



DPP-4 Inhibitor Exposure Among Patients with Pancreatic Cancer: A Single-Center Retrospective Study

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Abstract Purpose: Pancreatic cancer is among the most lethal gastrointestinal malignancies, and type 2 diabetes mellitus (T2DM) is both a modest risk factor for the disease and, when of recent onset, a possible early manifestation of it. Concern has been raised that dipeptidyl peptidase-4 (DPP-4) inhibitors, one of the two classes of incretin-based therapy, may be associated with pancreatic disease. The aim of this study was to describe the frequency of documented long-term DPP-4 inhibitor exposure before diagnosis in a single-center series of patients with pancreatic cancer, and to compare routinely available clinical and laboratory characteristics between exposed and non-exposed patients. By design, the study does not evaluate whether DPP-4 inhibitor therapy causes or increases the risk of pancreatic cancer. **Materials and Methods:** This was a single-center, retrospective, case-only study. The records of 87 patients diagnosed with pancreatic cancer at Sivas Cumhuriyet University Faculty of Medicine between April 2021 and April 2023 were screened. Ten patients who had attended the institution only to receive treatment, and for whom institutional data were unavailable, were excluded; 72 patients with complete institutional records constituted the analytic sample. Demographic data, laboratory values obtained at the time of diagnosis and pre-diagnostic medication histories were extracted from the hospital database. Documented DPP-4 inhibitor use for at least three years before the diagnosis was applied as the predefined exposure criterion. Exposed and non-exposed patients were compared using independent-samples t tests; because sixteen laboratory variables were compared, results were additionally evaluated against Bonferroni- and false-discovery-rate-corrected thresholds and are otherwise reported as exploratory. **Results:** Of the 72 patients analyzed, 16 (22.2%) had documented DPP-4 inhibitor exposure meeting the predefined criterion and 56 (77.8%) did not. The mean duration of exposure among users was 44.50 ± 17.22 months. The sample comprised 37 women (51.4%) and 35 men (48.6%) with a mean age of 66.03 ± 10.71 years; 24 patients (33.3%) had a recorded diagnosis of diabetes mellitus. HbA1c was higher in exposed than in non-exposed patients (7.727 ± 0.969 vs 6.135 ± 1.098 ; $p < 0.001$), and this was the only difference that remained significant after correction for multiple comparisons. Nominally significant differences in lipase, hematocrit, alkaline phosphatase and gamma-glutamyl transferase did not survive correction and are reported as exploratory. **Conclusion:** In this single-center retrospective sample of patients with pancreatic cancer, 22.2% had documented DPP-4 inhibitor exposure meeting the predefined three-year criterion. Because the study lacks a comparison group without pancreatic cancer and includes only a small exposed subgroup, these findings cannot determine whether DPP-4 inhibitor therapy increases pancreatic cancer risk. The higher HbA1c among exposed patients is most plausibly explained by the indication for treatment rather than by a drug effect. Large, multicenter, controlled and preferably longitudinal studies with adequate adjustment for confounding are required.

Key Words Pancreatic Cancer, Dipeptidyl Peptidase-4 Inhibitors, Incretin-Based Therapy, Type 2 Diabetes Mellitus, Retrospective Studies, Pharmacoepidemiology

INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies of the gastrointestinal tract. According to GLOBOCAN estimates, approximately 511,000 new cases and 467,000 deaths from pancreatic cancer occurred worldwide in 2022,

making it the sixth leading cause of cancer death [1]. Prognosis remains poor: in the United States the 5-year relative survival rate is approximately 13% for pancreatic cancer overall and approximately 8% for pancreatic ductal adenocarcinoma (PDAC), the predominant histological

subtype [2]. The early detection of this disease remains particularly challenging due to the absence of specific clinical symptoms and reliable diagnostic biomarkers. As a result, many patients are only diagnosed at an advanced stage, which limits treatment options. In advanced disease, distant metastases are present in the majority of patients, precluding curative resection and limiting the effectiveness of chemotherapy and radiotherapy. The etiology of pancreatic cancer is multifactorial and remains incompletely understood; recognised contributors include tobacco use, obesity, chronic pancreatitis, family history and diabetes mellitus [3].

Diabetes mellitus (DM) is a chronic metabolic disorder that has been identified as a potential contributing factor in the development of pancreatic cancer. The relationship between DM and pancreatic malignancy is complex and bidirectional. Meta-analytic evidence indicates that long-standing type 2 diabetes mellitus (T2DM) is associated with a modestly increased risk of pancreatic cancer [4], and epidemiological studies have linked T2DM to an increased incidence of several other malignancies, including haematological cancers [5,6]. Two distinct phenomena must nevertheless be distinguished. Long-standing T2DM appears to act as a modest risk factor for pancreatic cancer, whereas diabetes of recent onset — typically within approximately three years of the cancer diagnosis — is frequently a paraneoplastic manifestation of an already established but clinically undetected tumour [6,7]. This reverse-causality relationship is central to the interpretation of any study of antidiabetic drugs and pancreatic cancer: patients with occult pancreatic cancer develop hyperglycaemia, are prescribed glucose-lowering therapy, and are subsequently diagnosed with the tumour, which can generate a spurious association between the drug and the malignancy.

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a widely utilized class of oral antidiabetic agents, frequently administered either in combination with metformin or as an adjunctive treatment option in the management of type 2 diabetes mellitus [8]. DPP-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are both classified as incretin-based therapies, but they are pharmacologically distinct and are not interchangeable. DPP-4 inhibitors are small, orally bioavailable molecules that block the catalytic site of DPP-4 without interfering with its other known functions, thereby preserving endogenous incretin peptides and raising their concentrations within a broadly physiological range. GLP-1 RAs, by contrast, are injectable peptide agonists that stimulate the GLP-1 receptor directly and at supraphysiological levels. Because DPP-4 cleaves a wide range of additional substrates, DPP-4 inhibition also modifies the availability of chemokines and neuropeptides that are unaffected by GLP-1 RAs [9]. Evidence obtained with one class therefore cannot be assumed to apply to the other. DPP-4 inhibitors do not lower blood glucose directly; their efficacy as antidiabetic agents depends on their ability to inhibit DPP-4 activity, which is mediated by the maintenance of incretin peptides [9,10].

DPP-4 is known to exert both proinflammatory and profibrotic effects, primarily through its enzymatic interactions with various substrates, as well as via multiple direct and indirect biological pathways [10–12]. In conditions such as insulin resistance, obesity, and diabetes, an upregulation of DPP-4 expression and activity has been observed across different tissues and cell types, accompanied by elevated circulating levels of its soluble form [13]. Consequently, increased DPP-4 activity in individuals with diabetes has been associated with pathological processes including chronic inflammation, metabolic imbalance, inflammation-related cellular injury and apoptosis, tissue remodeling, and the progression of fibrosis, particularly in disorders such as liver cirrhosis and end-stage renal disease (ESRD) [14–16].

DPP-4 is expressed ubiquitously and exists both as a transmembrane protein and in a soluble, circulating form. Both forms are catalytically active and cleave proteins containing an alanine or proline in the second position. This catalytic activity can inactivate certain peptides or generate new bioactive fragments with distinct effects [9].

DPP-4 was first characterized as a molecule involved in the regulation of T-cell activation and proliferation. Elevated levels and increased enzymatic activity of DPP-4 have been reported in T cells derived from individuals with autoimmune and inflammatory conditions, including rheumatoid arthritis [17]. This observation prompted the investigation of DPP-4 inhibitors as potential treatment agents for immune diseases characterized by abnormal T-cell function [18]. Given that DPP-4 expression is altered in various malignancies and shows interactions with extracellular matrix components, its inhibition has attracted interest as a potential therapeutic target in both malignant T-cell disorders and solid tumor metastasis. In this context, non-selective inhibitors targeting DPP-4 along with related enzymes such as FAP, DPP8, and DPP9 — particularly Val-Boro-Pro (PT-100, talabostat) — have been evaluated in clinical studies for the management of solid tumors and advanced non-small cell lung cancer [19,20]. Early-generation, non-selective DPP-4 inhibitors were reported to exert notable influences on immune system function and to modify the proliferation of neoplastic cells. Subsequent findings indicated that these effects were largely attributable to their non-selective actions rather than to specific inhibition of DPP-4, and they should therefore not be equated with the selective DPP-4 inhibitors used in clinical diabetes care.

The safety of incretin-based therapies with respect to the exocrine pancreas has been debated since 2007, when the U.S. Food and Drug Administration (FDA) issued an alert describing postmarketing reports of acute pancreatitis in patients treated with exenatide, a GLP-1 receptor agonist. The prescribing information for the DPP-4 inhibitor sitagliptin was revised for the same reason in 2009, and in 2013 the FDA announced that it was evaluating reports of pancreatitis and pre-cancerous pancreatic findings associated with the incretin mimetic class as a whole, while

stating explicitly that it had not concluded that these drugs cause pancreatic cancer [21,22]. The initial signal therefore arose predominantly from a GLP-1 receptor agonist and was subsequently extended to DPP-4 inhibitors. Analyses of spontaneous reporting systems have suggested that both GLP-1 receptor agonists and DPP-4 inhibitors may be associated with reports of acute pancreatitis and pancreatic cancer [23]. Such databases can generate pharmacovigilance signals, but they lack a population denominator and cannot estimate incidence, risk or causality; they are also strongly susceptible to reporting bias and to stimulated (notoriety) reporting following regulatory warnings [24]. It must also be emphasised that individuals with diabetes have a higher baseline risk of both pancreatitis and pancreatic cancer than people without diabetes, irrespective of any specific drug exposure [23,26].

Inflammation is a key component in the pathogenesis of pancreatic cancer, acting both as a contributing factor and as a result of disease progression. In particular, individuals with chronic pancreatitis are at a significantly elevated risk of developing pancreatic cancer. Initial observational studies investigating incretin-based therapies indicated a higher frequency of pancreatic-related adverse events [23]. Later observational studies examining pancreatic-related adverse events produced inconsistent findings. Furthermore, post-hoc evaluations of relevant randomized controlled trials (RCTs) have not clearly demonstrated a significant difference in the incidence of pancreatic adverse events between control groups and patients receiving incretin-based therapies [27]. Despite this, the possible relationship between incretin-based therapies and pancreatic cancer remains a subject of ongoing pharmacovigilance interest, and continued monitoring has been recommended in view of the long latency of pancreatic malignancy.

The mechanisms proposed to link incretin-based therapies to pancreatic carcinogenesis are hypothetical and derive largely from animal and in vitro work; they centre on persistent low-grade inflammation and increased cellular proliferation. A schematic summary of these proposed pathways is presented in Figure 1. The occurrence of pancreatic cancer and pancreatitis is higher among individuals with untreated T2DM [23,26]. It has been hypothesised that prolonged use of DPP-4 inhibitors or GLP-1 receptor agonists in patients with T2DM might intensify pre-existing chronic inflammatory processes and, in combination with additional genetic alterations, contribute to neoplastic progression. This hypothesis has been investigated in multiple studies employing animal models, especially rodents carrying an activated mutant Kirsten rat sarcoma virus (K-RAS) gene. Mutations in the K-RAS gene are observed in more than 90% of human pancreatic cancer cases [28]. In a murine model, prenatal induction of a single activating K-RAS mutation (G12D) across all exocrine cell lineages in KC mice led to histological alterations consistent with pancreatitis, indicating a potential synergistic interaction between K-RAS activation and inflammatory processes [29]. Additional animal studies have shown that

the presence of a K-RAS mutation alone is insufficient to drive the level of activity required for tumor progression. However, inflammatory stimuli may amplify K-RAS signaling, increasing its activity beyond the threshold necessary for carcinogenesis. Moreover, continuous activation of the nuclear factor-kappa B signaling pathway in acinar cells has been reported to markedly promote carcinogenesis, whereas inhibition of cyclooxygenase has been linked to a reduced risk of PDAC [30].

Incretin-based treatments, such as GLP-1 receptor agonists and DPP-4 inhibitors, have been associated with the development of pancreatitis in experimental animal models. However, the majority of PDAC cases arise in the absence of clinically evident acute or chronic pancreatitis [31]. This may indicate that low-grade, subclinical inflammation could facilitate carcinogenesis when combined with additional oncogenic influences, or alternatively that the observed changes relate to early phases of tumour development; neither possibility has been demonstrated in humans.

In addition to inducing mild, asymptomatic inflammation in experimental models, incretin-based agents have been reported to promote proliferative alterations in pancreatic tissue. Precursor lesions of PDAC, termed pancreatic intraepithelial neoplasia (PanIN), are detected in up to half of middle-aged individuals, although only a small proportion progress to invasive PDAC [31]. The transition from PanIN lesions to PDAC is driven by the stepwise accumulation of additional somatic mutations; accordingly, any stimulus that enhances cellular proliferation within PanINs may theoretically elevate the risk of PDAC. Both PanIN and PDAC tissues express the human GLP-1 receptor, and exposure to GLP-1 receptor agonists has been shown to promote proliferation of acinar and ductal cells, resulting in increased pancreatic mass [32]. These observations derive from rodent models and from direct GLP-1 receptor agonism rather than from DPP-4 inhibition in humans, and their clinical relevance remains uncertain.

Beyond GLP-1, DPP-4 is capable of cleaving a wide range of polypeptides, including chemokines and neuropeptides. Recognized also as a cluster of differentiation marker, DPP-4 contributes significantly to inflammatory processes by regulating the inactivation of cytokines and chemokines [33]. DPP-4 inhibition has been reported to strengthen antitumor immune responses by maintaining the activity of CXC chemokine ligands and by facilitating tumor control through interleukin-33 (IL-33)-mediated pathways [34,35]. These findings show that DPP-4 inhibition may also exert antitumour effects and that the biological direction of the effect is context dependent. The impact of DPP-4 on cancer cells appears to be variable and is influenced by factors such as tumor type, disease stage, microenvironmental conditions, and host characteristics. For instance, reduced DPP-4 expression has been linked to more aggressive tumor behavior in breast cancer and small cell lung cancer, whereas elevated DPP-4 levels have been associated with poorer prognosis in patients with pancreatic cancer [33].

These concerns prompted a series of database-based investigations aimed at evaluating the frequency of pancreatic adverse events. In particular, Elashoff et al. analyzed data from the FDA Adverse Event Reporting System between 2004 and 2009 and highlighted a potential association with PDAC, which subsequently attracted considerable media attention. Their findings indicated that the reported odds of pancreatitis were approximately sixfold higher among individuals using sitagliptin or exenatide compared to those receiving alternative therapies, and that the reported odds of pancreatic cancer were nearly three times greater [36]. These are reporting odds ratios derived from a spontaneous reporting system; they describe reporting patterns and do not represent incidence, relative risk or causality, and they combine a DPP-4 inhibitor with a GLP-1 receptor agonist.

Against this background, the present study was designed as a descriptive, single-center, case-only analysis. Its objective was to determine the proportion of patients with pancreatic cancer treated at our institution who had documented DPP-4 inhibitor exposure of at least three years before diagnosis, and to compare routinely recorded demographic and laboratory characteristics between exposed and non-exposed patients. The study includes no comparison group of individuals without pancreatic cancer and therefore cannot, by design, estimate the incidence of pancreatic cancer, the risk associated with DPP-4 inhibitor therapy, or any causal relationship between the two.

METHODS

Study Design and Setting

This research was designed as a single-center, retrospective, case-only study conducted at Sivas Cumhuriyet University Faculty of Medicine. All patients diagnosed with pancreatic cancer at the institution between April 2021 and April 2023 were eligible for screening, and a total of 87 patients were identified and retrospectively evaluated. Because the analysis relied entirely on institutional records, complete availability of hospital data was a prerequisite for inclusion; ten patients who had presented to the institution only in order to receive treatment, and for whom no institutional data were available, were therefore excluded. The final analytic sample comprised 72 patients. The reasons for the exclusion of the remaining screened patients are not documented in the study records, and this is acknowledged as a reporting limitation.

Variables and Data Sources

Clinical and laboratory parameters recorded at the time of the pancreatic cancer diagnosis were retrieved from the hospital database. Laboratory variables comprised blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total and direct bilirubin, amylase, lipase, haemoglobin (Hb), haematocrit (Hct), platelet count (PLT), fasting blood glucose, glycated haemoglobin (HbA1c), thyroid-stimulating hormone (TSH) and thyroxine (T4).

Demographic variables comprised age and sex. The date of diagnosis, the presence and recorded duration of a diagnosis of diabetes mellitus, and all medications used before the diagnosis of pancreatic cancer together with their recorded durations of use were also extracted.

Definition of DPP-4 Inhibitor Exposure

Exposure was defined a priori as documented use of a DPP-4 inhibitor, recorded in the retrospective medication history, for at least three years before the date of the pancreatic cancer diagnosis. Patients meeting this criterion were classified as exposed and all remaining patients as non-exposed. This threshold was a predefined study criterion and does not correspond to an established or externally validated definition in the published literature. A minimum exposure window is commonly applied in this field because associations between incretin-based drugs and pancreatic cancer are strongest in the months immediately following treatment initiation and attenuate substantially when lag periods are applied, a pattern consistent with reverse causality [37,38]. The specific three-year threshold used here has not been validated, may itself introduce selection bias, and should be regarded as a study-specific operational definition. Individual DPP-4 inhibitor agents, doses, dosing frequency, exact start and stop dates, continuity versus intermittency of therapy, and treatment adherence could not be retrieved from the available records and were therefore not analysed.

Statistical Analysis

The data obtained from the study were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). First, a descriptive analysis was performed, followed by a Kolmogorov–Smirnov test to assess the normality of the data distribution. As the data met the assumptions for parametric analysis, parametric tests were performed. Continuous variables are presented as mean±standard deviation and were compared between two independent groups using the independent-samples t test; categorical variables are presented as counts and percentages.

It must be emphasised that these analyses compare measured laboratory values between exposed and non-exposed patients, all of whom already had pancreatic cancer. They do not test the development, incidence or risk of pancreatic cancer, and no such inference can be drawn from them.

Sixteen laboratory variables were compared by sex (Table 1) and sixteen were compared according to DPP-4 inhibitor exposure (Table 2). To limit the type I error rate arising from this multiplicity, the reported p values were re-evaluated against a Bonferroni-corrected threshold ($\alpha = 0.05/16 = 0.003$) and using the Benjamini–Hochberg false discovery rate procedure at $q = 0.05$. Both corrections were computed from the complete set of p values already reported and required no additional data. Comparisons that did not remain significant after correction are described as exploratory and hypothesis-generating. No multivariable or

adjusted analyses were performed: the small number of exposed patients ($n = 16$) and the absence of individual-level covariate data — including smoking status, body mass index, diabetes duration and concomitant antidiabetic therapy — preclude meaningful adjustment. A two-sided p value below 0.05 was regarded as nominally significant.

RESULTS

A total of 72 eligible patients were included in the study. Among the participants, 16 patients (22.2%) had documented DPP-4 inhibitor exposure meeting the predefined three-year criterion, whereas 56 patients (77.8%) had no such documented exposure. The mean duration of DPP-4 inhibitor use among the 16 exposed patients was 44.50 ± 17.22 months, and the mean age of the participants was 66.03 ± 10.71 years. The mean age was 64.65 ± 10.99 years in female patients and 67.49 ± 10.37 years in male patients. The sample comprised 37 women (51.4%) and 35 men (48.6%). A recorded diagnosis of diabetes mellitus was present in 24 patients (33.3%), while 48 patients (66.7%) had no recorded diagnosis of diabetes. The mean recorded duration of diabetes among these 24 patients was 28.26 ± 44.82 months; because the standard deviation

exceeds the mean, the distribution is markedly skewed and this figure should be interpreted with caution (Figure 1).

DPP-4 inhibitors are indicated for the treatment of type 2 diabetes mellitus, so patients with documented long-term exposure would be expected to fall within the group of 24 patients carrying a recorded diagnosis of diabetes mellitus. The study records do not contain a cross-tabulation of DPP-4 inhibitor exposure against recorded diabetes status, diabetes duration, glycaemic control or concomitant antidiabetic therapy, and this relationship therefore cannot be characterised further from the available data. The figure of 22.2% describes documented prior exposure within a series of patients who already had pancreatic cancer; it is not an incidence, a population prevalence, or a measure of risk.

A significant difference was found in the creatinine parameter according to sex ($p = 0.012$). No significant difference was found in other blood parameters ($p > 0.05$) (Table 1). After correction for the sixteen comparisons performed, this difference no longer reached the adjusted significance threshold and is therefore reported as an exploratory finding.

Comparison of laboratory values between patients with and without documented DPP-4 inhibitor exposure showed nominally significant differences in HbA1c ($p < 0.001$),

Table 1: Comparison of Laboratory Parameters between Female and Male Patients with Pancreatic Cancer ($n = 72$)

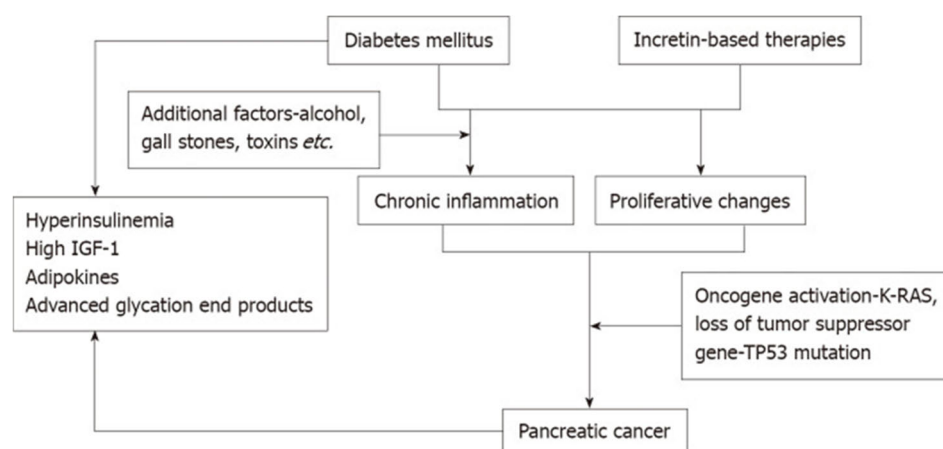
Parameter	Group	n	Mean	SD	t	p
BUN	Female	37	12.385	7.406	-1.635	0.107
	Male	35	15.054	6.368		
Creatinine	Female	37	0.693	0.282	-2.593	0.012
	Male	35	0.847	0.219		
HbA1c	Female	37	6.717	1.227	-0.199	0.843
	Male	35	6.799	1.407		
Fasting blood glucose	Female	37	142.135	75.239	0.692	0.491
	Male	35	131.429	53.562		
Amylase	Female	37	61.919	88.950	-0.628	0.532
	Male	35	74.971	87.295		
Lipase	Female	37	63.405	138.401	-0.036	0.971
	Male	35	64.371	78.283		
ALT	Female	37	55.541	73.954	-0.591	0.556
	Male	35	74.229	176.708		
AST	Female	37	50.541	51.845	0.511	0.485
	Male	35	66.886	131.146		
Hb	Female	37	11.789	1.581	-1.216	0.228
	Male	35	12.317	2.083		
Hct	Female	37	35.503	5.169	-1.179	0.242
	Male	35	37.111	6.374		
PLT	Female	37	263.108	90.629	0.160	0.873
	Male	35	259.543	98.521		
TSH	Female	37	1.867	1.143	-0.545	0.588
	Male	35	2.062	1.626		
ALP	Female	37	292.200	272.655	-0.011	0.991
	Male	35	292.909	244.095		
GGT	Female	37	341.943	466.797	0.207	0.836
	Male	35	321.091	350.573		
Total bilirubin	Female	37	2.796	4.117	-1.585	0.118
	Male	35	4.914	6.673		
Direct bilirubin	Female	37	2.310	3.717	-1.478	0.144
	Male	35	4.013	5.642		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; Hb, haemoglobin; HbA1c, glycated haemoglobin; Hct, haematocrit; PLT, platelet count; SD, standard deviation; TSH, thyroid-stimulating hormone. Groups were compared using the independent-samples t test. Sixteen comparisons were performed; after Bonferroni correction ($\alpha = 0.003$) and Benjamini-Hochberg correction ($q = 0.05$), none of the differences remained statistically significant. Measurement units are not reported in the source data

Table 2: Comparison of Laboratory Parameters between Patients with and without Documented Dpp-4 Inhibitor Exposure (N = 72)

Parameter	Group	n	Mean	SD	t	p
BUN	Not exposed	56	13.179	6.133	-1.143	0.257
	Exposed	16	15.444	9.482		
Creatinine	Not exposed	56	0.747	0.220	-1.236	0.220
	Exposed	16	0.839	0.379		
HbA1c	Not exposed	56	6.135	1.098	-4.733	<0.001
	Exposed	16	7.727	0.969		
Fasting blood glucose	Not exposed	56	135.089	69.446	-0.445	0.658
	Exposed	16	143.375	49.855		
Amylase	Not exposed	56	60.428	60.845	-0.932	0.365
	Exposed	16	95.687	147.852		
Lipase	Not exposed	56	45.500	58.783	-2.707	0.009
	Exposed	16	128.187	203.767		
ALT	Not exposed	56	66.196	148.163	0.186	0.853
	Exposed	16	59.125	61.557		
AST	Not exposed	56	57.732	109.206	-0.121	0.904
	Exposed	16	61.125	44.923		
Hb	Not exposed	56	12.208	1.686	1.411	0.163
	Exposed	16	11.475	2.301		
Hct	Not exposed	56	37.144	5.217	2.433	0.018
	Exposed	16	33.275	6.862		
PLT	Not exposed	56	252.589	96.682	-1.498	0.139
	Exposed	16	292.125	78.470		
TSH	Not exposed	56	1.999	1.591	0.334	0.740
	Exposed	16	1.863	0.571		
ALP	Not exposed	56	253.480	221.481	-2.331	0.023
	Exposed	16	419.500	326.113		
GGT	Not exposed	56	275.942	372.953	-2.067	0.043
	Exposed	16	513.437	487.503		
Total bilirubin	Not exposed	56	3.493	5.432	-0.880	0.382
	Exposed	16	4.896	6.044		
Direct bilirubin	Not exposed	56	2.828	4.609	-0.955	0.343
	Exposed	16	4.136	5.373		

DPP-4, dipeptidyl peptidase-4. Abbreviations for laboratory parameters are as defined for Table 1. Exposure was defined as documented DPP-4 inhibitor use for at least three years before the diagnosis of pancreatic cancer. Groups were compared using the independent-samples t test. Sixteen comparisons were performed; only the difference in HbA1c remained statistically significant after Bonferroni correction ($\alpha = 0.003$) and Benjamini–Hochberg correction ($q = 0.05$), and the remaining nominally significant differences (lipase, Hct, ALP, GGT) are reported as exploratory. Measurement units are not reported in the source data



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Figure 1: Proposed (Hypothetical) Mechanistic Framework Linking Type 2 Diabetes Mellitus and Incretin-Based Therapies to Pancreatic Carcinogenesis. The Pathways Shown are Hypotheses Derived from Experimental, Animal and Observational Studies; none of them was Measured or Tested in the Present Study. Chronic Inflammation is Depicted as a Shared Downstream Pathway of Diabetes and of Additional Exposures, Whereas Proliferative Changes in Acinar and Ductal Cells have been Demonstrated Principally with Glp-1 Receptor Agonists in Rodent Models Rather than with Dpp-4 Inhibitors in Humans. Igf-1, Insulin-Like Growth Factor-1; K-Ras, Kirsten Rat Sarcoma Virus Gene; Tp53, Tumour Protein 53. Figure Reproduced from Suryadevara *et al.* [21] Under the Creative Commons Attribution–Noncommercial (Cc By-Nc 4.0) Licence

lipase ($p = 0.009$), haematocrit ($p = 0.018$), ALP ($p = 0.023$) and GGT ($p = 0.043$); the remaining parameters did not differ significantly ($p > 0.05$) (Table 2). After correction for the sixteen comparisons performed, only the difference in HbA1c remained significant under both the Bonferroni and the Benjamini–Hochberg procedures (7.727 ± 0.969 in exposed versus 6.135 ± 1.098 in non-exposed patients). The differences in lipase, haematocrit, ALP and GGT did not survive correction and are reported as exploratory findings requiring confirmation in larger, adequately powered studies.

DISCUSSION

This single-center retrospective analysis describes the frequency of documented long-term DPP-4 inhibitor exposure in a series of 72 patients diagnosed with pancreatic cancer. Sixteen patients (22.2%) had documented use of a DPP-4 inhibitor for at least three years before diagnosis. Among the laboratory variables compared, only HbA1c differed between exposed and non-exposed patients after correction for multiple comparisons.

The design of this study places firm limits on what these observations can mean. Because every participant already had pancreatic cancer and no comparison group free of pancreatic cancer was assembled, the study cannot estimate the incidence of pancreatic cancer, the relative or absolute risk associated with DPP-4 inhibitor therapy, or any causal relationship between exposure and disease. A proportion of 22.2% exposed patients would be interpretable only in relation to the expected prevalence of long-term DPP-4 inhibitor use in a comparable population without pancreatic cancer, and no such reference group was available. The figure should therefore be read as a description of treatment history within a case series and nothing more.

DPP-4 inhibitors are widely utilized as oral antidiabetic agents across the world and are commonly selected at the second or third step of glucose-lowering treatment, in part because they reduce HbA1c by approximately 0.5–0.7% with a low risk of hypoglycaemia [8]. Since their introduction into diabetes management, numerous retrospective, prospective, and meta-analytic studies have been conducted worldwide to investigate the potential association between incretin-based therapies and pancreatic cancer as well as pancreatitis. The resulting evidence is inconsistent, and the studies differ substantially in design, comparator selection, follow-up duration and handling of latency.

Several observational studies have reported positive associations. In a nationwide Korean cohort of patients with newly diagnosed T2DM, DPP-4 inhibitor use was associated with an increased risk of pancreatic cancer (adjusted hazard ratio [aHR] 1.81, 95% CI 1.16–2.82) when a six-month drug-use lag period was applied; notably, the risk did not increase with longer exposure duration, and the authors themselves interpreted this pattern as compatible with reverse causality [38]. In two retrospective European cohorts comprising 33,292 incretin users and 525,733 users of other non-insulin

antidiabetic drugs, incretin-based therapies were associated with a higher short-term risk of pancreatic cancer (aHR 2.14, 95% CI 1.71–2.67); the association was strongest in the first months after the initial prescription and attenuated with time and with the application of a lag period, again consistent with reverse causality rather than with carcinogenesis [37]. A large Korean claims-based analysis reported modestly increased adjusted hazards of liver cirrhosis, ESRD, liver cancer and pancreatic cancer with DPP-4 inhibitor use relative to specified active comparators [47]. An analysis of the FDA Adverse Event Reporting System likewise identified a disproportionality signal for pancreatic carcinoma with DPP-4 inhibitors, although such analyses characterise reporting patterns rather than risk [41].

A substantial body of evidence, however, does not support an increase in risk. An international multicenter cohort study published in 2016 analyzed data from six regions across Canada, the United States, and the United Kingdom and followed 972,384 patients who initiated antidiabetic treatment between January 2007 and June 2013, with follow-up continuing until June 2014. This study did not identify a significant increase in pancreatic cancer risk associated with incretin-based medications, and the findings were consistent across drug classes and durations of treatment. Because the upper limit of the confidence interval did not exclude a modest increase in risk, the authors recommended ongoing monitoring, particularly in view of the long latency period of the disease [48]. A systematic review and meta-analysis of observational studies published in 2023 similarly did not support an increased risk of pancreatic cancer with incretin-based therapies in routine clinical practice, while noting that the available studies had limited follow-up and were affected by comparator selection and by the inclusion of frequent users [49]. Post-hoc analyses of randomized controlled trials have also failed to demonstrate a clear excess of pancreatic adverse events [27]. Taken together, the human evidence is inconsistent, and those studies that account most carefully for latency and reverse causality tend to report attenuated or null associations.

The mechanistic case rests largely on animal and in vitro data. Chronic GLP-1 receptor stimulation increases acinar and ductal proliferation and pancreatic mass in rodents [32], and inflammation markedly accelerates the progression of K-RAS-driven lesions in genetically modified mice [29,30]. The discussion regarding pancreatic adverse effects associated with incretin-based therapies was further intensified by findings reported by Butler et al., who suggested that incretin-based therapies in humans may result in enlargement of both the exocrine and endocrine pancreas, potentially progressing to neuroendocrine tumors. That work was based on a small number of organ-donor pancreata, attracted substantial methodological criticism, and has not been independently replicated [39,40]. Experimental studies have shown that the DPP-4 inhibitors saxagliptin and sitagliptin can activate the nuclear factor E2-related factor 2 (NRF2) antioxidant pathway and promote metastasis in

tumour models [42], whereas other studies demonstrate that DPP-4 inhibition enhances antitumour immunity through preservation of CXC chemokines and IL-33-dependent mechanisms [34,35]. The mechanistic literature therefore points in both directions and does not establish a pro-carcinogenic effect in humans.

Diabetes is the dominant confounder in this field. Patients receiving DPP-4 inhibitors have diabetes by definition, and diabetes is itself associated with pancreatic cancer [4,7]. Any comparison between exposed and non-exposed patients within a pancreatic cancer series is therefore also, and inseparably, a comparison between patients with and without diabetes; the drug and the indication cannot be distinguished. Reverse causality compounds this problem, because new-onset diabetes may be the earliest manifestation of an occult pancreatic tumour, so that glucose-lowering drugs are prescribed to patients who already have the disease [7]. The present study, which holds no information on the timing of diabetes onset relative to tumour-related symptoms, cannot separate these possibilities.

A recurrent difficulty in this literature is the conflation of DPP-4 inhibitors with GLP-1 receptor agonists. Both increase incretin signalling, but the magnitude, route of administration and receptor specificity of that signalling differ, and DPP-4 inhibition additionally alters non-incretin substrates [9]. The original regulatory signal concerned exenatide, a GLP-1 receptor agonist [21,22]; several influential database analyses pooled sitagliptin with exenatide [36]; and much of the mechanistic rodent work employed GLP-1 receptor agonists rather than DPP-4 inhibitors [32]. Where the evidence concerns mixed incretin-based therapies it has been described as such above, and it should not be read as evidence specific to DPP-4 inhibitors. The same caution applies to reports concerning organ-specific cancers other than pancreatic cancer — including thyroid cancer and cholangiocarcinoma — which have been reported for incretin-based drugs with inconsistent findings across studies and across drug classes [43–46].

The laboratory differences observed in the present study require conservative interpretation. HbA1c was higher among patients with documented DPP-4 inhibitor exposure, and this was the only difference to survive correction for multiple comparisons. This is the expected consequence of the treatment indication: patients receiving a DPP-4 inhibitor have diabetes, whereas most non-exposed patients do not. It reflects the presence and control of diabetes rather than an effect of the drug on the pancreas. The nominally higher lipase concentration among exposed patients did not remain significant after correction, was accompanied by a very large standard deviation (128.187±203.767), and cannot be interpreted as evidence of drug-induced pancreatic injury in the absence of clinical, biochemical and radiological criteria for pancreatitis, none of which were assessed in this study. The differences in haematocrit, ALP and GGT likewise did not survive correction; in a pancreatic cancer population such values are strongly influenced by tumour stage, biliary

obstruction, hepatic or metastatic involvement, nutritional status, anaemia of malignancy and prior interventions, none of which were recorded. These findings are exploratory and are reported for completeness rather than as evidence of a pharmacological effect.

Limitations

This study has substantial limitations, several of which are intrinsic to its design and cannot be remedied by analysis.

- **Design:** The study is retrospective, single-center and case-only. It includes no comparison group of individuals without pancreatic cancer, and therefore cannot estimate the incidence of pancreatic cancer, the risk associated with DPP-4 inhibitor exposure, or any causal relationship between the two
- **Sample Size and Precision:** The analytic sample comprised 72 patients, of whom only 16 were exposed. Statistical power is correspondingly low, effect estimates are imprecise, and the possibility of type II error for genuine differences is considerable, while the number of laboratory comparisons increases the risk of type I error. Only the difference in HbA1c remained significant after correction for multiplicity
- **Selection Bias:** Patients were identified at a single tertiary referral centre over a two-year period, and those without complete institutional records were excluded. Referral patterns and record completeness may not be representative of the wider pancreatic cancer population
- **Exposure Misclassification:** Exposure was ascertained from medication histories recorded in the hospital database. Individual agents, doses, dosing frequency, exact start and stop dates, continuity of therapy and adherence were not available, and misclassification of exposure in either direction is possible
- **Exposure Definition:** The three-year exposure threshold was a study-specific criterion without external validation; it may have excluded patients with shorter but clinically relevant exposure and may itself have introduced selection bias
- **Confounding by Indication and by Diabetes:** Exposed patients have diabetes by definition, whereas most non-exposed patients do not, so the effects of the drug and of the underlying disease cannot be separated
- **Reverse Causality:** Diabetes of recent onset may be a manifestation of an occult pancreatic tumour rather than a risk factor for it, and the available data do not permit the timing of diabetes onset relative to tumour development to be established
- **Unmeasured Confounders:** Smoking status, alcohol consumption, body mass index and obesity, history of acute or chronic pancreatitis, family history and genetic predisposition, duration of diabetes relative to symptom onset, longitudinal glycaemic control, and concomitant or previous antidiabetic medications (including metformin, insulin, sulfonylureas and GLP-1 receptor agonists) were not available and could not be adjusted for

- **Cancer Characteristics:** Tumour stage, anatomical location, histopathological subtype, presence of metastasis, biliary obstruction and treatment received were not recorded, although these factors strongly influence several of the laboratory parameters compared
- **Laboratory Reporting:** The measurement units, assay platforms and reference intervals for the laboratory parameters are not stated, and the number of valid observations for individual analytes may differ from the overall group sizes
- **Multiple Comparisons:** Thirty-two independent-samples t tests were performed across the two tables, and the results are interpreted accordingly
- **Generalizability:** The findings derive from a single centre in one country over a limited period and may not generalise to other settings or populations

CONCLUSION

In this single-center retrospective series of 72 patients with pancreatic cancer, 16 patients (22.2%) had documented DPP-4 inhibitor exposure of at least three years before diagnosis. Because the study contains no comparison group without pancreatic cancer, includes only a small number of exposed patients, and lacks data on major confounders, it cannot determine whether DPP-4 inhibitor therapy increases the risk of pancreatic cancer, and no causal inference should be drawn from these observations. The higher HbA1c observed among exposed patients is most plausibly explained by the underlying indication for treatment. The remaining laboratory differences did not survive correction for multiple comparisons and are exploratory. These findings do not justify any change to current prescribing practice for DPP-4 inhibitors. Determining whether a genuine association exists will require large, multicenter, controlled and preferably longitudinal epidemiological studies using active-comparator designs, adequate lag periods to address reverse causality, and appropriate adjustment for smoking, obesity, pancreatitis, diabetes duration and glycemic control.

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