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MINIREVIEWS

Incretin based therapy and pancreatic cancer: Realising the reality

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Abstract

Incretin-based therapies like glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors help maintain the glycaemic control in patients with type 2 diabetes mellitus with additional systemic benefits and little risk of hypoglycaemia. These medications are associated with low-grade chronic pancreatitis in animal models inconsistently. The incidence of acute pancreatitis was also reported in some human studies. This inflammation provides fertile ground for developing pancreatic carcinoma (PC). Although the data from clinical trials and population-based studies have established safety regarding PC, the pathophysiological possibility that low-grade chronic pancreatitis leads to PC remains. We review the existing literature and describe the relationship between incretin-based therapies and PC.

Key Words: Diabetes mellitus; Dipeptidyl peptidase-4 inhibitor; Glucagon-like peptide-1 receptor agonist; Incretin; Pancreatitis; Pancreatic Cancer

Core Tip: Incretin-based therapies are increasingly being used to treat patients with type 2 diabetes mellitus . The early literature regarding pancreatic safety of incretin-based therapies was discordant. However, the follow-up data of various randomised trials have consistently shown that these medications are safe.

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INTRODUCTION

Incretin-based therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4Is) are being increasingly used to treat patients with type 2 diabetes mellitus (T2DM). GLP-1 RAs mimic the action of endogenous GLP-1, whereas DPP-4Is prevent the degradation of GLP-1. These medications can control blood glucose levels without an increased risk of hypoglycemic episodes or weight gain. The initial clinical trials for GLP-1 RA and DPP-4I were conducted in 2003 and 2004, respectively[1,2]. The United States Food and Drug Administration (FDA) issued an alert regarding the potential risk of acute pancreatitis in 2007[3]. DPP-4Is have been widely used owing to the oral administration and low risk of hypoglycemia. However, the use of GLP-1 RA was limited until 2015. But the data from cardiovascular outcome trials (CVOTs) of GLP-1 RAs changed the scenario. The significant reduction in cardiovascular deaths with GLP-1 RAs such as liraglutide and semaglutide tilted the benefit-risk relationship. These therapies have become the next treatment choice after metformin in patients with or at high risk of atherosclerotic vascular disease[4]. Newer generation incretin-based therapies [coagonists of GLP-1 with gastric inhibitory peptide (GIP) or glucagon] are in the pipeline. They are presumed to have higher efficacy than GLP-1 RAs and DPP-4Is. Various incretin-based medications categorised according to their mechanism of action are shown in Table 1.

Incretin-based therapies are speculated to induce overstimulation of the GLP-1 receptor, leading to pancreatitis and pancreatic carcinoma (PC). However, the risk of both PC and pancreatitis is increased in DM compared to non-diabetic counterparts[5]. For PC, inflammation is relevant both as a risk factor and an effect of cancer. Patients with chronic pancreatitis carry a higher risk of developing PC. The initial postmarketing surveillance studies for incretin-based therapies revealed an increase in pancreatic adverse events[6]. Further observational studies of pancreatic adverse events showed conflicting results. Post hoc analyses of pertinent randomized controlled trials (RCTs) failed to distinguish pancreatic adverse events between controls and patients on incretin-based therapies[7]. However, the theoretical plausibility of PC in patients receiving incretin-based therapies still remains valid. It is worth reviewing the status of the incretin-based therapies now as an increasing number of therapies based on incretin are becoming available. The treating clinician must be aware of the benefit-risk ratio (RR) when prescribing incretin-based therapy.

SEARCH STRATEGY

Two authors (VS, AR) conducted the initial search in PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/) database for relevant articles. The references of these articles were searched for additional relevant studies. The keywords used in the search were: 'Incretin'; 'pancreatic cancer'; glucagon-like peptide-1 receptor agonist'; 'dipeptidyl peptidase-4 inhibitor'; incretin and pancreatic cancer; 'GLP1-RA and pancreatic cancer'; 'DPP-4I and pancreatic cancer'. Only English language publications were included. SK, DN, and JS selected the appropriate articles to be included.

PATHOPHYSIOLOGY

The critical pathophysiologic mechanisms for developing PC in patients using incretin-based therapies are chronic low-grade inflammation and proliferative changes. A flowchart outlining the pathophysiology of pancreatic cancer is shown in Figure 1.

Role of inflammation

Even without any therapy, both PC and pancreatitis incidence is increased in T2DM[8,9]. Long term treatment of T2DM patients with DPP-4Is/GLP-1 RAs may exacerbate the pre-existing chronic inflammation. Any additional mutations in the background of inflammation can tilt the balance toward the

Table 1 Various incretin-based therapies

Class of drugs	Medications
GLP-1RA (oral/subcutaneous)	Subcutaneous-Exenatide, Albiglutide, Lixisenatide, Liraglutide, Semaglutide. Oral-Semaglutide
DPP-4I (oral)	Saxagliptin, Vildaglipitn, Sitagliptin, Aloglipitn, Linagliptin, Teneligliptin
Newer drugs/drugs in development	Tirzepatide (GLP1 + GIP co-agnoist)
	Cotadutide (GLP1 + glucagon co-agonist)
	Teduglutide (GLP-2 RA)
	Triple agnoists (GLP1 + Glucagon + GIP agnoists)

GLP-1RA: Glucagon like peptide receptor-1 receptor agonist; DPP-4I: Dipeptidyl peptidase-4 inhibitor; GIP: Gastric inhibitory peptide; GLP-2RA: Glucagon like peptide receptor-2 receptor agonist.

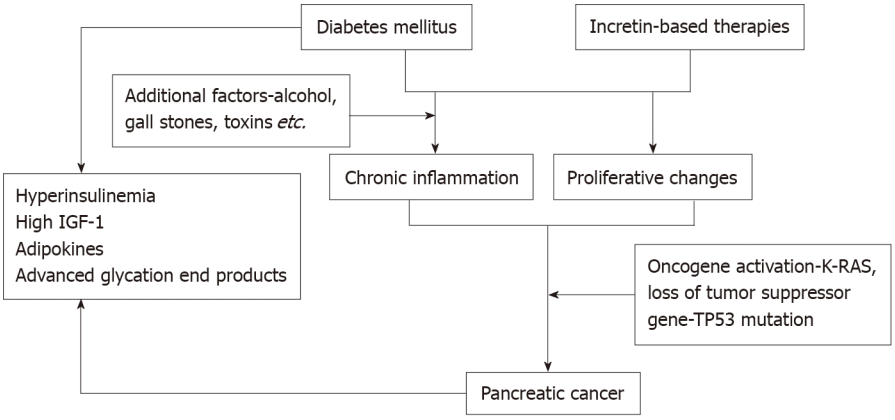

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Figure 1 Flowchart explaining the mechanism of development of pancreatic cancer. IGF-1: Insulin-like growth factor-1; K-RAS: Kirsten rat sarcoma virus gene.

progression of neoplasia. Various researchers conducted animal studies to substantiate this hypothesis using rodents with mutant Kirsten rat sarcoma virus gene (K-RAS), leading to constitutive activation. The K-RAS gene is mutated in > 90% of human PC cases[10]. KC mice model has a single activating mutation (G12D) in the K-RAS gene. Prenatal expression of mutant K-RAS in all exocrine lineages of KC mice resulted in histological changes suggestive of pancreatitis, implying a cooperative relationship between K-RAS activation and inflammation. Treatment of KC mice with the pancreatitis-inducing agent caerulein (a cholecystokinin analog) dramatically accelerates the progression to pancreatic ductal adenocarcinoma (PDAC) within a few weeks[11]. Further animal experiments have shown that K-RAS mutation alone cannot reach the expected theoretical levels of activity required for the progression of carcinogenesis. Nevertheless, agents which cause inflammation can hyperstimulate K-RAS by modulating its activity above the putative threshold necessary for carcinogenesis. The constitutive activation of nuclear factor kappa B pathway in addition to K-RAS in acinar cells significantly accelerates carcinogenesis, whereas cyclooxygenase inhibition is associated with a reduced risk of PDAC. These findings highlight the importance of inflammation in the progression of PDAC[12].

Incretin-based medications induced pancreatitis in animal experiments[13-15]. However, most PDAC cases develop without clinically apparent acute or chronic pancreatitis[16]. This observation can be explained by low-grade subclinical inflammation being sufficient to promote carcinogenesis in the presence of additional drivers of carcinogenesis. On the other hand, it can also be a consequence of the earliest events in carcinogenesis.

Role of proliferative changes

In addition to low-grade asymptomatic chronic pancreatitis, incretin-based medications induce proliferative changes in the islets. Premalignant changes that precede the onset of PDAC are known as pancreatic intraepithelial neoplasia (PanIN) lesions. They herald the start of PDAC. PanINs can be found in up to 50% of the middle-aged population. However, only a few progress to PDAC[17]. As progression of PanINs to PDAC occurs *via* the accumulation of additional somatic mutations, any factor that increases cellular replication in PanINs is likely to increase the likelihood of PDAC. Both PanINs and PDAC express the human GLP-1 receptor. Acinar and duct cells proliferate in response to incretin-

based medications in the normal pancreas with an increase in pancreatic weight[18]. In the setting of chronic pancreatitis, as shown in animal models treated with incretin-based therapies, this proliferation may be sufficient to initiate carcinogenesis event sequences. Treatment with exenatide in KC mice resulted in the formation and growth of dysplastic PanIN lesions in addition to pancreatitis.

Histological changes following incretin-based therapies

The controversy about pancreatic adverse events due to incretin-based therapies was amplified by a publication by Butler *et al*[19]. The authors examined age-matched organ donor samples obtained from the Network for Pancreatic Organ Donation (nPOD). They included a total of 34 subjects with T2DM treated with incretin-based therapies (n = 8) or non-incretin-based therapies (n = 12) and nondiabetic control subjects (n = 14). The incretin group had an increase in pancreatic mass by 40% with increased exocrine cell proliferation and dysplasia. The authors also noticed alpha and beta-cell hyperplasia along with glucagon-expressing microadenomas in incretin-treated subjects. Islet cell costaining for insulin and glucagon was higher in DM subjects than non-DM control subjects and increased further with incretin therapy. The authors concluded that incretin therapy in humans results in the expansion of both exocrine and endocrine pancreatic compartments and that there is a potential for evolution into neuroendocrine tumors. However, this study was met with sharp criticism owing to methodological flaws. Harja *et al*[20], in a more detailed analysis of the nPOD database, found that the baseline characteristics were not comparable between the incretin group and the other two groups. Pancreatic weight data were missing for half of the subjects. The increase in PanINs can be explained by the nearly 20-year age difference between the incretin group and the other two groups. Bonner-Weir *et al*[21] and Kahn[22] also re-analyzed the data from nPOD and reached similar conclusions.

Despite the flaws in the study methodology, this study caught the attention of the FDA and the European Medicines Agency (EMA). Both agencies reviewed all available animal and human data for incretin-based therapies. Microscopic examinations from animal studies did not reveal pancreatic lesions or pancreatitis. Even at doses greater than human clinical exposure to incretin-based therapies, there were no tumours in rodents for up to 2 years (lifespan of rodents). The FDA studied the effect of exenatide in Zucker diabetic fatty rat, a chemical-induced pancreatitis model, and C57 black 6 (C57BL/6) high-fat diet mouse model. There was no identifiable pancreatic pathology in the pancreatitis mouse model and Zucker diabetic fatty rat model. After three months of exenatide in the C57BL/6 high-fat diet mouse, a minimal-to-moderate worsening of background findings was noted. Based on the available data, they could not draw any conclusions about the risk of pancreatic adverse events in patients using incretin-based therapies[23].

Ueberberg *et al*[24] conducted a study on cadaveric pancreata, similar to Butler *et al*[19]. They obtained pancreatic tissue during surgery from 13 diabetic patients (7 in the incretin group and 6 in the non-incretin group), 11 non-diabetic controls, and nine brain-dead organ donors. There were no differences between groups in the alpha cell area, beta and alpha cell replication, acinar, and ductal cell replication. Coexpression of insulin and glucagon has not been demonstrated. PanIN lesions were more common in the diabetic group, although the prevalence was low. Considering the small sample size and large interindividual variability, the authors advised caution on coming to any conclusion from such studies.

Chadwick *et al*[25] attempted to determine the background incidence of spontaneous pancreatic lesions in different rat strains fed a standard or high-fat diet over four months. They found that the pancreatic lesions previously thought to be due to incretins are common baseline findings. These lesions can be seen without any drug treatment. These lesions were independent of diet or glycaemic status. The authors concluded that we need to be cautious when interpreting patients' pancreatic findings on incretin-based therapies. Aston-Mourney *et al*[26] tried to characterize the amyloidogenic potential of sitagliptin in rodents. Human islet amyloid polypeptide transgenic mice, untreated nontransgenic mice, and those on treatment with sitagliptin, metformin, or the combination were followed up for one year. There was no increase in amyloid formation or ductal proliferation. However, there was an improvement in β-cell secretion, suggesting endocrine protective effects without associated toxicity to the exocrine compartment of the pancreas.

Effect of incretin-based therapies on cancer cells

The effect of incretin-based therapies on PC cells has also been studied *in vitro*. Lu *et al*[27] found that liraglutide in combination with metformin has synergistic anti-tumor effects *in vitro*. Yan *et al*[28] examined the effect of exendin-4 on a xenograft tumor model. Exendin-4 suppressed the PC cell proliferation by attenuating the function of pancreatic stellate cells (PSC) and suppressing extracellular matrix deposition. Zhao *et al*[29] examined the effect of liraglutide on PC cell line (PANC-1) cocultured with and without PSCs and found that liraglutide significantly reduced the migration and invasion of the PANC-1 cells. The authors hypothesized that the effect is probably mediated by calcium and calcium-binding proteins. In another study, Zhao *et al*[30] examined the effects of liraglutide on the chemosensitivity of PC cells to gemcitabine in PANC-1 and gemcitabine resistant cell lines (PANC-GR). Liraglutide inhibited proliferation and promoted apoptosis of the PANC-GR cells in a dose-dependent manner. It also increased GLP-1 receptor and protein kinase-A expression in the PANC-GR cells. In rodent studies, liraglutide treatment was observed to increase the chemosensitivity of PC cells to

gemcitabine.

DPP4 and cancer

DPP-4 cleaves many other polypeptides, such as chemokines, neuropeptides in addition to GLP-1. DPP-4, also known as cluster differentiation marker 26, plays a vital role in inflammation by modulating the inactivation of cytokines and chemokines. DPP-4 is expressed in various malignancies. The overexpression of DPP-4 exerts an antitumour effect predominantly through immunomodulation[31]. DPP-4 inhibition has been shown to improve antitumor immune response by preserving the function of a chemokine C-X-C motif ligand and through interleukin 33 (IL-33) mediated tumour control[32,33]. The effects of DPP-4 on cancer cells appear to be heterogeneous, depending on tumor types, stages, microenvironment, and host condition. In breast cancer and small cell lung cancers, decreased expression of DPP-4 is associated with more aggressiveness of the tumour. However, increased DPP-4 expression levels have been associated with poor prognosis in patients with PC[31].

INCRETIN-BASED THERAPIES AND PC-HUMAN STUDIES

Data from observational studies

Early case reports of pancreatitis following exenatide and sitagliptin led to the issue of FDA alert in 2007. These reports led to many database analyses to look for the prevalence of pancreas-related adverse events. Elashoff *et al*[6] raised concern regarding PDAC by studying the FDA adverse events reporting system (FDA AERS) during 2004-09. This study resulted in widespread coverage in media regarding the risk of PC. Elashoff *et al*[6] examined FDA AERS database for adverse events associated with exenatide and sitagliptin in this study. The odds ratio for reported pancreatitis was 6-fold higher for sitagliptin or exenatide users than other therapies. PC was also more frequent (approximately 3-fold) among patients who took sitagliptin or exenatide. However, we must understand that this was a retrospective, record-based study. The likelihood of reporting events is higher with new drugs than with the patients on older drugs. A series of observational studies followed this study and showed discordant results. Most of the observational studies were retrospective and record-based. Both the FDA and the EMA reviewed their clinical safety databases, and the pooled data did not reveal any compelling evidence of an increased risk of pancreatitis or PC.

The latest observational study from Montvida *et al*[34] used Centricity Electronic Medical Records from the United States. The authors assessed the time to pancreatic events for incretin-based and nonincretin therapies (sulfonylurea, thiazolidinedione, and insulin). This study surprisingly found that the group treated with insulin had higher pancreatitis events with a short time to event as compared to incretin-based therapies. For PC, the time to event rate was not significantly different between the groups. Among the older studies, few studies showed an increased risk of pancreatitis and PC, but most studies could not find any association between pancreatic adverse events and incretin-based therapies [34-38]. Although the sample size was adequate for these studies, we must keep in mind the unaccounted confounders. The baseline characteristics and the comparator drugs varied among different studies. A summary of these studies is compiled in Table 2.

Data from randomised controlled trials

Data from RCTs have conventionally been considered superior to data from observational studies. There have been many follow-up studies of the patients recruited for CVOT of the incretin-based therapies. Among the individual CVOT data, there was a non-significant trend for or against the development of PC for different incretin-based therapies. Many researchers also assessed the PC risk with incretin-based therapies using meta-analyses and systematic reviews. Alves *et al*[39] evaluated the association of liraglutide or exenatide with PC in a meta-analysis that included 25 longitudinal studies in 2012. Neither GLP-1 RAs nor DPP-4Is were associated with increased risk for PC.

The first meta-analysis evaluating PC association with all types of incretin-based therapies was published by Chen *et al*[40] in 2016. This meta-analysis included 24 RCTs enrolling 47904 patients. This meta-analysis also could not identify any increased risk of PC either as monotherapy (RR = 0.62, 95%CI: 0.38–1.01) or combination therapy (RR = 0.92, 95%CI: 0.45–1.90). This result was followed by a series of meta-analyses with a similar conclusion[41-43]. The latest meta-analysis is from Abd El Aziz *et al*[43], which evaluated 11 CVOTs studying 55921 patients. In the individual study data, lixisenatide and semaglutide were associated with nominally reduced RR, whereas liraglutide was associated with a slightly elevated RR. However, none of these RRs were statistically significant. In this meta-analysis, neither GLP-1 RAs nor DPP-4Is were associated with a significant increase or decrease in risk of PC [RR for PC- for GLP-1 RA 0.99 (95%CI: 0.9-1.08); DPP-4I 0.92 (95%CI: 0.83-1.01)]. The summary of the data from various meta-analyses is compiled in Table 3.

Newer incretin-based therapies

Tirzepatide is a dual agonist at GLP-1 and GIP receptors. It was formulated as a fatty acid-modified

Table 2 Important observational studies which evaluated the relationship between incretin-based therapies and pancreatic carcinoma

Ref.	Study design	Population	Findings
Elashoff *et al* [6], 2011	Retrospective study (Control drugs-rosiglitazone, glinides, glipizide), 2004-09	Database-FDA AERS. Patients of T2DM on exenatide and sitagliptin. *n* = 1541 events (exenatide). *n* = 322 (sitagliptin). *n* = 691 (controls)	PC was more common among patients who took sitagliptin (2.7-fold) or exenatide (2.9-fold) as compared with other therapies
Montvida *et al*[34], 2019	Retrospective record-based study. 2005 onwards. Follow-up duration 2.27-4.3 yr	Centricity electronic medical record, United States. DPP-4i *n* = 50095. GLP-1 RA *n* = 12654. SU *n* = 110747. TZD *n* = 17597. Insulin *n* = 34805	Compared with DPP-4i, the GLP-1 RA group developed PC 3 yr later (95%CI: 0.84-5.16). No other significant differences were observed between groups
Nagel *et al* [35], 2016	Retrospective study (Control drugs-rosiglitazone, glinides, glipizide), 1968-2013	Database-FDA AERS. Patients of T2DM on sitagliptin, saxagliptin, linagliptin, and alogliptin. *n* = 156 PC patients	EB05 was 10.3 for sitagliptin, 7.1 for saxagliptin, 4.9 for linagliptin, and 1.4 for alogliptin, compared with all other agents
Azoulay *et al* [36], 2016	Nested case control analysis (control drug- sulfonylureas), 2007-2014. Follow-up 1.3-2.8 yr	Database-CNODES (Canada, United States, United Kingdom). *n* = 972384	Compared with SUs, incretin-based drugs were not associated with an increased risk of PC-pooled aHR 1.02 (95%CI: 0.84-1.23)
Tseng *et al* [37], 2017	Retrospective population-based cohort study, 1997-2010. Follow up-till occurrence of adverse pancreatic event	Database-The Taiwan National Health Insurance Research Database. *n* = 13171 incretin. *n* = 13171 non-incretins	PC occurred in 6 (0.05%) and 10 (0.08%) patients in the incretin and non- incretin cohort, respectively
Boniol *et al* [38], 2018	Retrospective cohort study, 2008-2013. Follow-up 1.8-2.3 yr	Public health insurance databases of Belgium, Lombardy (Italy). *n* = 33292 incretin. *n* = 525733 control	The aHR for PC was 2.14 (95%CI: 1.71–2.67) for incretin group compared with control

FDA AERS: Food and drug administration adverse event reporting system; T2DM: Type 2 diabetes mellitus; PC: Pancreatic carcinoma; EB05: Empirical Bayesian fifty centile; aHR: Adjusted hazard ratio; CI: Confidence interval; CNODES: Canadian network for observational drug effect studies; SU: Sulfonylurea; OHA: Oral hypoglycemic agent; RR: Risk ratio; TZD: Thiazolidinedione.

Table 3 Important systematic reviews and meta-analyses which evaluated the relationship between incretin-based therapies and pancreatic cancer

Ref.	Description	Findings
Alves *et al* [39], 2012	All studies (25 RCT/longitudinal observational) assessing the estimate of pancreatitis/PC in patients with T2DM using exenatide or liraglutide	For PC risk, the OR of exenatide was 0.86 (95%CI: 0.29-2.60) and liraglutide was 1.35 (95%CI: 0.70-2.59)
Chen *et al* [40], 2016	All RCTs reporting PC with use of incretin-based therapies compared with placebo or non-incretin anti-diabetic drugs in patients with T2DM	Overall, no increased risk of PC was detected in association with incretin-based treatment (RR = 0.7, 95%CI: 0.37–1.05). The incidence of PC was even lower among incretin-based groups than controls (RR = 0.50, 95%CI: 0.29–0.87) in trials with duration more than 104 wk
Zhang *et al* [41], 2017	6 prospective randomized controlled trials (EXAMINE, SAVOR-TIMI 53, TECOS, ELIXA, LEADER and SUSTAIN-6)-3 trials for DPP-4is and 3 trials for GLP-1 RAs	Incretin-based agents did not significantly affect PC-OR: 0.71 (95%CI: 0.45–1.11)
Pinto *et al* [42], 2019	12 RCTs with GLP-1 RAs as an intervention, from database inception till 2017	GLP-1 RAs did not increase the risk for pancreatic cancer when compared to other treatments-OR: 1.06 (95%CI: 0.67-1.67)
Abd El Aziz *et al* [43], 2020	Meta-analysis of cases of acute pancreatitis and PC as well as any malignant neoplasm reported in 11 CVOTs with GLP-1 RAs and DPP-4i	Neither GLP-1 RAs nor DPP-4is were associated with a significantly elevated or reduced risk of PC. For GLP-1 RA OR was 1.14 (95%CI: 0.77-1.7) and for DPP4i OR was 0.94 (95%CI: 0.52-1.68)

PC: Pancreatic cancer; RCT: Randomised controlled trial; T2DM: Type 2 diabetes mellitus; OR: Odds ratio; RR: Risk ratio; CVOT: Cardiovascular outcome trial; GLP-1 RA: Glucagon like peptide-1 receptor agonists; DPP-4i: Dipeptidyl Peptidase-4 inhibitors; OHA: Oral hypoglycemic agent.

peptide based on the native GIP sequence. Tirzepatide demonstrated a more significant reduction in glycosylated hemoglobin, superior weight loss, and comparable adverse effects compared to semaglutide in a phase 3 trial. Pancreatitis was observed in four patients in the tirzepatide arm and three patients in the semaglutide arm during the study duration[44]. Cotadutide is a balanced GLP-1 and glucagon receptor dual agonist. Phase 2 clinical trials for cotadutide were published recently. The efficacy of cotadutide also appears to be better than that of semaglutide, although no head-to-head comparison is available. No case of pancreatitis has been reported in the phase 2a study of cotadutide, although the frequency of nausea and vomiting was increased in the cotadutide arm[45]. We must therefore wait until we have sufficient data on these new drugs. It is premature to make comment on the pancreatic safety of these drugs at present.

CONCLUSION

We have collected extensive data on the safety of incretin-based therapies over the past two decades. It seems that incretin-based therapies do not increase the risk for PC. Instead, new pre-clinical experimental data have shown beneficial effects on cancer cell lines that require further evaluation. The uncertain risks of PC appear to be smaller compared to the beneficial pleiotropic effects of incretin-based therapies. However, with newer incretin-based therapies, we should keep the theoretical possibility of PC in mind and be cautious until we obtain sufficient data.

FOOTNOTES

Author contributions: Suryadevara V and Roy A did the literature search and wrote the first draft; Sahoo J, Kamalanathan S and Naik D supervised the writing, gave intellectual inputs, and critically revised the manuscript; Mohan P and Kalayarasan R gave intellectual inputs and critically revised the manuscript; all of them approved the final version of the manuscript to be published.

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