

# Potential linkage between dipeptidyl peptidase-4 inhibitor use and the risk of pancreatitis/pancreatic cancer

Dipeptidyl peptidase (DPP)-4 inhibitors, a class of oral hypoglycemic agents, are widely used, especially in Asian populations, as they have been shown to be well-tolerated and to cause relatively few hypoglycemic events, despite exerting a potent glucose-lowering effect by promoting endogenous insulin secretion, besides also having extrapancreatic effects. Meanwhile, the use of DPP-4 inhibitors has been reported to be associated with the development of bullous pemphigoid, a rare autoimmune blistering skin disease<sup>1</sup>, even though the absolute increase in the risk of development of bullous pemphigoid is relatively low. While some large-scale clinical trials and meta-analyses have provided evidence to show that DPP-4 inhibitors have no significant effects on the cardiovascular risk profile, the trials also offered an opportunity to identify other potential adverse effects of this class of drugs. A meta-analysis of the results of three large interventional trials, namely, SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53), EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care) and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), reported that treatment with DPP-4 inhibitors significantly increased the risk of acute pancreatitis, with an odds ratio (OR) of 1.79 and *P*-value of 0.013<sup>2</sup>. Another meta-analysis of 38 trials involving 59,404

patients showed no relationship between DPP-4 inhibitor use and the risk of pancreatic cancer (OR 0.65, 95% confidence interval [CI] 0.36–1.21), but a significant association of DPP-4 inhibitor use with the risk of acute pancreatitis (OR 1.72, 95% CI 1.18–2.53)<sup>3</sup>. A report of a retrospective study of cohorts in Belgium and Italy showed that the use of incretin drugs was associated with an increased risk of pancreatic cancer (OR 2.14, 95% CI 1.71–2.67)<sup>4</sup>. In contrast, a considerable number of studies have also shown the lack of any significant association between DPP-4 inhibitor use and the risk of pancreatitis or pancreatic cancer. Hence, the link between exposure to DPP-4 inhibitors and the risk of development of pancreatitis and pancreatic cancer remains under debate.

Lee *et al.*<sup>5</sup> from the Yonsei University College of Medicine in Korea also investigated the associations between DPP-4 inhibitor use and the risk of pancreatitis and pancreatic cancer, using the Korean National Health Insurance Service-Health Screening Cohort database. They carried out their study from 2007 to 2013 to assess the risk of development of pancreatitis/pancreatic cancer in 33,208 adults (mean age 62.1 years, 57.8% men, 42.2% female) with newly diagnosed type 2 diabetes mellitus who were receiving antidiabetic drug treatment. In that study, a total of 10,218 patients were new users of DPP-4 inhibitors, including sitagliptin, vildagliptin, linagliptin, saxagliptin and gemigliptin, and 22,990 were new users of other antidiabetic drugs. Pancreatitis was diagnosed 1,084 times in that cohort, including chronic pancreatitis 215 times and acute pancreatitis 869 times. The overall incidence rate of pancreatitis in

the DPP-4 inhibitor use group was 1,073 per 100,000 person-years, whereas that in the group taking other drugs was 935 per 100,000 person-years. After adjustments for multiple confounding factors, DPP-4 inhibitor use was found to be associated with a 27% increase in the risk of development of pancreatitis (adjusted hazard ratio [HR] 1.27, 95% CI 1.07–1.52, *P* = 0.007; Table 1). Those who were using DPP-4 inhibitors were also 24% more likely to develop pancreatitis when a 6-month exposure lag period was considered (adjusted HR 1.24, 95% CI 1.01–1.52, *P* = 0.037). Subgroup analysis showed that the association of DPP-4 inhibitor use with the risk of pancreatitis was not affected by age, sex, body mass index, history of gallbladder or common bile duct stones and the Charlson Comorbidity Index score. As for pancreatic cancer, pancreatic cancer was diagnosed in 237 patients, including 35 from the DPP-4 inhibitor use group and 202 from the other-drug use group. The overall incidence rate of pancreatic cancer in the DPP-4 inhibitor use group was 236 per 100,000 person-years, and that in the other-drug use group was 200 per 100,000 person-years. After adjustments for multiple confounding factors, the analysis showed that those treated with DPP-4 inhibitors had a 50% higher risk of developing pancreatic cancer (adjusted HR 1.50, 95% CI 1.02–2.20, *P* = 0.042; Table 1). Those who were receiving DPP-4 inhibitors were also 81% more likely to develop pancreatic cancer when a 6-month exposure lag period was considered (adjusted HR 1.81, 95% CI 1.16–2.82, *P* = 0.009). In the first 12 months, and 1 year after the initial prescription, the risks for pancreatitis and pancreatic cancer were

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**Table 1** | Adjusted hazard ratios (95% confidence intervals) for pancreatitis and pancreatic cancer associated with DPP-4 inhibitor use in the report from Lee *et al.*<sup>5</sup>

	No time lag	Time since the initial prescription			
		<3 months	3 to <6 months	6 to <12 months	≥12 months
Pancreatitis	1.27 (1.07–1.52)	1.32 (1.00–1.75)	1.09 (0.71–1.66)	1.39 (1.01–1.90)	1.19 (0.93–1.52)
Pancreatic cancer	1.50 (1.02–2.20)	1.93 (1.17–3.21)	1.39 (0.57–3.42)	2.00 (1.01–3.96)	1.95 (1.16–3.29)

generally consistent, without a tendency to increase according to the exposure duration (Table 1).

Inconsistent results have also been reported from other large observational case-control or cohort studies about the association between DPP-4 inhibitor use and the risk of pancreatitis<sup>6</sup>. In a nationwide cohort study carried out using the Taiwan National Health Insurance claim database<sup>7</sup>, after stratification for propensity score quintiles, sitagliptin was not found to be associated with an increased risk of acute pancreatitis (adjusted HR 0.95, 95% CI 0.79–1.16), as compared with acarbose in diabetes patients with a prior history of hospitalization for pancreatitis or hypertriglyceridemia. Why were different results obtained between Korean and Taiwanese studies among East-Asian studies? Differences in the diagnostic criteria for pancreatitis could have had some influence; another possible reason is the difference in the drug use pattern between the two countries. In Korea, DPP-4 inhibitors are used as second-line treatment for patients with severe hyperglycemia not showing satisfactory response to the initial monotherapy.

The relationship between DPP-4 inhibitor use and pancreatic cancer also remains highly controversial. A propensity score-matched cohort study carried out in Korea showed no elevated risk of pancreatic or thyroid cancer in participants with type 2 diabetes mellitus receiving DPP-4 inhibitor treatment as compared with those receiving metformin treatment<sup>8</sup>. The inconsistent results call into question the appropriateness of DPP-4 inhibitor use for the control of hyperglycemia in cancer patients. What is the mechanism by which DPP-4 inhibition could potentially increase the

risk of pancreatic cancer? Some preclinical studies have shown that DPP-4 inhibitors can prevent cancer cell proliferation. In contrast, activation of stromal cell-derived factor 1 or nuclear factor erythroid 2-related factor 2 by DPP-4 inhibition might be related to the development of pancreatic cancer. Further basic and clinical studies are warranted to determine whether DPP-4 inhibitors might have oncogenic activity.

One remaining question is whether DPP-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) behave differently in relation to the risk of pancreatitis and pancreatic cancer. Some previous reports have suggested the possibility that DPP-4 inhibitors can cause pancreatitis, but that GLP-1RAs do not aggravate the disease<sup>9</sup>. However, there is much conflicting evidence as to the influences of DPP-4 inhibitor use and GLP-1RA use on both pancreatitis and pancreatic cancer. The differences in the potential influence between DPP-4 inhibitors and GLP-1RAs might be related to the larger number of substrates of DPP-4, including neuropeptides, chemokines, vasoactive peptides, and growth factors, besides GLP-1. Receptors for GLP-1 are thought to be expressed predominantly in the pancreatic islets, but not the acinar cells. Therefore, the effect of DPP-4 inhibitors on the risk of pancreatitis and pancreatic cancer does not seem to be mediated through their direct actions on the acinar cells. In this context, investigation of the role of glucose-dependent insulinotropic peptide and its receptor signaling in the development of pancreatitis or pancreatic cancer would be interesting.

According to a study by Lee *et al.*<sup>5</sup>, the treatment duration with DPP-4

inhibitors did not appear to influence the risk profiles for pancreatitis and pancreatic cancer associated with DPP-4 inhibitor use, although the follow-up period of the study was limited. Because a trend toward an increase of the risk with the exposure duration was absent, there is a chance of reverse causality having influenced the results of that study. Insufficient glycemic control generally causes both pancreatitis and pancreatic cancer in patients with type 2 diabetes mellitus. To exclude the influence of reverse causation, a study with a longer observation period in newly diagnosed drug-naïve patients is warranted.

Inflammation of the pancreas due to acute or chronic pancreatitis might initiate carcinogenesis in pancreas. An association has been shown between acute pancreatitis and the risk of pancreatic cancer<sup>10</sup>. The relationship between incretin drug-induced pancreatitis/pancreatic cancer is an important issue that needs to be addressed. At present, DPP-4 inhibitors are suspected to have scarce effects on the risk of any cancer other than pancreatic cancer. However, previous reports have suggested that thyroid cancer risk might be increased by incretin drugs, mediated through GLP-1 expressed on the thyroid C cells<sup>11</sup>. DPP-4 inhibitors also increase the levels of endogenous DPP-4 substrates, such as neuropeptide Y or substance P, and might thereby have effects on the immune system through DPP-4, DPP-8 or DPP-9. Therefore, further study is required to clarify the influence of DPP-4 inhibitors on tumor immunity.



Particularly in Asian individuals with type 2 diabetes mellitus, pancreatic cancer is one of the most important issues to consider for improving quality of life

and extending the lifespan, because the risk of pancreatic cancer is higher in Asians than Caucasians. As hypoglycemia might cause higher mortality and dementia in diabetes patients, DPP-4 inhibitors could be ideal agents to avoid hypoglycemia, especially in older adults with type 2 diabetes. Taking into consideration the relatively low frequency of pancreatic adverse events associated with the use of DPP-4 inhibitors, the merit of using DPP-4 inhibitors still surpasses those of many other antidiabetic drugs. At least for now, we need to pay attention to early detection and treatment of pancreatitis and pancreatic cancer in patients receiving DPP-4 inhibitors. How we can identify individuals who are at an elevated risk? Measurement of serum amylase or lipase levels is not sufficient for the prediction of pancreatitis, because mild elevation in the levels of these enzymes is seen in patients receiving DPP-4 inhibitors or GLP-1RAs. However, measurement of the serum levels of these pancreatic enzymes along with those of the serum levels of bilirubin and alkaline phosphatase should be considered in patients receiving DPP-4 inhibitors who present with symptoms related to pancreatitis. Therefore, these patients should be carefully observed for the development of symptoms potentially related to diseases of the pancreas. It is difficult to carry out imaging examinations, such as computed tomography or abdominal ultrasound, in all patients. Pancreatic cancer often leads to poor glycemic control because of deteriorating pancreatic functions, such as by causing pancreatic duct obstruction. Imaging examination for early detection of pancreatic or other cancer is warranted in patients receiving antidiabetic drugs who

present with worsened glycemic control or a decrease of bodyweight without apparent cause. The concept of DPP-4 inhibitors-induced pancreatitis and pancreatic cancer remains in doubt. However, at present, the possibility should be taken into account when choosing DPP-4 inhibitors for treating patients with diabetes mellitus.

#### DISCLOSURE

The authors declare no conflict of interest.

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