression of the transcription factor pancreatic-duodenal homeobox-1 (PDX-1) (Stoffers DA et al. 2000, Perfetti R et al 2000). PDX-1 is critical for normal pancreatic development, and has been shown to be overexpressed in PC (Koizumi M et al 2003, Wang XP et al 2005). Furthermore, PDX-1 increases cell proliferation, invasion, and colony formation of transformed cell lines in vitro, and stimulates PC formation in SCID mice, thereby fulfilling criteria as an oncogene (Liu SH et al 2011). The gene NR5A2 (also known as LRH1) has been identified as a PC susceptibility gene (Petersen GM et al 2010), and is a target gene of PDX-1 expression (Annicotte JS et al 2003). PDX-1-expressing endocrine cells can be transformed into a malignant, ductal cell phenotype after induction of pancreatitis by cerulein in mice (Gidekel Friedlander SY et al 2009), which supports the epidemiologic findings of a striking association of chronic pancreatitis with the development of PC (Greer JB & Whitcomb DC 2009). These findings suggest that Kras activation, either by genetic or non-genetic (inflammatory) events, may therefore activate neoplastic transformation within the pancreas to PDX-1-expressing islet- and/or ductal-cells. Agents which increase PDX-1 expression, such as GLP-1 and its analogs, may therefore facilitate this process.
Most recently, Elashoff and colleagues examined the database of adverse outcomes reported to the US Food and Drug Administration and discovered that compared with other anti-diabetic therapies, the use of sitagliptin or the GLP-1 analog exenatide was associated with a 2- to 3-fold increase in the reporting incidence of PC (Elashoff M et al. 2011). Although subject to multiple methodologic limitations, these findings nevertheless raise concerns regarding an increased risk for pancreatitis and PC with GLP-1-based therapy. Further epidemiologic studies are clearly needed to define the possible hazards of incretin-based anti-diabetic therapy, particularly in patients with T3cDM due to chronic pancreatitis (Cui Y & Andersen DK 2011).

Evidence for Decreased Pancreatic Cancer Incidence in Patients Treated with Metformin

Although insulin and insulin-secretagogue therapy is associated with an increased risk of PC, numerous clinical studies have demonstrated that the administration of metformin in DM patients exhibits a protective effect which is manifested by a decreasing incidence of different tumors and an improved prognosis of patients with cancer. Metformin has been widely used for the treatment of T2DM for almost 50 years, and its effectiveness has been attributed to enhanced sensitivity to insulin, rather than to an insulinotropic action. Its safety and efficacy are so well established that it is recommended as the first line of therapy for T2DM (Nathan DM et al 2009). In 2005, Evans et al evaluated metformin use in diabetics who were admitted to hospital with a diagnosis of cancer between 1993-2001 in Tayside, Scotland, and compared this cohort with diabetic controls who were not admitted for cancer (Evans JM et al. 2005). They found that any exposure to metformin was associated with a significant reduction in cancer risk (RR = 0.77). The same group subsequently examined the database of all diabetic patients in the region and compared outcomes based on the national registry of cancer deaths (Libby G et al. 2009). When the outcome of 4,804 metformin users was compared to 4,085 non-users, a reduced risk (RR 0.63) for cancer mortality was found among diabetic patients treated with metformin, whereas a (non-significantly) increased risk of cancer mortality was seen among insulin and sulfonylurea users. In 2009, Li and colleagues analyzed 978 patients with PC, including 259 diabetics, and 863 controls, including 109 diabetics, to assess the effects of diabetes treatment on the risk of PC (Li D et al. 2009). They found that whereas insulin treatment was associated with an increased risk (RR 2.78 for insulin users of more than 5 years), metformin therapy was associated with a 70% decreased risk (RR 0.30) for similar long term users of the drug. The implications are further supported by a more recent cohort study from Taiwan in which metformin users were found to have a 85% decreased risk of pancreatic malignancy (HR 0.15, 95% CI: 0.03-0.79) (Lee MS et al. 2011). Sadeghi et al performed a retrospective cohort study of 302 patients to investigate the survival benefit of metformin in patients with DM and pancreatic malignancy (Sadeghi N et al. 2011). They report the median
survival to be longer in metformin users when compared to non-users: 16.6 vs. 11.5 months (P=0.0044). They also report a 33% decrease risk of death in patients who used metformin compared to those who did not. In addition to studies of its anti-cancer effects in PC, metformin has also been shown to have anti-cancer effectiveness in diabetic breast cancer patients (Jeralerspong S et al. 2009, Chlebowski RT et al. 2012) and in colon cancer patients (Zhang ZJ et al. 2011).

These clinical studies corroborated the initial findings of Schneider et al who found a therapeutic effect of metformin in a hamster model of carcinogen-induced PC (Schneider MB et al. 2001). In these animals metformin treatment significantly decreased islet cell hyperplasia and pancreatic ductal proliferation and completely prevented the development of pancreatic adenocarcinoma. Additional evidence showed that metformin can inhibit PC cell growth and proliferation by disrupting the crosstalk between insulin/insulin-like growth factor-1 (IGF-1) receptors and G-protein coupled receptors through the activation of the liver kinase B1-adenyl monophosphate (LKB1-AMP) protein-activated kinase (AMPK) pathway, which serves not only to suppress hepatic glucose production and reduce the need for insulin, but also inhibits the signaling mechanisms which regulate cellular proliferation (Rozengurt E et al. 2010). LKB1 is a known tumor-suppressor which activates AMPK, a potent inhibitor of mammalian target of rapamycin (mTOR) complex 1 (mTORC1) which serves as a regulator of protein synthesis and replication (see Figure 4). Bao B et al found that metformin significantly decreased cell survival, clonogenicity, wound healing capacity, sphere-forming capacity (pancreatospheres), and increased disintegration of pancreatospheres in both gemcitabine-sensitive and gemcitabine-resistant PC cells (Bao B et al. 2011). Metformin also decreased the expression of cancer stem cell (CSC) markers, CD44, EpCAM, EZH2, Notch-1, Nanog and Oct4, and caused re-expression of miRNAs (let-7a, b, miR-26a, miR-101, and miR-200b,c) that are typically lost in PC. These results suggest that the biological effects of metformin as an anti-neoplastic agent are mediated through re-expression of miRNAs and decreased expression of CSC-specific genes which are affected by carcinogenesis, and numerous laboratory and clinical studies are now underway to examine the anti-tumor applications of metformin.

**DIABETES AS A CONSEQUENCE (AND HARBINGER) OF PANCREATIC CANCER**

**The Prevalence of Diabetes is Increased in Pancreatic Cancer Patients**

Many cohort and case-control studies indicate that 25% to 50% of patients with a diagnosis of PC will have developed DM within 1 to 3 years before their diagnosis of malignancy (Huxley R et al. 2005, Chari ST et al. 2008). This implies that recent-onset DM associated with PC is caused by
pancreatic malignancy, and suggests that DM is a biomarker of early-stage PC. The problem is
that new-onset DM, per se, is not a powerful enough predictor of PC to stand alone as an
indication for radiological or endoscopic screening, as 98% of patients with adult-onset DM will
never develop PC (Chari ST et al. 2005). Imaging protocols applied to patients with new-onset
DM older than the age of 50 have not been shown to be either practical or reliable as an early
detection method, based on studies in Japan (Ogawa Y et al 2002), France (Damiano J et al
2004), and the United States (Chari ST et al. 2005).

In addition to the frequent development of DM just proximate to the diagnosis of PC, the
concept that PC is a cause of new-onset DM is supported by several observations. Patients with
pre-malignant pancreatic lesions from kindreds in which PC is highly prevalent typically have
concurrent DM (Brentnall TA et al. 1999). Furthermore, new-onset DM associated with PC has
been seen to resolve after the successful resection of the tumor (Permert J et al 1993, Fogar P
et al 1994, Pannala R et al 2008) (FIGURE 6). In laboratory studies, PC-derived cell lines induce
hyperglycemia in severe combined immunodeficiency (SCID) mice (Basso D et al 1995), and a
PC-derived S-100A8 N-terminal peptide has been identified as a diabetogenic agent (Basso D et
al 2006).

Despite vigorous clinical investigation, no biomarker specific for PC-associated DM has been
validated, and tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate
antigen 19-9 (CA19-9) are insufficiently sensitive to detect early stage disease. Permert et al
identified elevated levels of islet amyloid polypeptide (IAPP), a beta-cell peptide co-secreted
with insulin, as a possible biomarker of PC (Permert J et al 1994), and demonstrated that PC
cells are capable of inducing IAPP release from beta-cells (Ding X et al 1998), but Chari et al
subsequently showed that IAPP was not sufficiently sensitive to serve as a biomarker of PC
(Chari ST et al 2001). Using microarray analysis, Pfeffer and colleagues identified connexin 26, a
gap junction protein, as being highly overexpressed in PC patients with DM (Pfeffer F et al
2004). Using similar methods, Huang and co-workers identified two upregulated genes in 27
patients with PC-associated DM, vanin-1 and matrix metalloproteinase 9, that together showed
the best correlation with the diagnosis (Huang H et al 2010). No large-scale studies have been
reported yet regarding the sensitivity and specificity of these possible biomarkers.

Pathogenesis of Pancreatic Carcinoma-associated Diabetes

The mechanism(s) responsible for the DM caused by PC are incompletely understood. Defects
in insulin sensitivity and insulin secretory capacity have been identified in patients with PC-
associated DM, and abnormalities in glucose metabolism in skeletal muscle and liver have been
observed in vitro as well. These multiple abnormalities suggest that one or more humoral
factors are likely involved in PC-associated DM, as reviewed by Pannala et al (Pannala R et al 2009).

Animal models of carcinogen-induced PC exhibit both hyperinsulinemia (Liu J et al 2000) as well as insulin secretory impairments (Ahren B & Andren-Sandberg A 1993, Perment J et al 2001), which implies that insulin resistance is an early event in PC-associated DM. Impaired sensitivity to insulin has been demonstrated in euglycemic glucose clamp studies and by means of the Homeostasis Model Assessment (HOMA) method in patients with PC-associated DM (Cersosimo et al 1991, Chari et al 2005), which improves after removal of the tumor despite reduced insulin secretory capacity after surgical resection (Perment et al 1993, Pannala et al 2008). Clinical studies on the pathophysiology of PC-associated DM have been confounded, however, by the inability of investigators to document whether the DM exhibited by each PC patient is pre-existing T2DM, or pancreatogenic (type 3c) DM caused by the tumor.

Distinguishing Type 3c Diabetes (T3cDM) from Type 2 Diabetes (T2DM)

Recalling that T3cDM is the form of DM which is a consequence of pancreatic exocrine pathology, and that T3cDM is in many ways distinct from T2DM (see Table 1), the issue therefore becomes how to feasibly distinguish individuals with T3cDM from the vastly more prevalent T2DM, so as to identify the subset of high risk patients in whom high resolution imaging tests might feasibly identify suspicious areas within the pancreatic parenchyma.

A retrospective cohort study of 2122 diabetic patients suggested that PC developed within 3 yr after the diagnosis of DM in 1% of the patients who were at least 50 yr old (Chari ST et al. 2005). Johnson et al found that the diagnosis of PC was highest within 3 months following the onset of DM (Johnson JA et al 2011), and Aggarwal et al showed that the duration of DM prior to the diagnosis of PC by primary care providers averaged 6.5 months (Aggarwal G et al 2012). A study by Lee at al reported that compared with the control group, PC patients were, on average, older, had more weight loss, lower usual body mass index (BMI), a greater family history of PC (3.3% vs. 0.7%; P=0.044), and had a lower family history of DM (13.9% vs. 37.4%; P<0.001) (Lee JH et al. 2011). These authors concluded that PC-associated DM (T3cDM) could be discriminated from new-onset T2DM based on clinical features, such as the lack of a family history of DM, age 65 years or older, recent weight loss of >2 kg or a premorbid or usual BMI <25 kg/m. A definitive diagnosis of T3cDM, however, requires further testing for confirmation in patients who lack a history of pancreatic disease or a family history of PC. Fecal elastase-1 levels less than 100 ug/g strongly suggest pancreatic exocrine impairments (Loser C et al 1996), but the most consistent laboratory finding in T3cDM due to any cause is a deficiency of the
pancreatic polypeptide (PP) response to ingested nutrients (Magruder JT et al 2011, Cui YF & Andersen DK 2011).

**Pancreatic Polypeptide (PP) Deficiency: A Marker of Type 3c DM**

Pancreatic polypeptide (PP) is localized predominantly to islets in the ventral portion (head) of the pancreas, and is promptly secreted in response to ingested nutrients. PP regulates the expression and availability of hepatic insulin receptors, and hepatic insulin resistance due to PP deficiency is reversed by PP administration in animals and man (Andersen DK 2007). T3cDM secondary to cystic fibrosis, chronic pancreatitis, pancreatic malignancy, or pancreatic resection, is uniformly characterized by a deficiency in the nutrient-stimulated release of PP (FIGURE 7), and a defect in hepatic insulin sensitivity (Cui YF & Andersen DK 2011). T2DM, on the other hand, is typically associated with an increase in basal and nutrient-stimulated levels of PP (Glaser B et al 1988). Furthermore, healthy elderly subjects with normal glucose tolerance also demonstrate elevations in basal and nutrient-stimulated levels of PP, compared to younger subjects (Magruder JT et al 2011) (FIGURE 8). Therefore the discrimination of T3cDM from T2DM is based on the failure of plasma PP levels to increase after nutrient ingestion. Basal levels of PP in PP-deficient subjects are similar to basal levels in normal subjects, so a nutrient stimulus is required to confirm PP deficiency. Glucose ingestion is a relatively weak stimulus for PP release, whereas a mixed nutrient meal is a strong inducer of PP release. A standardized mixed-nutrient stimulus is 8-ounces of a liquid dietary supplement such as Ensure-Plus®; peak levels of PP are seen within 30-60 minutes after ingestion. Studies are currently in progress to establish the prevalence of PP deficiency in PC patients with and without DM, but a diagnosis of new-onset T3cDM based on PP deficiency is a strong indicator that the patient is in a high-risk category for PC, and warrants further investigation to identify a pancreatic parenchymal abnormality.

**Prevalence of Type 3c Diabetes**

Patients who have a known history of pancreatic disease and who are also diabetic require special surveillance for PC. The most common cause of T3cDM is chronic pancreatitis (CP), which harbors a 10- to 20-fold increased risk of PC; the combination of CP and DM increases this risk 33-fold. Unless drug side effects (principally gastrointestinal sensitivity) or a contraindication (such as renal insufficiency) is present, metformin should be prescribed to all
T3cDM patients, even if other anti-diabetic drugs such as insulin have to be added for adequate glycemic control (Cui YF & Andersen DK 2011).

T3cDM had been estimated to account for only 1% to 2% of all diabetic patients in North America (Ganda O 1994) but is known to affect as many as 15% to 20% of diabetic patients in the Indian and Southeast Asian continents, where tropical or fibrocalcific pancreatitis is endemic (Abu-Bakare A et al. 1986). In a careful evaluation of almost 2000 diabetic patients referred to an academic medical center in Germany, Hardt et al discovered that 8% of all diabetic patients harbored T3cDM (Hardt PD et al 2008) (FIGURE 9). Furthermore, Ewald et al subsequently showed that nearly half of the T3cDM patients had been previously misdiagnosed as either T1DM (6%) or T2DM (40%) (Ewald N et al 2011). With the advent of improved imaging methods to detect pancreatic pathology, and the availability of a practical screening method to quantify exocrine pancreatic function, previous estimates of the prevalence of T3cDM are now understood to have been spuriously low (Ewald N et al. 2009).

In the German cohort study, 78.5% of T3cDM patients had CP as the underlying etiology of their T3cDM. In an older study of 500 patients with CP due to alcoholism, DM developed in 83% within 25 years of the clinical onset of CP, and more than half of the diabetic patients ultimately required insulin therapy (Malka D et al. 2000). With the increasing prevalence of CP worldwide (Rothenbacher D et al. 2005), the population of patients at greatest risk for the development of PC is clearly expanding. Therefore, an aggressive approach to the identification, surveillance, and management of patients at high-risk for PC is an important strategy in order to reduce the mortality rate of PC.

Drugs used to treat pancreatic cancer may cause diabetes

A recently emerging issue is the possible adverse effect on glucose metabolism of anti-cancer therapies. Cancer patients commonly exhibit hyperglycemic states or DM following glucocorticoid administration (Saylor PJ & Smith MR 2009). The increasing use of targeted chemotherapy directed against components of the IGF-I pathway may amplify the frequency of anti-cancer drug-related diabetes. IGF-I and insulin, their receptors and their intracellular signaling pathways, share multiple similarities. Likewise, the biological (metabolic and mitogenic) effects of insulin and IGFs overlap. Hyperglycemia was observed in some patients enrolled in studies with an anti-IGF-IR antibody (Haluska P et al. 2006, Lacy et al. 2008). This is likely to be a consequence of a compensatory increase in the circulating concentration of growth hormone (GH) after IGF-I blockade, with the consequent increase in GH-induced insulin
resistance (del Rincon JP et al. 2007). Hyperglycemia, hypertriglyceridemia, and hypercholesterolemia were also observed in about 20% of patients treated with the mTOR inhibitors (Bellmunt J et al. 2008). Recent reports also documented increased blood glucose levels in 26% of temsirolimus-treated patients (Bellmunt J et al. 2008, Malizia LI & Hsu A 2008). However, tyrosine kinase inhibitor therapy directed at IGF-IRs was associated with less hyperglycemia than IGF-IR-blocking antibodies (Pollak M 2008). At present, insufficient data are available to assess the possible diabetogenic effects of phospho-inositol-3-kinase- and AKT-inhibitor therapy.

CONCLUSIONS AND CLINICAL RECOMMENDATIONS

Epidemiological data clearly demonstrate an etiologic link between long-standing T2DM, and probably T1DM, and PC. Successful treatment of T2DM and obesity has been shown to reduce the risk of PC, but treatment with insulin, insulin analogs, and insulin secretagogues increases or maintains the risk. Metformin has been shown to reduce the risk of PC owing to its anti-diabetic and anti-neoplastic actions, and should be considered as first-line therapy in all new-onset DM patients over the age of 50. In addition, metformin, as well as lifestyle alterations, have been shown to reduce the incidence of T2DM when administered to obese individuals with impaired glucose tolerance (Knowler et al 2002, Cefalu 2012). Such successful prevention strategies need to be more fully utilized in order to reverse the increasing incidence of PC.

New-onset DM can be a consequence, and therefore a harbinger, of PC. DM caused by PC is classified as type 3c DM, which occurs in up to 30% of patients with PC. If a new-onset DM patient does not have family history of DM, is aged 65 years or older, or has had a stable BMI <25 kg/m, PC-associated DM (T3cDM) should be considered, especially within 3 months following onset of DM. If the patient has a family history of 2 or more relatives with PC, high resolution imaging (preferably computer tomographic scanning followed by endoscopic ultrasound) of the pancreas should be considered to identify suspicious areas within the parenchyma (Brentnall TA et al. 1999).

If no family history of PC is present, T3cDM can be confirmed by documenting the absence of a rise in PP levels after a test meal or liquid mixed-nutrient challenge. Patients with confirmed T3cDM, with or without a history of pancreatic disease, are candidates for periodic high-resolution pancreatic imaging to detect early pathological changes within the pancreas. With an
aggressive approach to distinguishing T3cDM from T2DM, many cases of early PC may be able to be identified when curative removal of the tumor is still possible.

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**Author contribution statement:**
Drs. Cui and Andersen contributed equally to this work.

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FIGURE LEGENDS

**Figure 1** Distribution of fasting blood glucose among pancreatic cancer cases and controls. Normal fasting glucose, <=99 mg/dL; impaired fasting glucose, 100-125 mg/dL; diabetes (DM), >=126 mg/dL (From Pannala R et al. 2008, with permission).

**Figure 2** Risk of pancreatic cancer based on history of pancreatitis or diabetes. The odds ratio of subsequent pancreatic cancer based on medical history of pancreatitis (upper panel) or diabetes (lower panel) in 823 patients with pancreatic cancer and 1679 controls surveyed in
Australia (Adelaide), Canada (Toronto and Montreal), the Netherlands (Utrecht), and Poland (Opole) (From Maisonneuve P et al 2010, with permission).

**Figure 3** Number of cytokeratin-staining pancreatic ductal cells positive for Ki67, a marker of cellular replication, in autopsy-harvested pancreata. LND indicates lean nondiabetic patients (n = 9); OND, obese nondiabetic patients (n = 11); LD, lean with type 2 diabetes (n = 12); OD, obese with type 2 diabetes (n = 13). Data are presented as mean ± SEM. *P < 0.0001, LND versus OND. †P < 0.001, LD versus OD and LND versus LD (From Butler AE et al. 2010, with permission).

**Figure 4** Insulin, Insulin-like Growth Factor-1 (IGF-1) and IGF-2 mediation of translation and proliferation, and the effects of metformin on these pathways. Phosphorylation of Insulin Receptor Substrate (IRS) proteins by insulin/IGF receptors activate phosphotidylinositol-3 kinase (PI3K) and the Ras-MAP-kinase signaling network. PI3K activates Akt which regulates protein synthesis and replication through the intermediate mammalian target of rapamycin (mTOR). Energy depletion or the drug metformin results in activation of AMP protein kinase (AMPK) through the intermediate liver kinase B1 (LKB). In the liver AMPK activation results in diminished hepatic glucose production, which results in lower levels of circulating insulin. In the pancreas and elsewhere, AMPK inhibits mTOR signaling (From Cui Y & Andersen DK 2011, with permission).

**Figure 5** Effects of sitagliptin and metformin on beta-cell replication. Panel A: Example of Islets stained for insulin (pink), the replication marker Ki67 (brown), and nuclear stain hematoxylin (blue) in wild type (WT) and transgenic rats expressing human islet amyloid polypeptide (HIP), a model of type 2 diabetes, treated with sitagliptin (200 mg/kg/day) (HIP + SIT) or metformin (200 mg/kg/day) (HIP + MET), or both (HIP + SIT + MET) for 12 weeks. Panel B: Frequency of beta-cell replication in WT rats (n=7), HIP rats (n=8), HIP rats treated with SIT (n=8), HIP rats treated with MET (n=9), or HIP rats treated with both SIT and MET (n=8). *p<0.05 vs. WT, HIP, and HIP + MET groups. Arrows indicate Ki67-positive cells (From Cui YF & Andersen DK 2011, with permission).

**Figure 6** Prevalence of postoperative diabetes after pancreaticoduodenectomy for pancreatic cancer. Data for patients with new-onset diabetes (2-yr duration), impaired fasting glucose (IFG), and normal fasting glucose (NFG) are shown: NFG, 126 mg/dL (7 mmol/L). Whereas postoperative diabetes was seen in all long-standing diabetic patients, and in some patients with IFG and NFG, diabetes resolved in more than 50% of patients with new-onset diabetes despite removal of half of the [beta]-cell mass (From Pannala R et al 2008, with permission).
**Figure 7** Serum PP responses to a test meal in 8 normal control subjects (open boxes), 4 non-PP-deficient patients who had recovered from distal pancreatic resection performed for trauma (closed diamonds), and 6 PP-deficient patients who had recovered from proximal pancreatic resection performed for trauma (closed boxes, broken line). Means +/- standard errors are shown (From Magruder JT et al. 2011, with permission).

**Figure 8** Serum PP responses to 75 g of glucose ingested at time = 0 in 10 healthy young (age younger than 40 years; NL young), 19 healthy elderly (age older than 65 years) with normal glucose tolerance (NL old), and 21 elderly subjects with T2DM (DM old). Data are shown as mean +/- SE (From Magruder JT et al. 2011, with permission).

**Figure 9** Distribution of types of diabetes (left figure), and causes of Type 3c (pancreatogenic) diabetes (right figure) based on studies of 1,922 diabetic patients referred to an academic medical center in Germany (From Hardt PD et al 2008, with permission).
## TABLES

### Table 1 Clinical and Laboratory Findings in Types of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3c</th>
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<td>NIDDM</td>
<td>Pancreatogenic</td>
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<td>Rare</td>
<td>Rare</td>
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<td>Usually Mild</td>
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<tr>
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<td>Common</td>
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<td>Increased</td>
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<td>Adulthood</td>
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</table>

Abbreviations: IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; PP, pancreatic polypeptide; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1. (from Cui YF & Andersen DK 2011, with permission)
Figure 1

Pancreatic cancer (n=512)
- Normal fasting glucose (14%)
- DM (47%)
- Impaired fasting glucose (38%)

Controls (n=933)
- Normal fasting glucose (59%)
- DM (7%)
- Impaired fasting glucose (34%)
Figure 4

[Diagram showing the insulin and IGF signaling pathways, including key molecules such as IRS proteins, PI3K, Akt, TSC, mTOR, S6K, and metabolic inhibitors like AICAR and Metformin.]
Figure 6

Percentage of diabetic patients post-operatively

- New-onset DM, n=30
- Long-standing DM, n=11
- IFG, n=48
- NFG, n=15

*P = 0.009 New-onset vs. long-standing DM
#P = 0.3 IFG vs. NFG

Pre-operative glycemic status
Figure 8
Figure 9

a Distribution of T1DM, T2DM and T3cDM

b Distribution of causes of T3cDM