GLP-1 Receptor Agonist Effects on Normal and Neoplastic Pancreata

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In this issue of *Diabetes*, two articles describe preclinical studies evaluating the effects of chronic glucagon-like peptide 1 (GLP-1)–based therapy on development of pancreatitis and pancreatic neoplasia (1,2). These studies were performed in light of recent case reports and a case-control study suggesting that diabetic individuals using sitagliptin or exenatide have a several-fold increased likelihood of developing pancreatitis and pancreatic cancer (3). Related to the latter association are recent case-control studies reporting that metformin therapy, which can counteract proliferative effects of GLP-1 receptor (GLP-1R) agonists, is associated with a reduced risk of pancreatic cancer (4). Some preclinical studies have found that GLP-1R agonists can cause pancreatitis in some mice, but others have found no such effect, and recent clinical trials found evidence for only a small increased risk of pancreatitis with liraglutide use (5).

In this issue, Nyborg et al. (2) find no evidence for an increased risk of pancreatitis in liraglutide-treated compared with control-treated animals. In contrast, Gier et al. (1) find exendin-4 had multiple effects, including increasing the extent of chronic pancreatitis-like changes in a genetically engineered mouse model (KrasG12D) of pancreatic neoplasia. How do we reconcile the different animal responses to GLP-1R agonists? It does not seem likely that these differences reflect variability in the properties of the different GLP-1R agonists in the two studies. The lack of effect of liraglutide in healthy mice, rats, and monkeys (2) probably reflects what generally occurs in individuals with normal pancreata. Any increase in cell proliferation by GLP-1R agonists may not have pathological effects if these agents have equal effects throughout the pancreas.

In contrast, in the KrasG12D mouse, pancreatic mutant *KRAS* expression leads to mouse pancreatic intraepithelial neoplasia (mPanIN) and eventually in some mice to pancreatic ductal adenocarcinoma. As mPanIN lesions grow they can cause focal obstruction of small ductules with chronic pancreatitis-like acinar atrophy and fibrosis. A similar atrophy is observed in some patients who have extensive PanIN that is associated with a familial predisposition

to pancreatic ductal adenocarcinoma (6). Notably, these patients are not at increased risk of developing acute pancreatitis. In contrast to healthy animals, Gier et al. (1) found exendin-4 increased the growth of mPanIN in KrasG12D mice. mPanIN cells may overproliferate relative to normal pancreatic cells in response to exendin-4 because of a higher density of GLP-1 receptors (1). Although there may be important differences in GLP-1 biology between preclinical models and humans, these results raise concerns that GLP-1R agonists could increase human PanIN proliferation. At the same time, it is unlikely that proliferative effects of GLP-1R agonists on microscopic PanIN cause acute pancreatitis. Although acute pancreatitis does occasionally arise as a complication of tumor obstruction of large pancreatic ducts, this scenario has not been described in incretin-treated patients.

The more important question is whether treatment with GLP-1R agonists increases the risk of developing pancreatic cancer. The duration of exendin-4 treatment was sufficient to allow for mPanIN development but not long enough to allow for pancreatic cancer to develop in the KrasG12D mice (1), so this important question remains unanswered. Given the effects of exendin-4 on mPanIN growth, additional studies are needed to determine if lifelong treatment of KrasG12D mice with GLP-1R agonists influences the development of pancreatic cancer.

Do these studies help us better understand the risk of pancreatic disease in patients treated with these agents? Adult pancreata commonly harbor low-grade PanIN and the prevalence of PanIN increases with age (rev. in 7). However, the extent of mPanIN in KrasG12D mice is much greater than that typically found in adults. Furthermore, increased PanIN proliferation does not assure neoplastic progression. Pancreatic ductal adenocarcinoma is a genetic disease that develops and progresses through a series of genetic and epigenetic events (8). Virtually all low-grade PanINs harbor oncogenic mutations, usually involving *KRAS* (9). Over time PanIN cells may acquire additional mutations in tumor suppressor genes and oncogenes that drive the progression of low-grade PanINs to high-grade PanINs and ultimately to invasive ductal adenocarcinoma. Although exendin-4 increased the proliferation of mPanIN, there is no evidence it stimulated mutational events or genetic instability. Gier et al. (1) found exendin-4 therapy produced low-grade PanIN-like lesions in young healthy rats, although we do not know if these lesions harbored oncogenic mutations that would confirm they were neoplastic. Human genetic studies estimate it takes over a decade for low-grade PanIN to develop and progress to invasive cancer (10). Since patients diagnosed with pancreatic cancers on GLP-1R agonists were only treated for a few months to a few years, it is unlikely that this duration of therapy would have had a major effect on the natural history of PanIN progression to invasive pancreatic cancer.

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It has been suggested that the increased pancreatic cancer diagnoses with GLP-based therapy is due to chronic subclinical pancreatitis also caused by these agents (11). However, it is unlikely that any risk of pancreatitis from these agents would explain the pancreatic cancer association. Pancreatic cancer arising from pancreatitis is thought to occur only after several decades of ongoing recurrent acute attacks of pancreatitis most clearly evident in patients with hereditary forms of the disease (12), much in the way chronic inflammation predisposes to the development of other cancers, and not as a consequence of a short duration of drug-induced pancreatitis. The cumulative risk of developing pancreatic cancer 20 years after a diagnosis of (nonhereditary) chronic pancreatitis has been estimated to be 4% (13). These data suggest that if GLP-1-based therapy can produce ongoing low-grade subclinical chronic pancreatitis, many years of therapy would be needed for such pancreatitis to have any influence on cancer risk. If these agents do increase pancreatic cancer risk, direct effects of GLP-1R agonists on PanIN growth are likely to be more important than the indirect effect of subclinical chronic pancreatitis.

Could GLP-1R agonists increase the growth of human pancreatic cancers? Gier et al. (1) show that mutant *KRAS* increases pancreatic ductal epithelial cell responses to exendin-4. Pancreatic ductal adenocarcinoma cells express GLP-1 receptors, raising the possibility that these agents could increase their proliferation in the same way they influence the growth of mPanIN cells. If true, the modest increase in pancreatic cancer diagnoses among GLP-1R agonist-treated patients could simply result from accelerated growth of subclinical pancreatic cancers. Consistent with this possibility, epidemiological studies indicate that almost 1% of adults over age 50 with new-onset diabetes will be diagnosed with pancreatic cancer within 3 years (14). Although pancreatic cancer is a rapidly progressive disease once diagnosed, it likely takes several years for an initial cancerous clone to grow into a tumor mass that presents clinically. So it is likely that most patients who developed pancreatic cancer on GLP-1R agonists already had a subclinical pancreatic ductal adenocarcinoma when they initiated this therapy.

Because older adults usually harbor PanIN, it is important to determine if these agents promote the growth or progression of PanIN. A related question is whether these agents also influence the proliferation of other pancreatic precursor neoplasms such as intraductal papillary mucinous neoplasms. Although it is difficult to investigate PanIN in the clinical setting, better mutation detection tests may help. For example, measuring the effects of chronic GLP-1R agonist therapy on concentrations of mutant DNA in pancreatic fluids could help determine if these agents promote PanIN growth and progression. Additional prospective studies are required to better determine if long-term treatment with GLP-1R agonists influences the risk of developing pancreatic cancer.

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