

GLP-1-Based Therapy for Diabetes: What You Do Not Know Can Hurt You

According to the *Oxford Dictionary of Proverbs*, the oldest written version of the saying “What you don’t know can’t hurt you” comes from *Petit Palace*, written in 1576 by G. Pettie: “So long as I know it not, it hurteth mee not.”

In this issue of *Diabetes Care*, Drucker et al. (1) conclude that the safety profile of the newly available glucagon-like peptide 1 (GLP-1) class of drugs is favorable in comparison to their benefits as therapy, and the class of drugs might be considered as next in line after metformin for treatment for type 2 diabetes. The purpose of this counterpoint is to suggest such a conclusion is premature. History has taught us that enthusiasm for new classes of drugs, heavily promoted by the pharmaceutical companies that market them, can obscure the caution that should be exercised when the long-term consequences are unknown. Of perhaps greatest concern in the case of the GLP-1-based drugs, including GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, is preliminary evidence to suggest the potential risks of asymptomatic chronic pancreatitis and, with time, pancreatic cancer.

The GLP-1-related drugs arrived in clinical practice with much fanfare and anticipation. As summarized in the article by Drucker et al., it is a class of drugs that has potential benefits in the treatment of type 2 diabetes. The concept of gut-related factors that enhance glucose-mediated insulin secretion, the incretin effect, has been recognized for many years (2). Once it was demonstrated that an intravenous infusion of GLP-1 could decrease blood glucose concentrations in patients with type 2 diabetes, the race was on to exploit the properties of this action. Many millions of dollars have been invested by the pharmaceutical industry in developing products, the first of which are now in clinical practice. Many millions of dollars therefore are now also invested to market the new agents, reminiscent of the period that followed the launch of the most recent new class of drugs for type 2 diabetes, the peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists.

The parallels with the launch of the PPAR- γ agonist and GLP-1 mimetic class of drugs is worthy of comparison. GLP-1 and PPAR- γ agonist therapies were devel-

oped as novel approaches for the treatment of type 2 diabetes building on elegant studies of basic physiology. There was a clear and rational initial therapeutic target with both classes of drugs: insulin resistance for PPAR- γ agonists and enhanced glucose-mediated insulin secretion for the GLP-1 class of drugs.

Before either class of drugs reached market, possible additional attractive attributes were identified mostly through rodent studies. In the case of the PPAR- γ agonist drugs, the most widely anticipated additional benefit was decreased vascular disease because of favorable effects of the drug class on risk factors for vascular disease supported by murine studies reporting protection against ischemic heart disease (3). Not until the European regulatory authorities required appropriately powered studies to demonstrate vascular benefit to support these claims were such studies undertaken (4,5). The results, despite optimistic interpretation by the sponsors, showed little if any cardiovascular benefit that could not have been a consequence of glucose lowering with some suggestion that the net effects of some agents might be harmful on vascular disease (6).

History may be repeating itself with the GLP-1 class of drugs. Putative benefits of GLP-1 mimetic therapy, in addition to enhanced insulin secretion, have been proposed and often arise from rodent studies. These benefits include cardiovascular protection against ischemia and prevention and/or reversal of the defect in β -cell mass that is characteristic of type 2 diabetes (7,8). While these attributes would be highly desirable, there is no current data available to support either of these claims in humans, and recent studies imply that the beneficial effects on β -cell mass in part may be an artifact of studies in juvenile rodents (9–11).

What is the risk profile of GLP-1 drugs? Perhaps the parallel with the PPAR- γ receptor agonists is again worth considering. The receptors targeted by each drug—the PPAR- γ receptor and the GLP-1 receptor, respectively—are widely distributed in numerous tissues with as yet ill-defined roles. As such, it is not surprising when unintended consequences of chronic receptor activation emerge. Po-

tential signals have already emerged in the case of GLP-1 mimetic therapy, one is pancreatitis (12–14) and another, which is currently confined to rodents studies, is thyroid cancer (11).

Pancreatitis first emerged as a potential side effect of therapy with exenatide, initially reported as case reports (12–14) and subsequently by numerous reports made through the U.S. Food and Drug Administration (FDA) adverse reporting mechanism. The Amylin Corporation’s response to this putative link has been to suggest that it was a consequence of guilt by association rather than a drug effect since pancreatitis is more common in individuals with obesity and type 2 diabetes (15). The Amylin Corporation also suggested that since no mechanism is known to link GLP-1 mimetic therapy to pancreatitis, the association is unlikely causal. Pancreatitis was also seen in clinical studies of the GLP-1 agonist liraglutide (16). More recently, the FDA has reported more than 80 documented cases of pancreatitis in patients treated with sitagliptin, a DPP-4 inhibitor (17). It is also Merck’s position that the reported pancreatitis with sitagliptin therapy is due to the increased risk of pancreatitis in type 2 diabetes rather than a consequence of drug therapy (18), mimicking the Amylin Corporation position.

In post-marketing studies sponsored by the marketing companies, no increased signal for acute pancreatitis has been identified (19,20). However, the duration of treatment in those studies is typically short, the quality of the patient follow-up is questionable, and evidence that prescriptions were actually taken is absent. Nonetheless, on the basis of the available clinical information, we agree with the conclusions of Drucker et al. (1) that the data required to link GLP-1 therapy and acute pancreatitis is currently incomplete. However, in the context of a new class of medical therapy, the proverb “What you do not know cannot hurt you” clearly does not apply. We feel that enough preliminary evidence has accumulated to suggest that there is a plausible risk that long-term recipients of GLP-1-based therapy may develop asymptomatic chronic pancreatitis (Fig. 1), and worse, subsequently a minority of individuals

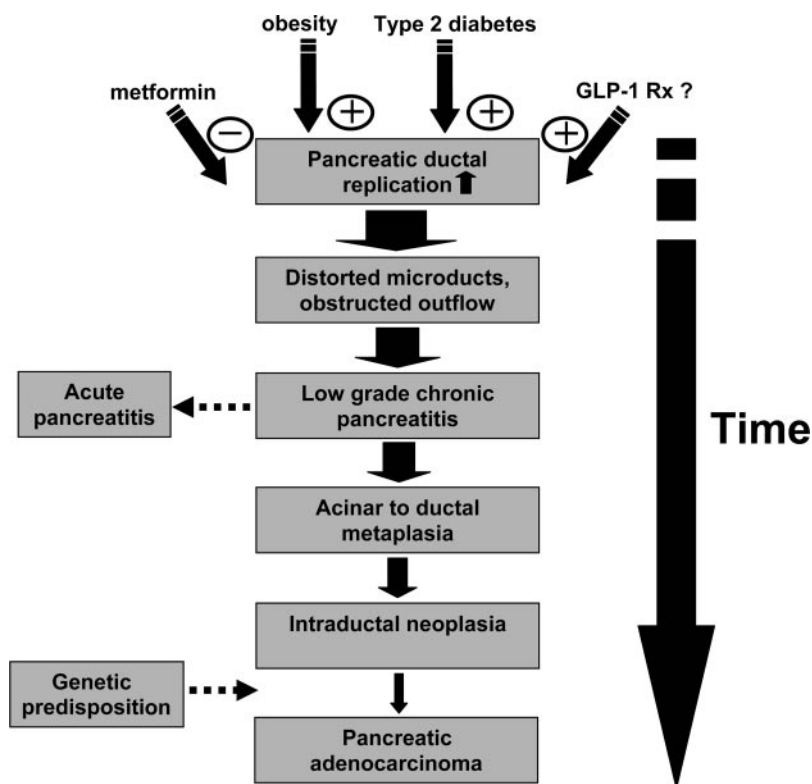


Figure 1—Theoretical model to explain currently available observations with increased risks for pancreatic cancer in individuals with obesity and type 2 diabetes, a risk that is decreased by metformin treatment and theoretically may be increased by GLP-1–based treatment.

treated by this class of drugs may develop pancreatic cancer.

The incidence of both pancreatitis and pancreatic cancer is increased in individuals with obesity and/or type 2 diabetes (21–23), although the underlying mechanisms are not well understood (Fig. 1). One potential link is the frequency of pancreatic duct replication, which is increased in humans with obesity and/or type 2 diabetes (24). It is not known why ductal turnover is increased with obesity and type 2 diabetes. One of the consequences of chronically increased ductal replication can be distortion of small pancreatic ducts with subsequent outflow obstruction of pancreatic enzymes providing a plausible mechanistic link between obesity and/or diabetes and the increased risk for pancreatitis. Moreover, increased ductal replication and chronic pancreatitis are both risk factors for pancreatic cancer (21). Given the apparent signal of occasional acute pancreatitis in patients treated with GLP-1–based therapy, how do we reassure ourselves that asymptomatic chronic pancreatitis is not also induced in some patients?

The most significant challenge is limited access to the human pancreas. To date there are also limited studies avail-

able in rodents. Koehler et al. (25) reported no evidence of GLP-1–induced pancreatitis based on RNA levels in mice, but histology was not provided and numbers of mice in most experimental groups ($n \sim 5$) were perhaps small to conclude a negative finding. On the other hand, both sitagliptin and exenatide have been shown to induce pancreatitis in rats (26,27). Sitagliptin administered to the high-fat–fed human islet amyloid polypeptide (HIP) rat model of type 2 diabetes amplified the increased pancreatic duct cell replication present in that model (27). Moreover, sitagliptin therapy induced acinar to ductal metaplasia in $\sim 30\%$ of treated animals. Acinar to ductal metaplasia follows increased ductal replication in the morphological progression of chronic pancreatitis to pancreatic adenocarcinoma (Fig. 1) (15).

Was this finding a quirk of the HIP rat model of type 2 diabetes? Perhaps, but it is of interest to note that increased ductal replication in the HIP rat model of type 2 diabetes compared with wild-type rats reproduces that which was observed in humans with type 2 diabetes compared with nondiabetic individuals (24). Moreover, metformin therapy in the HIP rat had the opposite effect of sitagliptin, decreasing the

frequency of ductal replication. Therefore, arguably the HIP rat successfully predicts both the increased risk of pancreatitis with sitagliptin and the decreased risk of pancreatic cancer in individuals with type 2 diabetes treated with metformin (28).

Exenatide therapy given over 75 days to rats induced low-grade chronic pancreatitis (26). Again, as in the case of the sitagliptin-treated HIP rats, there was no discernable clinical manifestation of the low-grade pancreatitis induced by exenatide, with the rats in no apparent pain. If GLP-1 mimetic therapy with either GLP-1 mimetic therapy or DPP-4 inhibition induces asymptomatic chronic pancreatitis in rats, how do we know that a similar effect is not present in humans using these therapies? If GLP-1–based therapy causes low chronic pancreatitis, why was this not established in toxicology studies? One possibility is that since ductal replication is increased with obesity or type 2 diabetes (24), and GLP-1 may amplify this, studies in lean nondiabetic animals may have had a limited propensity to GLP-1–induced pancreatitis. Also, most toxicology studies are carried out in juvenile mice in which the pancreas is still growing. Enhanced ductal replication under these circumstances may simply lead to pancreas growth as observed by Koehler et al. (25) rather than distortion of the architecture of the acinar to duct relationship, thus predisposing to chronic pancreatitis.

While low-grade asymptomatic pancreatitis in and of itself as a result of GLP-1–based therapy would not be a cause for major concern, the problem is that it represents a risk for pancreatic cancer (21). The risk for developing pancreatic cancer increases with the duration of chronic pancreatitis (22). Because medications for type 2 diabetes may be taken for many years, if GLP-1–based therapy did induce low-grade asymptomatic pancreatitis, there is a real concern that such a therapy might increase the risk for pancreatic cancer. Even if this is a relatively small risk (which we do not know), how many of us practicing physicians would choose a therapeutic strategy for ourselves with insight into the potential for this risk? Since metformin has been shown to decrease the risk of pancreatic cancer, at the least we would suggest that GLP-1–based medications should be reserved for patients taking metformin.

In conclusion, we believe it is premature to conclude that the GLP-1 class of drugs has been established as having a good safety profile and is appropriate for a relatively early choice of therapy for type 2 di-

abetes. There are grounds for concern that the GLP-1 class of drugs may induce asymptomatic pancreatitis and, over time in some individuals, induce pancreatic cancer. At present, these concerns are based on limited data. However, the implications of the data are sufficiently serious that continuing to promote this class of drugs without establishing clear experimental evidence to permit the concern to be rejected is irresponsible. Moreover, arguably patients prescribed these drugs should be made aware of the potential risks of pancreatic cancer. Otherwise, we collectively subscribe to the proverb "What you do not know cannot hurt you" and, in the case of new drug therapy, this proverb has already been shown to be flawed.

PETER C. BUTLER, MD
SARAH DRY, MD
ROBERT ELASHOFF, PHD

From the Larry L. Hillblom Islet Research Center, Department of Pathology and Department of Biomathematics, University of California, Los Angeles, Los Angeles, California.

Corresponding author: Peter Butler, pbutler@mednet.ucla.edu.

DOI: 10.2337/dc09-1902

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

- Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010;33:428–433
- Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol* 2009;297:127–136
- Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 2005;54:2460–2470
- Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Scherthauer G, Schmitz O, Skrha J, Smith U, Taton J, the PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–1289
- Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125–2135
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–2471
- Noyan-Ashraf MH, Momen MA, Ban K, Sadi AM, Zhou YQ, Riaz AM, Baggio LL, Henkelman RM, Husain M, Drucker DJ. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009;58:975–983
- Buteau J. GLP-1 receptor signaling: effects on pancreatic beta-cell proliferation and survival. *Diabetes Metab* 2008;34(Suppl 2):S73–S77
- Tschen SI, Dhawan S, Gurlo T, Bhushan A. Age-dependent decline in beta cell proliferation restricts the capacity of beta cell regeneration in mice. *Diabetes* 2009
- Rankin MM, Kushner JA. Adaptive β -cell proliferation is severely restricted with advanced age. *Diabetes* 2009;58:1365–1372
- Parnaud G, Bosco D, Berney T, Pattou F, Kerr-Conte J, Donath MY, Bruun C, Mandrup-Poulsen T, Billestrup N, Halban PA. Proliferation of sorted human and rat beta cells. *Diabetologia* 2008;51:91–100
- Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care* 2006;29:471
- Cure P, Pileggi A, Alejandro R. Exenatide and rare adverse events. *N Engl J Med* 2008;358:1969–1970
- Tripathy NR, Basha S, Jain R, Shetty S, Ramachandran A. Exenatide and acute pancreatitis. *J Assoc Physicians India* 2008;56:987–988
- Whitcomb DC. Mechanisms of disease: advances in understanding the mechanisms leading to chronic pancreatitis. *Nat Clin Pract Gastroenterol Hepatol* 2004;1:46–52
- Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L, the LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009;374:39–47
- U.S. Food and Drug Administration. Sitagliptin (marketed as Januvia and Janumet)—acute pancreatitis [Internet], 25 September 2009. Available from <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm183800.htm>. Accessed 12 October 2009
- Heavey S. UPDATE 3-US FDA sees pancreatitis link with Merck's Januvia [article online], Reuters, 25 September 2009. Available from <http://www.reuters.com/article/companyNewsAndPR/idUSN2550919420090925>. Accessed 12 October 2009
- Williams-Herman D, Round E, Swern AS, Musser B, Davies MJ, Stein PP, Kaufman KD, Amatruda JM. Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis. *BMC Endocr Disord* 2008;8:14
- Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009;25:1019–1027
- Jura N, Archer H, Bar-Sagi D. Chronic pancreatitis, pancreatic adenocarcinoma and the black box in-between. *Cell Res* 2005;15:72–77
- Rebours V, Boutron-Ruault MC, Schneé M, Férec C, Le Maréchal C, Hentic O, Maire F, Hammel P, Ruszniewski P, Lévy P. The natural history of hereditary pancreatitis: a national series. *Gut* 2009;58:97–103
- Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009;137:482–488
- Butler AE, Galasso R, Matveyenko AV, Rizza RA, Dry S, Butler PC. Pancreatic duct replication is increased with obesity and type 2 diabetes in humans. *Diabetologia*, In Press, 2009
- Koehler JA, Baggio LL, Lamont BJ, Ali S, Drucker DJ. Glucagon-like peptide-1 receptor activation modulates pancreatitis-associated gene expression but does not modify the susceptibility to experimental pancreatitis in mice. *Diabetes* 2009;58:2148–2161
- Nachnani JS, Bulchandani DG, Nookala A, Herndon B, Molteni A, Pandya P, Taylor R, Quinn T, Weide L, Alba LM. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. *Diabetologia*, 2009 [Epub ahead of print]
- Matveyenko AV, Dry S, Cox HI, Moshaghian A, Gurlo T, Galasso R, Butler AE, Butler PC. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. *Diabetes* 2009;58:1604–1615
- Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009;52:1766–1777