Editorial

Incretin-based therapy and pancreatitis: accumulating evidence and unresolved questions

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Incretin-based therapy consists of two different classes of medication: glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors. Since the approval of exenatide, the first GLP-1 RA, and sitagliptin, the first DPP-4 inhibitor, by the U.S. Food and Drug Administration (FDA) in 2005 and 2006, respectively, incretin-based therapy is becoming a major option for the treatment of type 2 diabetes (T2DM) (1). While DPP-4 inhibitors enhance endogenous incretin [GLP-1 and glucose-dependent insulinotropic polypeptide (GIP)] action, GLP-1 RAs stimulate the GLP-1 receptor at a supra-physiological level. Since both agents enhance glucose-dependent insulin secretion and also suppress glucagon secretion in a glucose-dependent manner, the risk of hypoglycemia is very low unless they are combined with sulfonylureas, glinides or insulin. In addition, GLP-1 RAs, but not DPP-4 inhibitors, suppress gastric emptying and satiety, thereby inducing weight reduction. Recent cardiovascular outcome trials (CVOTs) have shown that GLP-1 RAs, liraglutide and semaglutide, improved CV outcomes in patients with T2DM and high CV risk (2,3). Liraglutide has also been shown to improve renal outcome (4). Based on these results, the American Diabetes Association (ADA) states that therapy with liraglutide should be considered for patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) (5).

Incretin-based therapy has generally been well-tolerated with few serious adverse events, although gastrointestinal symptoms are commonly seen in subjects treated with GLP-1 RAs, which usually resolve spontaneously 2 to 4 weeks after the initiation of therapy. However, a rare but serious adverse event associated with incretin-based therapy is acute pancreatitis (AP).

After marketing of incretin-based drugs, cases of AP have been reported and the FDA has ordered a warning label (6,7). Several cohort studies suggested increased risk of AP with incretin-based therapies (8,9), and this subject has been extensively discussed (10,11). Although pooled analysis of phase 3 trials has shown no excess risk of AP with incretin-based therapy (12), the number of events was small.

In 2017, a meta-analysis of three CVOTs of DPP-4 inhibitors including 18,238 patients treated with DPP-4 inhibitors and 18,157 placebo-treated patients has been reported (13), showing increased risk of AP with treatment with DPP-4 inhibitors (odds ratio =1.79; 95% CI, 1.13–2.82; P=0.013). On the other hand, a meta-analysis of three CVOTs of GLP-1 RAs showed no excess risk of AP compared with placebo (14). Therefore, it is under debate whether DPP-4 inhibitors and GLP-1 RAs have different risk profiles of AP.

Recently, Steinberg *et al.* have provided new evidence regarding liraglutide and the risk of AP (15,16). They conducted a secondary analysis of pooled data from the Satiety and Clinical Adiposity-Liraglutide Evidence in individuals with and without diabetes (SCALE) clinical development program (15). The analysis included four randomized, placebo-controlled trials comprising the

SCALE phase 3a clinical trial program of liraglutide 3.0 mg for weight management (n=5,358 with BMI ≥30, or 27 to <30 kg/m^2 with ≥1 comorbid condition). Of these, 1,723 subjects had normoglycemia, 2,789 had prediabetes and 846 had T2DM. Participants were randomized to liraglutide 3.0 mg (n=3,302), liraglutide 1.8 mg (n=211, only T2DM) or placebo (n=1,845). Subjects with a history of idiopathic AP or chronic pancreatitis were excluded from the SCALE program. Relationships between serum amylase/lipase activity at baseline and during treatment and events of AP were investigated.

Over 56 weeks, liraglutide 3.0 mg versus placebo was associated with a 7% increase in mean level of amylase and a 31% increase in mean level of lipase activity. Similar changes in amylase/lipase levels were observed with liraglutide 1.8 mg. However, few subjects had elevations to 3 times the upper limit of normal (ULN) for amylase or lipase (<0.1% and 2.9% with liraglutide 3.0 mg), and the enzymes returned to baseline levels after liraglutide discontinuation. Twelve participants developed AP during (n=9, 0.3%) or after (n=3, 0.1%) liraglutide 3.0 mg treatment versus one (0.1%) with placebo, all of whom were from SCALE Trial 1. Five of 12 AP cases with liraglutide 3.0 mg had gallstone disease evident at AP onset. Amylase/lipase elevations before AP onset showed very low positive predictive value for AP (<1%).

Strengths of the study include a prospective, randomized, controlled study design with a large sample size and relatively long duration of follow-up. Amylase/lipase activity was measured regularly, and the diagnosis of AP was adjudicated by an independent, blinded committee.

Accompanying this paper, a sub-analysis of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) trial regarding relationships between amylase/lipase levels and AP onset in patients with T2DM treated with liraglutide 1.8 mg has been reported in the same issue of *Diabetes Care* (16). The LEADER trial included a total of 9,340 patients with T2DM and high CV risk randomized to either liraglutide or placebo with median follow-up of 3.84 years. During the study, 18 (0.4%) liraglutide-treated and 23 (0.5%) placebo patients developed AP confirmed by adjudication. Prior history of pancreatitis did not increase the risk of AP onset after liraglutide treatment. Compared with the placebo group, liraglutide-treated patients had increases in serum amylase and lipase of 7.0% and 28.0%, respectively. Similar to the analysis of the SCALE trial, elevations of amylase and lipase levels did not predict future risk of AP in patients treated with liraglutide.

These results provide a clearer picture of the association between liraglutide and AP onset. First, liraglutide increases serum amylase/lipase levels by approximately 7% and 30%, respectively, in a dose-independent manner, irrespective of the presence or absence of diabetes. Second, the increases in amylase/lipase levels are seen as early as 4 weeks after introducing liraglutide therapy. Third, the increases in amylase/lipase levels are reversible after discontinuing the therapy. Fourth, the elevations of amylase/lipase levels are not predictive of AP onset.

Although elevations of amylase/lipase levels with GLP-1 RAs therapy were confirmed by these studies, the mechanisms by which GLP-1 RAs increase these serum enzyme levels remain unclear. Recent studies have shown that the GLP-1 receptor is weakly expressed in acinar cells (17) and, in mice, GLP-1 increases amylase secretion from acinar cells (18,19). A study in mice also has shown that 4 weeks of GLP-1 treatment increases protein synthesis in acinar cells and pancreatic mass, reflecting an increase in acinar cell mass without changes in ductal compartments or beta cell mass (20). Therefore, GLP-1 may enhance acinar cell protein synthesis including amylase and lipase. However, the effects of GLP-1 on exocrine function and pancreatic morphology have not been confirmed in non-human primates or humans (21-25). Another hypothesis is that GLP-1 increases the permeability of the basolateral membrane of acinar cells, resulting in enhanced transfer of pancreatic enzymes into blood, which needs further investigation.

The other mechanism of AP onset in patients with incretin-based therapy is gallstone-related pancreatitis. Increased incidence of gallbladder-related adverse events such as cholelithiasis and acute cholecystitis have been reported in patients treated with GLP-1 RA therapy (26) and also in both the LEADER and SCALE trials (2,27). Since GLP-1 suppresses gastrointestinal movement, gallbladder and biliary tract motility may also be suppressed by GLP-1, leading to gallstone formation (28). Weight loss and change in food components after GLP-1 RA therapy may also contribute to production of gallstones. The relatively longer duration between initiation of GLP-1 RA therapy and onset of AP seems to be consistent with this hypothesis, and indeed 50% of AP was attributable to gallstones in the SCALE program (15).

The results of pancreatic enzymes in the SCALE and LEADER trials seem almost identical and complementary (*Table 1*). However, a striking difference is that the

Table 1 Summary of results of SCALE and LEADER trials regarding acute pancreatitis

Variables	SCALE trials (liraglutide ~3.0 mg)	LEADER trial (liraglutide 1.8 mg)
N (female, %)	5,358 (70.8)	9,340 (35.7)
Mean age (years)	47.0	64
Mean BMI (kg/m^2)	38.0	32.5
Glucose tolerance status	Normoglycemia 1,723; prediabetes 2,789; T2DM 846	All T2DM
Observation period	56 weeks	Median 3.84 years
Increase in amylase level	7%	7.0%
Increase in lipase level	31%	28.0%
Incidence of AP (liraglutide *vs.* placebo)	12 (0.4%) *vs.* 1 (0.1%)	18 (0.4%) *vs.* 23 (0.5%)
Duration before AP onset	Two peaks (<60 days and >5–6 months)	Mostly >12 months
Positive predictive values of amylase/lipase for AP	<1%	<1%

T2DM, type 2 diabetes; AP, acute pancreatitis.

Table 2 Pancreatic effects of DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1 RAs)

Pancreatic effects	DPP-4 inhibitors	GLP-1RAs
Amylase/lipase levels	Increase or no change	Increase
Acute pancreatitis	Increase	No change or increase? (liraglutide 3.0 mg)
Cholelithiasis/cholecystitis	No change	Increase

incidence of AP was numerically increased with liraglutide therapy in the SCALE trials (15), while it was comparable between the liraglutide and placebo groups in the LEADER trial (2). It can be assumed that the different doses of liraglutide (1.8 *vs.* 3.0 mg) might affect the incidence of AP. Since a higher dose (3.0 mg) of liraglutide is aimed at weight loss, the effects of GLP-1 on gastrointestinal motility including the gallbladder and biliary tract, weight loss and change in food components, all of which could contribute to gallstone synthesis, may be exaggerated compared with those with 1.8 mg of liraglutide. These factors might accelerate the production of gallstones, resulting in the increased incidence of AP seen in the SCALE program.

Thus, gallstone-related pancreatitis might explain the different incidence of AP between the two trials. However, it does not seem to explain the increased risk of AP related to DPP-4 inhibitors, since DPP-4 inhibitors do not usually affect gastrointestinal motility or induce weight loss. The use of DPP-4 inhibitors does not appear to increase gallbladder-related adverse events (26), and inconsistent results regarding changes in serum amylase/lipase levels after the use of DPP-4 inhibitors have been reported (29-33) (*Table 2*).

Because the increased risk of AP was originally reported in patients treated with sitagliptin or exenatide, and the proinflammatory/proliferative effects of GLP-1 on the exocrine pancreas have been suggested as the mechanism of AP onset with incretin-based therapy (34-36), AP has been thought to be a common adverse event with incretin-based therapy. However, recent meta-analyses have shown that the incidence of AP is in fact increased in patients treated with DPP-4 inhibitors, but not with GLP-1 RAs (13,14). Inhibition of DPP-4 affects not only GLP-1 level but also various other substrates including GIP, cytokines, growth factors and neuropeptides. DPP-4 (also namely CD26) is also expressed on the surface of T cells (37). Thus, DPP-4 inhibitors may affect the immune system and tissue inflammation. Recently, the development of bullous pemphigoid (BP) in patients treated with DPP-4 inhibitors has been reported (38). This adverse event may be associated with genetic factors (39). Thus, the increased risk of AP in patients treated with DPP-4 inhibitors could also be associated with inflammatory response within the pancreas predisposed by genetic factors.

Accumulating evidence has shed light on the different risk profiles of AP onset between DPP-4 inhibitors and GLP-1 RAs. The mechanisms by which DPP-4 inhibitors and GLP-1 RAs increase the risk of AP may be different, and further investigation is needed to clarify this unresolved question.

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Footnote

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