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The relationship between diabetes and pancreatic cancer

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Abstract

About 80% of pancreatic cancer patients have glucose intolerance or frank diabetes. This observation has led to the following two hypotheses: *i.* pancreatic cancer causes the associated diabetes and *ii.* the conditions associated with diabetes promote the development of pancreatic cancer. Evidence supporting both hypotheses has been accumulated in previous studies. This article reviews these studies, especially those that have been conducted recently.

Review

The early symptoms of pancreatic cancer, such as abdominal pain, weight loss, fatigue, jaundice, and nausea, are nonspecific and may occur late in the course of the disease [1,2]. As a result, pancreatic cancer is usually diagnosed at an advanced stage, frequently after the tumor has already metastasized. Pancreatic cancer is insensitive to pharmacological and radiological intervention and often recurs after apparently curative surgery. All these factors contribute to the dismal prognosis of the disease [3].

About 80% of pancreatic cancer patients have glucose intolerance or frank diabetes [4,5]. This observation has led to the following two hypotheses: *i.* pancreatic cancer causes diabetes and *ii.* diabetes is a risk factor for the development of pancreatic cancer. Numerous studies have been performed in order to elucidate the relationship between these two diseases.

Evidence suggesting that pancreatic cancer causes diabetes

The majority of diabetes associated with pancreatic cancer is diagnosed either concomitantly with the cancer or during the two years before the cancer is found [6]; 71% of the glucose intolerance found in pancreatic cancer patients is unknown before the cancer is diagnosed [5]. These suggest that recently-developed glucose intolerance or diabetes may be a consequence of pancreatic cancer and that recent onset of glucose intolerance or diabetes may be an early sign of pancreatic cancer. Several studies have demonstrated that diabetes in pancreatic cancer patients is characterized by peripheral insulin resistance [4,5,7]. Insulin resistance is also found in non-diabetic or glucose intolerant pancreatic cancer patients, though to a lesser degree [7]. Insulin sensitivity and overall diabetic state in pancreatic cancer patients who undergo tumor resection are markedly improved three months after the surgery [7]. These data suggest that pancreatic tumors are causally related to the insulin resistance and diabetes seen in pancreatic cancer patients. In their study of sera from patients with pancreatic cancer and culture media conditioned by human pancreatic cancer cells, Basso *et al.* found a 2030 MW peptide that they considered to be a putative pancreatic cancer associated diabetogenic factor [8].

A number of investigators have studied insulin resistance at the organ, tissue, and cellular levels in pancreatic cancer [7–13]. Studies of the initial steps in the insulin signaling cascade in human skeletal muscles showed no significant differences in insulin receptor binding, tyrosine kinase ac-

tivity, and insulin receptor substrate-1 content between pancreatic cancer patients and healthy controls [9]. However, phosphatidylinositol 3-kinase (PI3-K) activity and glucose transport, which are located downstream to the initial insulin signaling steps, were impaired in pancreatic cancer patients [10]. In addition, glycogen synthase activity was reduced in skeletal muscles of humans and rodents with pancreatic carcinoma [9,11] and in isolated rat skeletal muscles exposed to human pancreatic tumor extracts *in vitro* [7]. These data show that the insulin signaling cascade in skeletal muscle is impaired at multiple steps by pancreatic cancer.

An Italian group has performed a series of studies to investigate the effects of pancreatic cancer cells on hepatic insulin sensitivity. When mice were treated with culture medium conditioned by the human pancreatic cancer cell line Mia PaCa2, blood glucose was elevated compared to the control value seen in mice treated with unconditioned medium [12]. In addition, isolated rat hepatocytes showed impaired glycolysis when incubated in culture media conditioned by four human pancreatic cancer cell lines [13].

Islet dysfunction is another etiological component underlying the diabetes associated with pancreatic cancer. Because the islet mass destroyed by the tumor is only a small proportion of the whole islet mass, the islet dysfunction is unlikely to be the result of decreased total islet volume. In fact, endocrine pancreatic function can be maintained even with a larger loss of pancreatic islets [14]. Reduced insulin release is seen in pancreatic cancer patients in response to classic stimuli [5,15,16]. Insulin release was also reduced when isolated rat pancreatic islets were incubated in culture media conditioned by the human pancreatic cancer cell lines Panc-1 and HPAF or co-cultured with Panc-1 and HPAF cells [17,18]. Studies of chemically-induced pancreatic cancer in hamsters found that glucose-stimulated insulin release was impaired *in vivo* [19] but not in isolated perfused pancreata [20]. Ishikawa *et al.* found an increase in proinsulin relative to insulin in pancreatic cancer patients [21], suggesting that the maturation of proinsulin may also be affected by the tumor.

Islet hormone profiles are changed in the circulation of pancreatic cancer patients, suggesting that secretion by different types of islet cells is disrupted by pancreatic cancer [22]. Changes in islet hormone concentrations in the circulation can also be seen in hamsters after induction of pancreatic cancer [23]. Human pancreatic islets adjacent to pancreatic carcinoma show morphological abnormalities characterized by abnormal co-localization of islet hormones in islet cells [24].

The diabetogenic potential of islet amyloid polypeptide (IAPP or amylin) has been investigated by several groups. IAPP is normally produced in islet beta cells and co-released with insulin at a constant ratio. In 1994, Permert *et al.* found elevated circulating levels of IAPP in patients with pancreatic cancer [25]. Similar results have been reported in more recent studies by other groups [26,27]. The islets adjacent to human pancreatic carcinomas show reduced IAPP staining. In contrast, the expression of IAPP mRNA in these islets is unchanged, suggesting normal production but increased release of IAPP [25].

The molar ratio of IAPP/insulin was increased when rat pancreatic islets were co-cultured with Panc-1 and HPAF cells or cultured in media conditioned by these cell lines [17,18]. The ratio was normalized after the co-cultured cancer cells were removed [18]. In a similar co-culture model, Ding *et al.* found that culture media conditioned by human pancreatic cancer cells contained a soluble molecule that selectively enhanced IAPP release from BRIN-BD11 beta cells [28]. Increased IAPP/insulin ratios were also seen in rats with azaserine-induced acinar pancreatic tumors and in hamsters with ductular pancreatic tumors induced by carcinogen *N*-nitrosobis(2-oxopropyl)amine (BOP) [29]. However, exposure of isolated rat pancreatic islets to hamster pancreatic cancer cells did not change the secretion of insulin and IAPP [17].

A physiological study of isolated rat pancreatic islets has shown that endogenous IAPP reduces arginine-stimulated insulin, glucagon, and somatostatin release [30]. Also, the improvement in glucose tolerance seen after tumor removal is associated with normalization of IAPP levels in the circulation [25]. Therefore, the increased IAPP release seen in pancreatic cancer patients may be responsible, at least in part, for the islet dysfunction seen in these individuals. However, when IAPP is infused in rats to create circulating concentrations comparable to the circulating IAPP levels in pancreatic cancer patients, the rats have normal glucose disposal [31]. Thus, the increased IAPP secretion found in pancreatic cancer patients is unlikely to be responsible for their peripheral insulin resistance.

Evidence for diabetes as a risk factor for pancreatic cancer

Everhart et al. examined 30 of the epidemiological studies that have looked at the association between diabetes and pancreatic cancer and used 20 of them in a meta-analysis [32]. The pooled relative risk from these studies was 2.1 for diabetes with a duration of at least l year prior to cancer diagnosis or death and 2.0 for diabetes with a duration of at least 5 years [32]. The authors concluded that pancreatic cancer could be added to the list of complications of diabetes [32]. Several epidemiological studies have analyzed relative risks associated with the different periods of time after the diagnosis of diabetes and have found a rel-

atively modest but persistent increased risk of death from pancreatic cancer even when the diagnosis of diabetes preceded death by many years [32–37]. A population-based case-control study in the United States with 526 incident cases and 2,153 population controls showed a significant positive trend (P = 0.016) in risk with increasing years prior to diagnosis of cancer [36]. In other studies, the relative risk decreased with increasing follow-up time but remained significant [34,35,37]. However, other epidemiological studies have concluded that diabetes is not a risk factor for pancreatic cancer or else that it is not a risk factor if recently-diagnosed cases are excluded [6,38–40].

Studies of the relationship between diabetes and pancreatic cancer are complicated by the fact that diabetes has two major forms that are different entities in terms of pathophysiology [41]. A number of studies have suggested that Type I diabetes is not associated with an increased risk for pancreatic cancer [37–39]. Most epidemiological studies, however, have not distinguished between Type I and Type II diabetes. It is likely that the large majority of diabetics in the studies have Type II diabetes because this form of the disease constitutes 80–90% of the cases and is typically found in older individuals [32,35,41].

In patients with Type II diabetes (non-insulin-dependent diabetes), the pancreas is generally exposed to substantial hyperinsulinemia for years [33], suggesting that insulin may be involved in the association between long-standing diabetes and pancreatic cancer. A number of experiments have tested the hypothesis that insulin may stimulate the growth of pancreatic cancers. Binding studies have shown the presence of insulin receptors on pancreatic cancer cells [42–45]. *In vitro* studies have shown that insulin promotes growth of the hamster pancreatic cancer cell line H2T [42], the rat acinar pancreatic cancer cell line AR42J [45], and numerous human pancreatic cancer cells lines [44,46–51]. However, the human pancreatic cancer cell line SOJ-6 was not stimulated by insulin [46], and one of the studies using PANC-1 cells reported no response to exogenous insulin [49]. In addition to hyperinsulinemia, the increased blood glucose and free fatty acids in diabetes may also promote the growth of pancreatic cancer [52].

The genesis of the cancer is also influenced by the endocrine pancreas. *In vivo* studies concerning the effects of administration of exogenous insulin and/or induction of diabetes on pancreatic cancer have provided inconsistent data that reflect the complex interactions that may be involved in tumor growth [53–56]. Exogenous insulin significantly reduced the induction of benign and malignant pancreatic lesions in hamsters when given 2 hours before BOP, but the reduction in incidence was not significant when insulin was given simultaneously with BOP or 2 hours after BOP [53]. Cancer incidence in hamsters receiving insulin twice daily starting before BOP administration and continuing through the experimental period did not differ significantly from that in controls that received BOP only [54].

When hamsters were given streptozotocin (SZ) injection to diminish insulin cells and given insulin from the following day untill the end of the experiment, the inhibition of carcinogenesis in hamsters receiving SZ+BOP+insulin treatment was greater than that seen in the SZ+BOP group, compared to group treated by BOP only [54]. Hamsters receiving SZ+insulin had significantly fewer insulinomas than SZ-only animals [54]. Because insulin administration was associated with inhibition of beta cell regeneration and persistence of severe diabetes in hamsters treated with SZ [57], the investigators in the SZ/BOP/insulin study concluded that intact islet cells, rather than the availability of insulin, are prerequisite for triggering the neoplastic effects of BOP [54]. The association of intact islets with pancreatic cancer induction is also shown in transplantation studies in which tumors develop in the submandibular gland after BOP treatment if normal islets are transplanted to that site but not when pancreatic ductal cells, thyroid, heart muscle, or starch are introduced into the gland [58–60]. Submandibular gland tumor incidence was not changed when hamsters were pre-treated with SZ before islet transplantation [60].

A study of pancreatic cancer in hamsters fed a high-fat diet that potentiated pancreatic cancer provided data suggesting that islet proliferation associated with insulin resistance enhances carcinogenesis [61]. In that study, high-fat-fed hamsters had elevated insulin levels but normal glucose levels, which was consistent with a state of insulin resistance [61]. The turn-over rate of cells in islets is significantly increased in the high-fat animals, suggesting a compensatory islet cell proliferation [61]. Administration of metformin, starting 2 weeks before the administration of BOP and continuing throughout the experiment, normalized insulin concentrations and the rate of islet cell turnover [61]. Malignant pancreatic lesions were found in 50% of the high-fat/BOP animals and none in the high-fat/BOP/metformin group (P < 0.05) [61].

Conclusion

Recent studies indicate that there is no simple answer to the question of which of the two hypotheses stated at the beginning of this review is right. However, it appears that these hypotheses are not mutually exclusive, since there is considerable experimental and epidemiological evidence in support of both of them. Clearly, the relationships between pancreatic cancer and alterations in glucose metabolism are very complex.

List of abbreviations used

PI3-K: phosphatidylinositol 3-kinase,

IAPP: islet amyloid polypeptide,

BOP: *N*-nitrosobis(2-oxopropyl)amine,

SZ: streptozotocin.

Authors' contributions

This article was drafted by WF and MH and revised by JL and JP. All authors read and approved the final manuscript.

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