AIBIS
Asia Islet Biology & Incretin Symposium

Debate session

'Does incretin-based therapy increase the risk of pancreatitis or pancreatic cancer?' Yes

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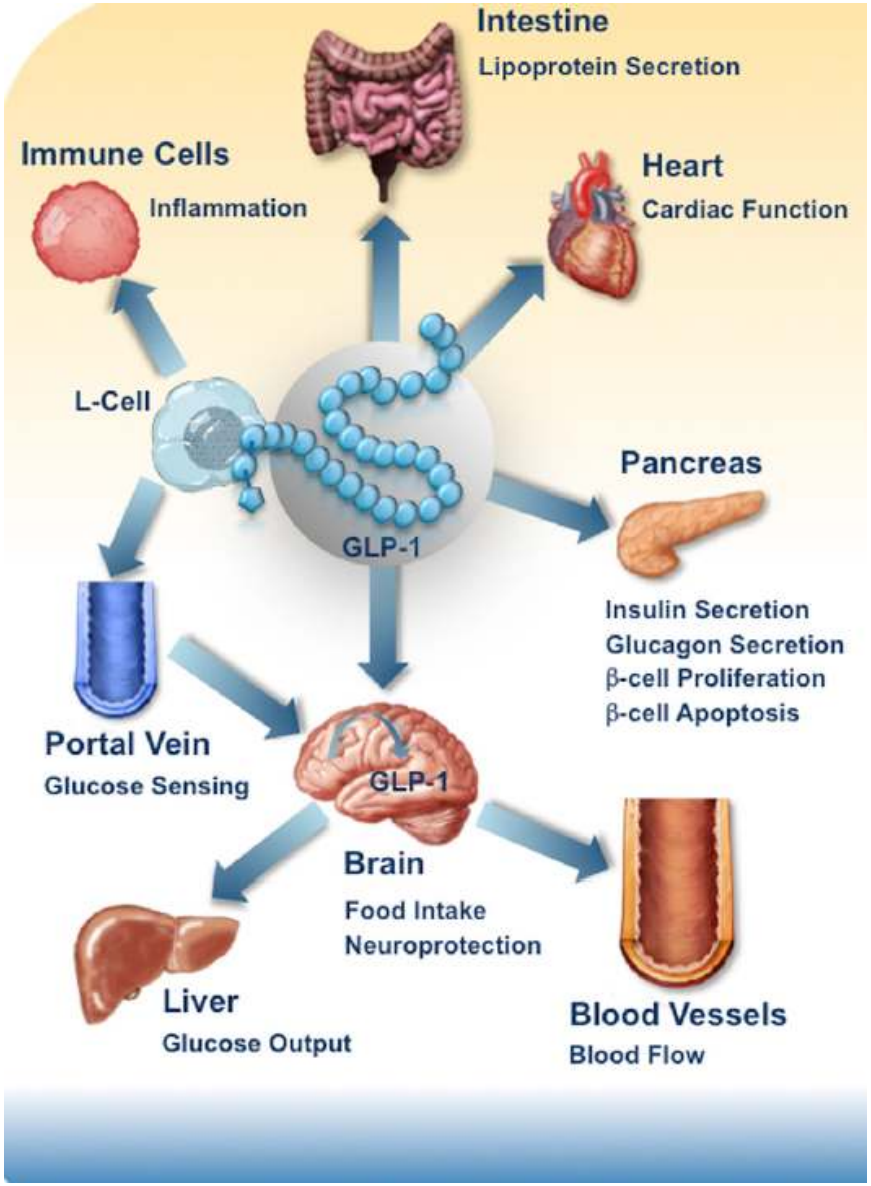
Introduction

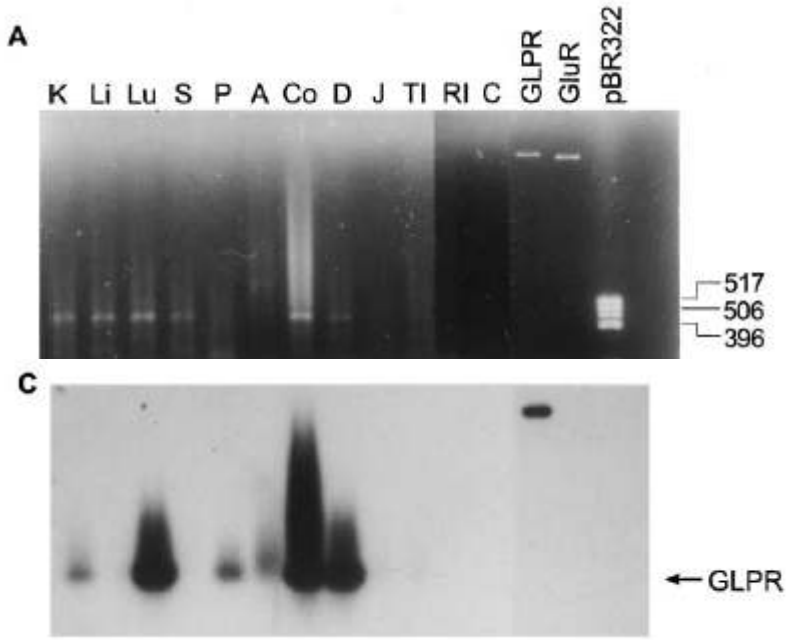
- There is no question that incretin-based glucose-lowering medications have proven to be effective glucose-lowering agents.
- Incretin-based therapies are becoming one of the most widely used anti-diabetic agents, with effects on weight loss or minimizing hypoglycemic events.
- They are known to have pleiotropic actions beyond glucose lowering effects.



Campbell JE & Drucker DJ, Cell Metab 2013

Introduction

➢ GLP-1 receptors are present in many tissues, including thyroid, exocrine pancreas, kidney, bone, lung, cerebral cortex, hypothalamus and gastrointestinal tract.



Dunphy JL, et al. Mol Cell Endo, 1998

➢ Activation of these receptors with supraphysiologic levels of GLP-1 has potential to produce unexpected off-target effects.

Case report

Exenatide-induced acute pancreatitis

- 69/M
- Type 2 diabetes for 5 yrs
- Diabetic neuropathy, retinopathy, coronary a. disease, GERD, RA, colonic polyposis

- Metformin 500mg bid, Pioglitazone 30mg, NPH 45u am, 20u pm, Insulin aspart
- Metoprolol, Gabapentin, Lovastatin, Irbesartan, Clopidogrel, Infliximab, Ezetimibe, Esomeprazole

- Midepigastric pain with radiation to the back developed within 24h of initiating exenatide.
- 5 days after Tx, the patient presented to ER.
- Sx. resolved by day 3 of discontinuation of exenatide.

- Temporal relation of the symptoms to the onset and cessation of therapy along with the normalization of laboratory parameters on drug withdrawal implicates exenatide as the cause.

Denker PS et al. Diabetes Care, 2006

Case report

Exenatide-induced acute pancreatitis

30 cases were reported by the Adverse Effect Reporting System (AERS) from Apr 2005 ~ Dec 2006.

- abdominal pain was reported in 23 patients
- symptoms began to resolve when exenatide was discontinued in 22 patients
- 3 patients had a recurrent symptom when exenatide was restarted

Ahmad SR et al. NEJM, 2008

Table 1. Selected Characteristics of 30 Patients with Exenatide-Associated Pancreatitis.*

Variable	Patients with Pancreatitis
Age	
Range — yr	43–72
Median — yr	60
Mean — yr	58
Not reported — no.	3
Sex — no. (%)	
Female	19 (63)
Male	11 (37)
Daily dose	
Range — μg/day	10–20
Median — μg/day	10
Mean — μg/day	14
Not reported — no.	5
Time to onset of symptoms	
Range — days	4–300
Median — days	34
Mean — days	53
Not reported — no.	1
Outcome at time of report submission — no.	
Patient had not recovered	2
Patient had recovered	22
Not reported	6
Serum amylase level	
Range — U/liter	40–1845
Median — U/liter	384
Mean — U/liter	508
Normal range — U/liter	30–170
Not reported — no.	13
Serum lipase level	
Range — U/liter	62–16,970
Median — U/liter	545
Mean — U/liter	1610
Normal range — U/liter	7–60
Not reported — no.	5

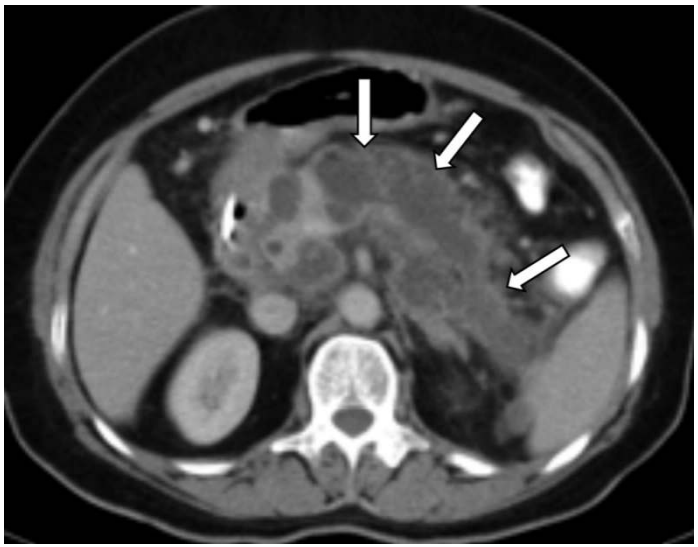
Case report

Vildagliptin-induced acute pancreatitis

- 61/F
- C/C : severe abdominal pain, vomiting, fever for 7 days
- Type 2 diabetes for 5 yrs
- Metformin + Sitagliptin -> Vildagliptin (changed 5wks before)

- Serum amylase : 1205 U/L
- Serum lipase : 8846 U/L

- Absence of an identifiable cause for the pancreatitis
- Improved with the cessation of vildagliptin



Girgis CM, et al. Endocr Pract, 2011

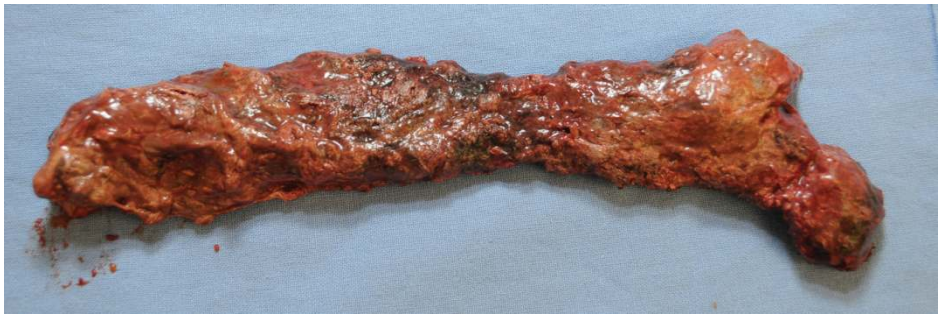
Case report

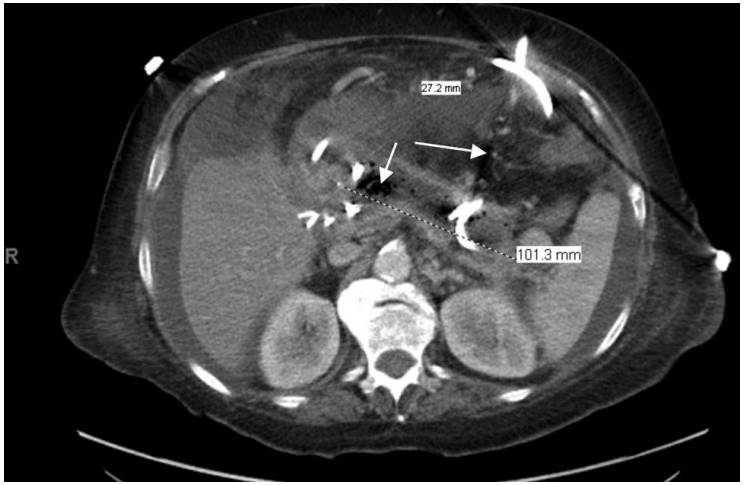
Acute necrotizing pancreatitis associated with combination treatment with exenatide and sitagliptin

- 76/F
- C/C : severe abdominal pain, vomiting, fever for 7 days
- Type 2 diabetes for 26 yrs
- Metformin + Exenatide (added 3-yrs-ago) + Sitagliptin (added a few weeks before)

- Serum amylase : 1136 U/L
- Serum lipase : 3500 U/L

- Absence of an identifiable cause for the pancreatitis





Iyer SN, et al. Endocr Pract, 2012

FDA AERS database (2004-2009)

Table 1. Test and Control Events for Exenatide and Sitagliptin vs Control Drugs

PANCREATITIS				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	971	1433	10.68	2×10^{-16}
Sitagliptin	131	306	6.74	2×10^{-16}
Controls	43	678	—	—
PANCREATITIS (2006 AND PRIOR)				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	152	748	2.57	8×10^{-7}
Sitagliptin	2	15	1.69	.37
Controls	32	405	—	—
PANCREAS CANCER				
Drug	Pancreas cancer events	Control events	Odds ratio vs control drugs	*P*-value vs control drugs
Exenatide	81	1433	2.95	9×10^{-5}
Sitagliptin	16	306	2.72	.008
Controls	13	678	—	—

- Control drugs: rosiglitazone, nateglinide, repaglinide, glipizide
- Control events: back pain, UTI, chest pain, cough, syncope

Elashoff M, et al. Gastroenterology, 2011

FDA AERS database (2004-2012Q2)

Exenatide and sitagliptin vs. controls (04Q1 to 12Q2)					
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Exenatide	2,327	1,660	19.17	(16.41–22.50)	<2.2e-16
Sitagliptin	718	411	23.89	(19.76–28.93)	<2.2e-16
Controls	207	2,832			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Exenatide	258	1,660	2.99	(2.41–3.73)	<2.2e-16
Sitagliptin	81	411	3.80	(2.80–5.11)	<2.2e-16
Controls	147	2,832			
Liraglutide vs. controls (10Q2 to 12Q2)					
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Liraglutide	888	259	56.81	(43.52–74.71)	<2.2e-16
Controls	84	1,393			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Liraglutide	63	259	5.64	(3.80–8.38)	<2.2e-16
Controls	60	1,393			
Saxagliptin vs. controls (09Q4 to 12Q2)					
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Saxagliptin	125	65	30.96	(21.33–45.35)	<2.2e-16
Controls	100	1,618			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Saxagliptin	18	65	6.04	(3.21–10.95)	6.85e-8
Controls	74	1,618			
Linagliptin vs. controls (11Q3 to 12Q2)					
Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Linagliptin	43	14	42.36	(20.86–90.82)	<2.2e-16
Controls	43	601			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Linagliptin	1	14	1.79	(0.04–12.72)	0.45
Controls	24	601			

Butler PC, et al. Diabetes Care 2013

A population-based matched case-control study

Table 1. Characteristics of Acute Pancreatitis Cases and Control Subjects[a]

Characteristic	Cases (n = 1269)	Controls (n = 1269)
Age, mean (SD), y[b]	51.76 (9.19)	52.26 (9.21)
Age, y[b]		
18-30	2.52	2.52
31-44	17.89	17.89
45-65	79.59	79.59
Male sex[b]	57.45	57.45
DCSI, mean (SD)[b]	0.78 (1.35)	0.74 (1.24)
DCSI[b]		
0	65.09	65.09
1	13.79	13.79
2	10.56	10.56
≥3	10.56	10.56
Duration from date of pancreatitis to date of diabetes[b]		
1-6 mo	36.30	36.30
7-12 mo	20.90	20.90
13-18 mo	13.47	13.47
19-24 mo	10.66	10.66
3 y	13.23	13.23
≥4 y	5.44	5.44
Hypertriglyceridemia[c]	12.92	8.35
Alcohol use[c]	3.23	0.24
Gallstones[c]	9.06	1.34
Tobacco abuse[c]	16.39	5.52
Obesity[c]	19.62	9.77
Billiary/pancreatic cancer[c]	2.84	0.00
Cystic fibrosis[c]	0.79	0.00
Neoplasm[c]	29.94	18.05
Resource utilization band[c,d]		
0	3.70	5.04
1	0.06	1.02
2	4.73	8.43
3	32.47	48.23
4	22.46	20.88
5	36.64	16.39

Table 2. Use of the Studied GLP-1–Based Therapies Based on Acute Pancreatitis Cases and Control Subjects in Prespecified Exposure Windows

Therapy[a]	No. of Cases (n = 1269)	No. of Controls (n = 1269)
Current exposure window		
Any GLP-1–based therapy	55	42
Exenatide	10	13
Sitagliptin	39	27
Combination of sitagliptin and metformin	6	2
None	1214	1227
Recent exposure window		
Any GLP-1–based therapy	72	48
Exenatide	29	16
Sitagliptin	38	29
Combination of sitagliptin and metformin	5	3
None	1197	1221
Any exposure window		
Any GLP-1–based therapy	87	58
Exenatide	34	24
Sitagliptin	47	31
Combination of sitagliptin and metformin	6	3
None	1182	1211

Odds of hospitalization for acute pancreatitis

- Current use **2.24** (1.36-3.69), *P* = 0.01
- Recent use **2.01** (1.37-3.18), *P* = 0.01
- Any use **2.07** (1.36-3.13), *P* = 0.01

Singh S, et al. JAMA Intern Med 2013

A population-based matched case-control study

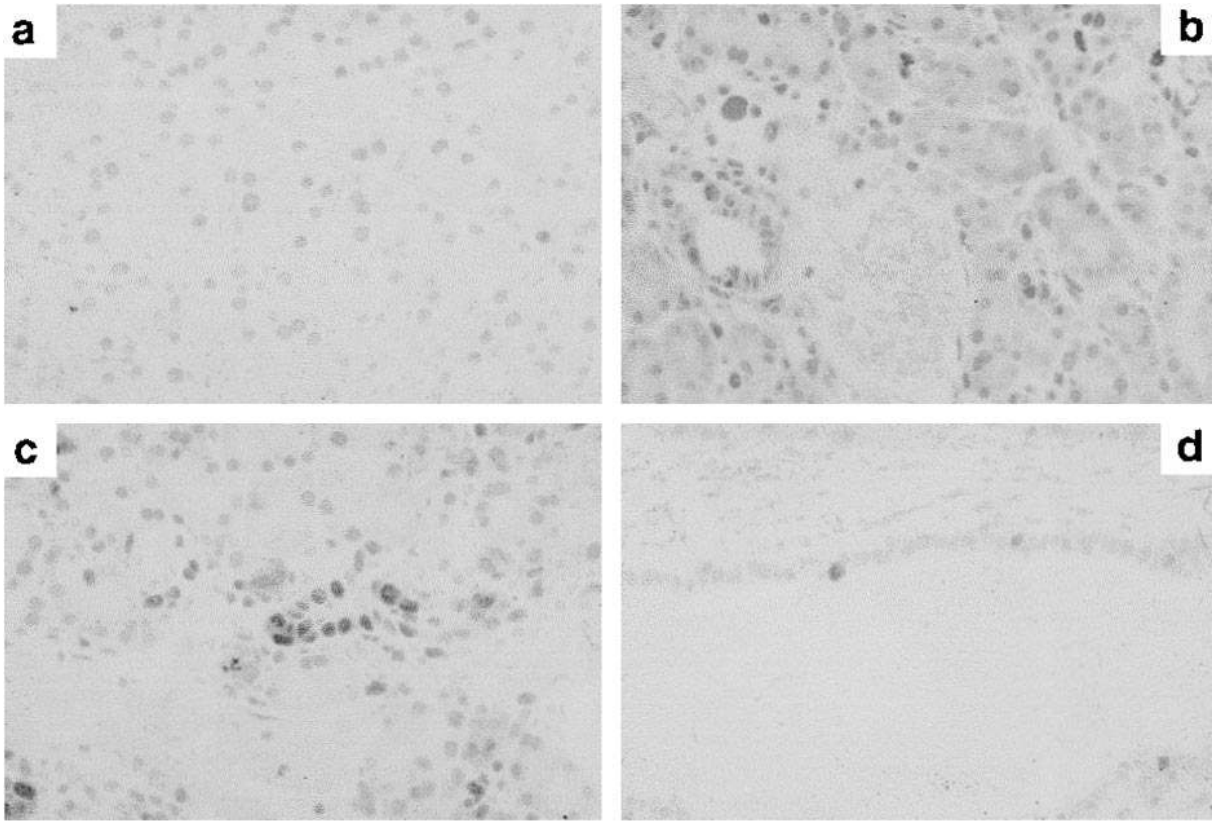
Significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes

Strength
- large number of cases
- adjusted for large number of confounders

Limitations
- residual confounding?
- small number of GLP-1 based therapy users
- misclassification of diagnosis
- misclassification of drug exposure
- not generalizable to older patients (>65)
- limited duration of follow-up

Singh S, et al. JAMA Intern Med 2013

Animal studies



PCNA immunostaining in 22 month-old Wistar rats,
GLP-1 infusion for 2 days

Perfetti R, et al. Endocrinology 2000

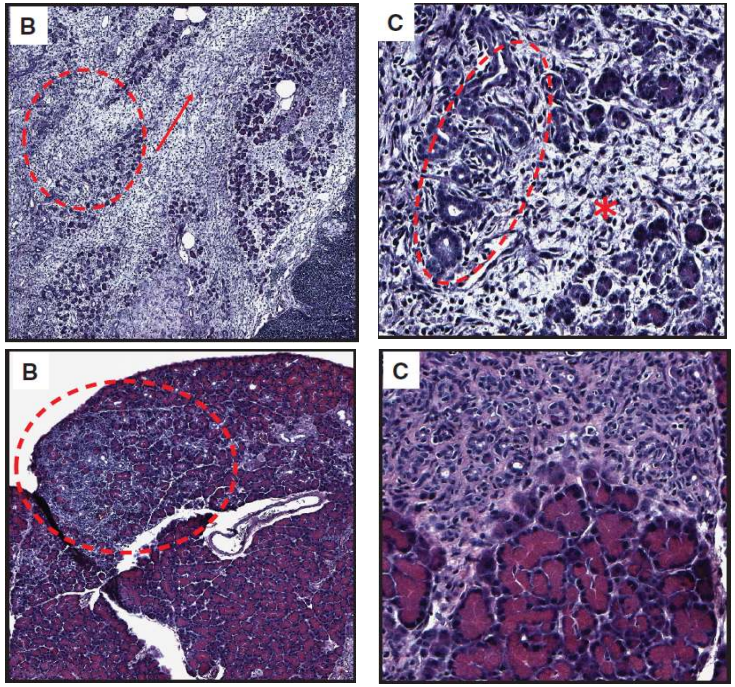
Beneficial Endocrine but Adverse Exocrine Effects of Sitagliptin in the Human Islet Amyloid Polypeptide Transgenic Rat Model of Type 2 Diabetes

Interactions With Metformin

Aleksey V. Matveyenko,[1] Sarah Dry,[2] Heather I. Cox,[1] Artemis Moshtaghian,[1] Tatyana Gurlo,[1] Ryan Galasso,[1] Alexandra E. Butler,[1] and Peter C. Butler[1]

TABLE 1
Incidence of pancreatitis, ductal metaplasia, and increased ductal turnover by group

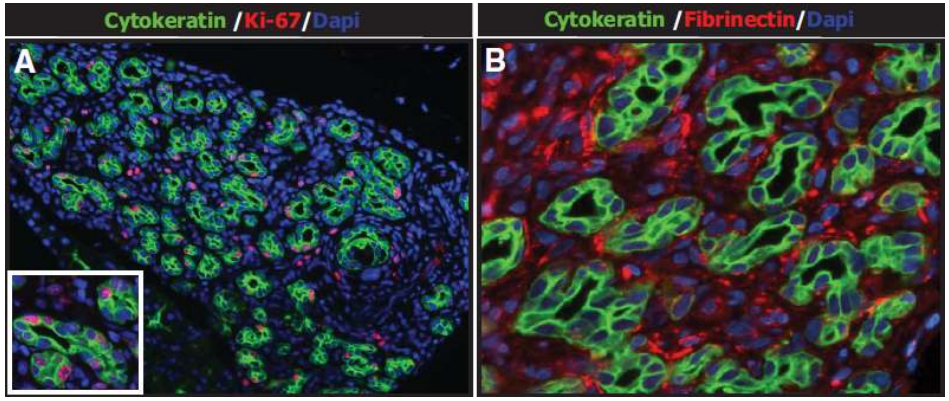
	Wild type	HIP	HIP + SIT	HIP + MET	HIP + SIT + MET
Number studied	7	8	8	9	8
Pancreatitis	0	0	1	0	0
Ductal metaplasia	0	0	2	0	1
Increased ductal proliferation*	—	4	8	2	1

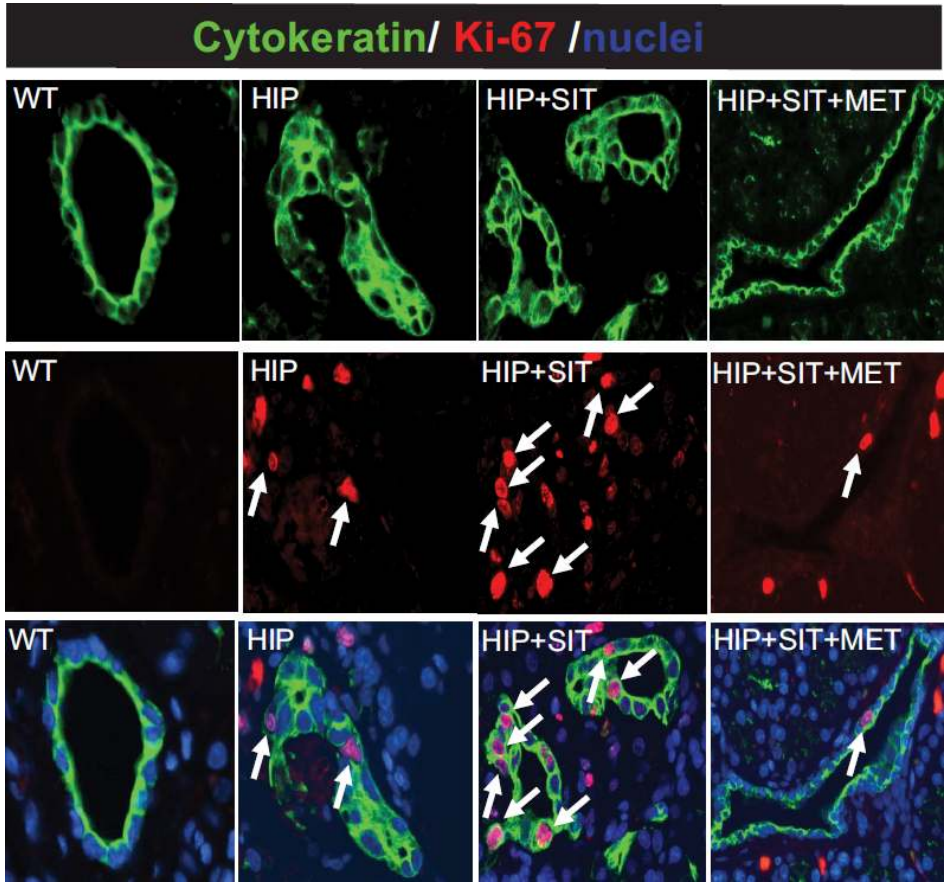


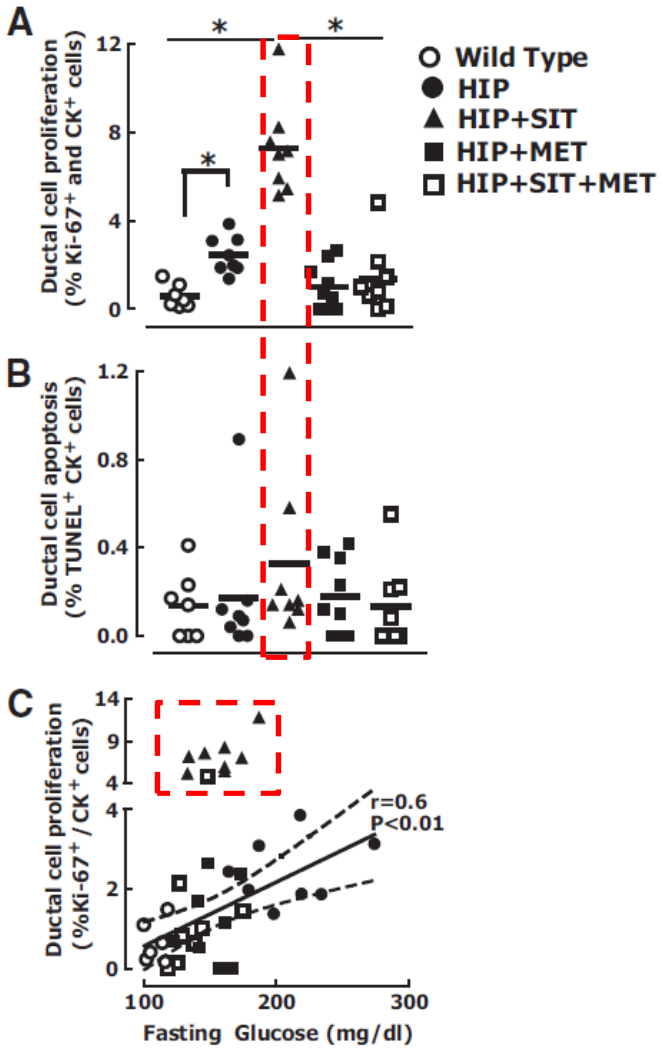
-> One case of hemorrhagic necrosis
(acinar cell injury, septal inflmmation, fibrosis)

-> Ductal metaplasia

Matveyenko AV, et al. Diabetes, 2009







Matveyenko AV, et al. Diabetes, 2009

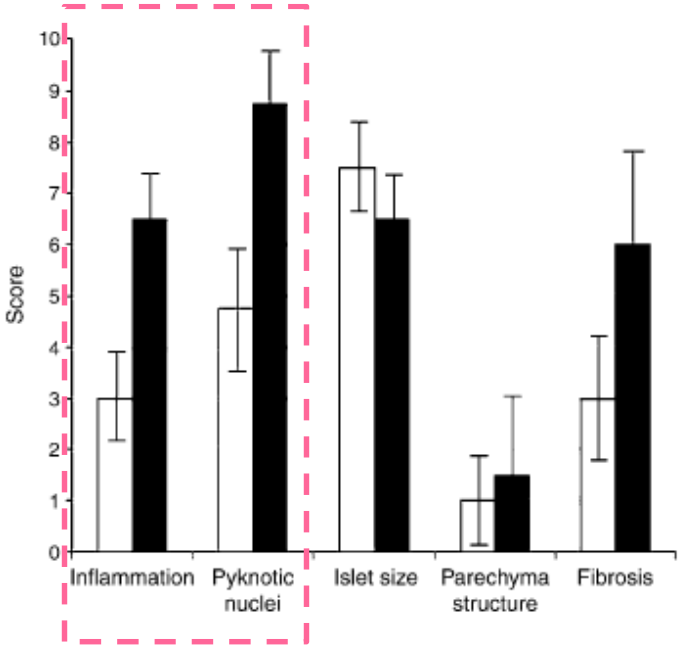
Diabetologia (2010) 53:153–159
DOI 10.1007/s00125-009-1515-4

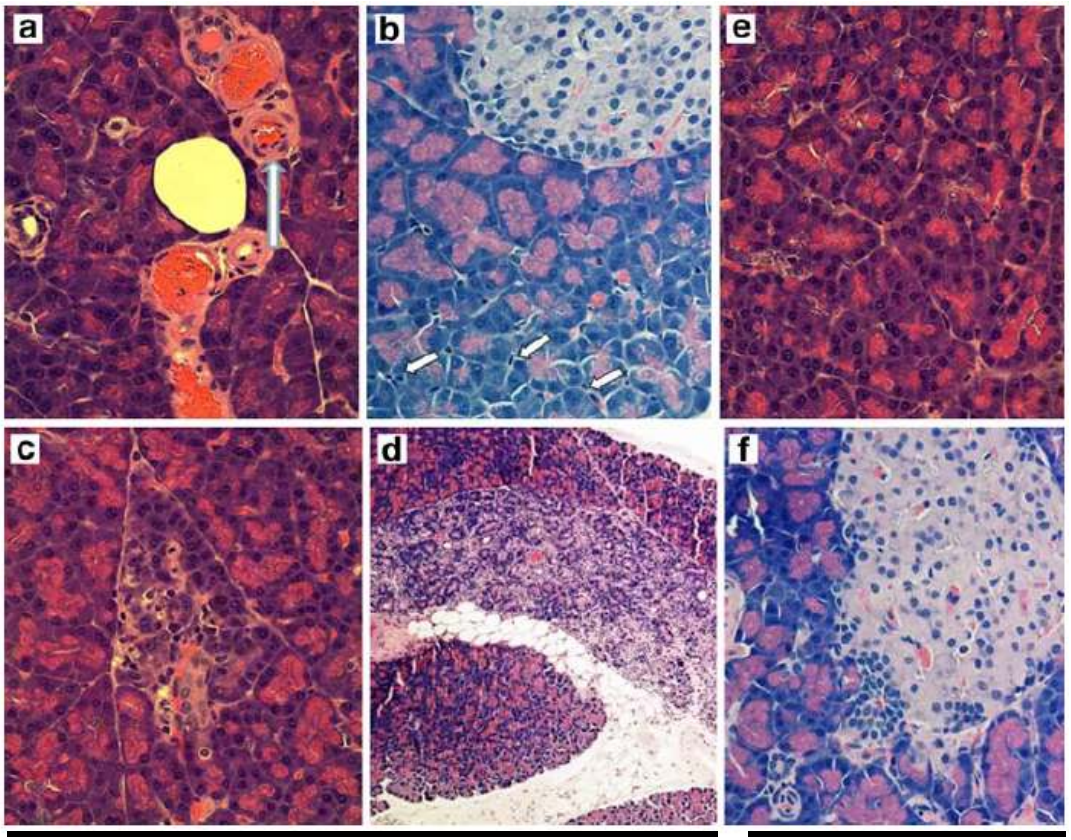
ARTICLE

Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas

J. S. Nachnani · D. G. Bulchandani · A. Nookala · B. Herndon · A. Molteni · P. Pandya · R. Taylor · T. Quinn · L. Weide · L. M. Alba

SD rats,
Exendin-4 10 ug/kg for 75 days





Exendin-4 Control

Nachnani JS, et al. Diabetologia, 2010

Chronic GLP-1 Receptor Activation by Exendin-4 Induces Expansion of Pancreatic Duct Glands in Rats and Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the Kras^{G12D} Mouse Model

Belinda Gier,[1] Aleksey V. Matveyenko,[1] David Kirakossian,[1] David Dawson,[2,3] Sarah M. Dry,[2,3] and Peter C. Butler[1,3]

Exendin-4 10 ug/kg for 12wks

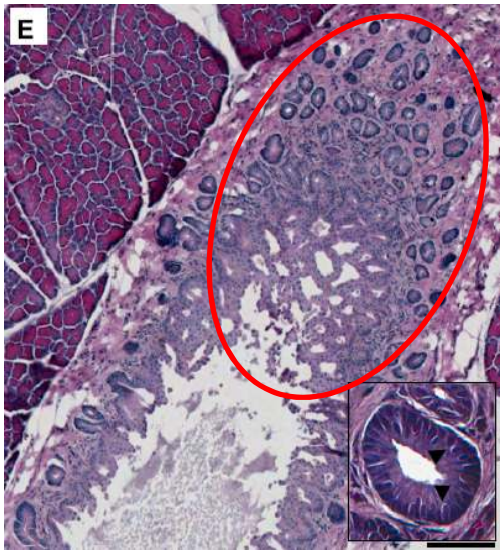
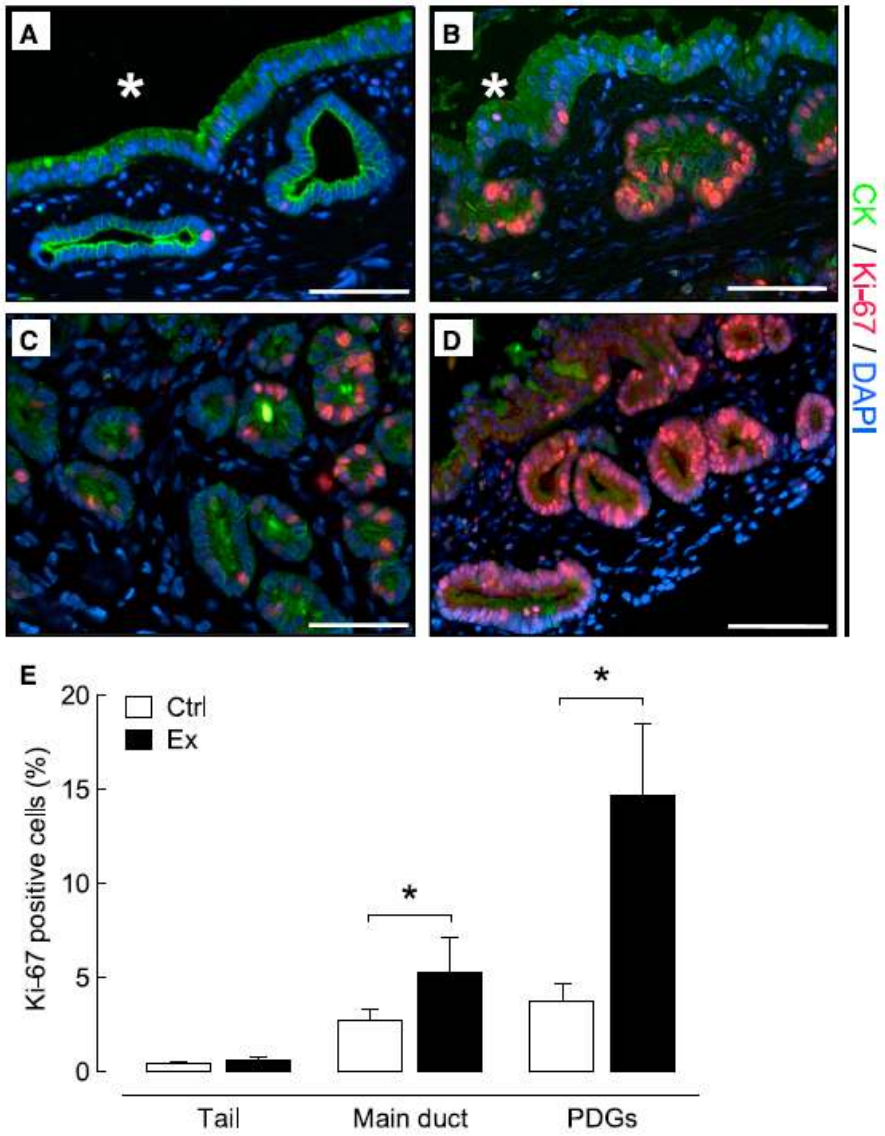


TABLE 1
Analysis of the PDG compartment

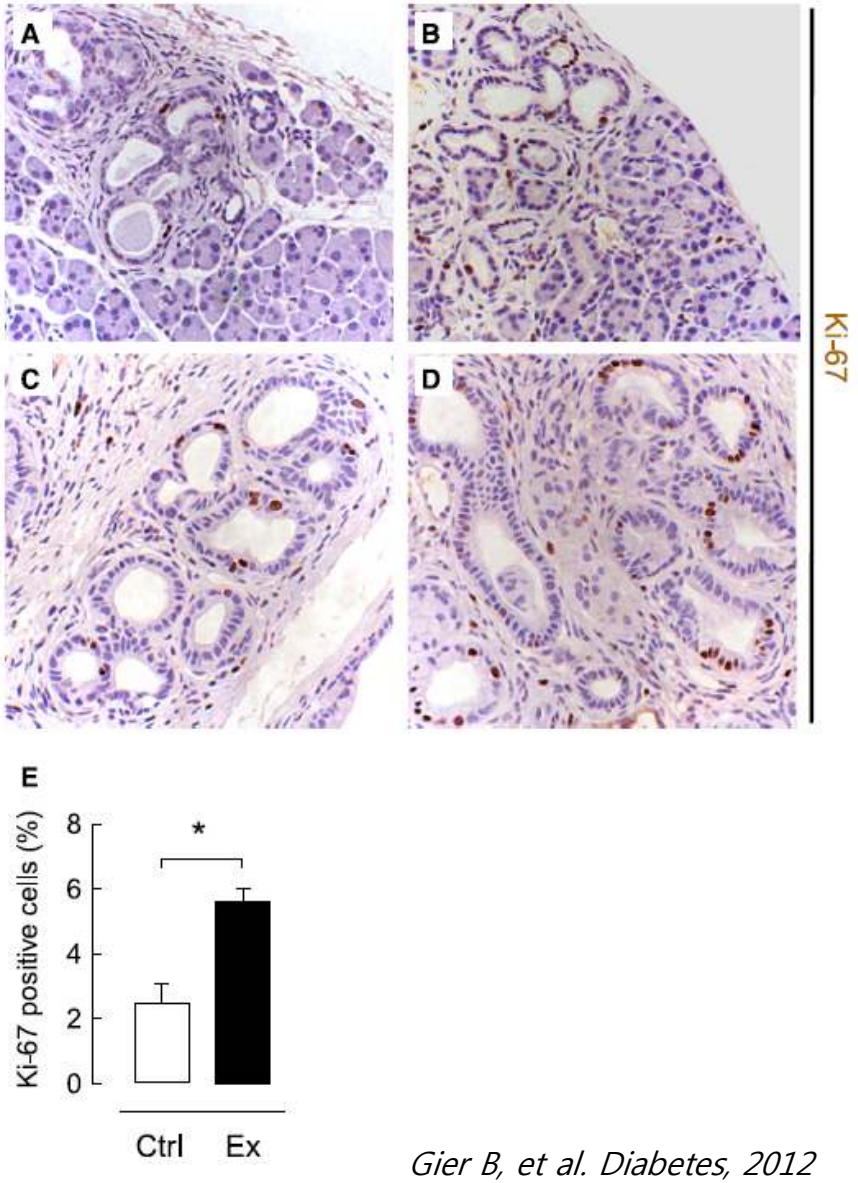
	Control	Exendin-4
Number of PDGs/mm main duct	31 ± 4	52 ± 7*
PDG area (μm^2)	910 ± 45	1,184 ± 102*
Main duct lining-to-length ratio	3.7 ± 0.3	5.0 ± 0.2†

Gier B, et al. Diabetes, 2012

Pancreatic duct gland cell replication (rat)



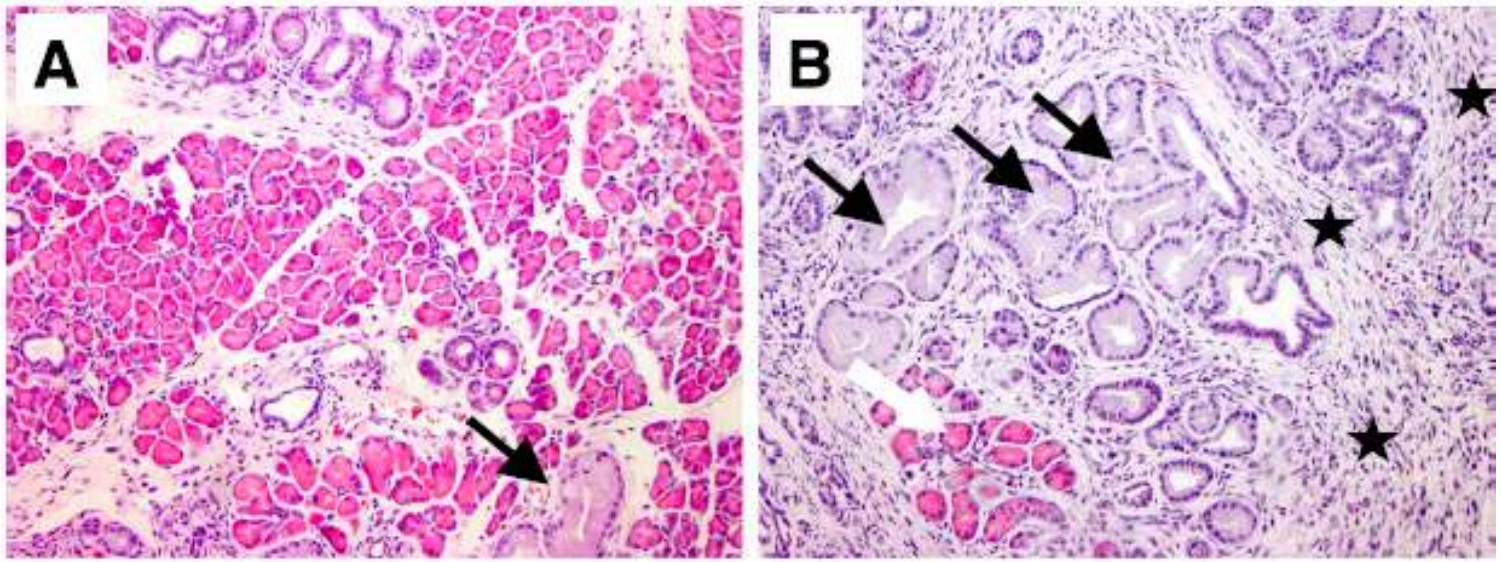
Duct cell replication (Kras^{G12D} mouse)



Gier B, et al. Diabetes, 2012

Vehicle

Exendin-4



- Scant residual intact acini
- Extensive inflammation and fibrosis
- More frequent PanIN

Gier B, et al. Diabetes, 2012

Animal studies

Table 1—*Animal studies of GLP-1–based therapy on the exocrine pancreas*

Reference	Species/age	Treatment/day duration#	Pancreas weight	Pancreas enzymes	Histology	Replication/ method
Perfetti et al., 2000 (5)	Wistar rat 22 months	GLP-1 1.5 pmol/kg · min, 5 days	↑	→	NR	↑ Ducts and acinar cells PCNA
Koehler et al., 2009 (6)	Mice 9–12 weeks	Exenatide 48 nmol/kg, 4 wks	↑	→	NR	NR
	Mice 9–12 weeks	Liraglutide 75 μg/kg, 1 wk	↑	→	NR	NR
Matveyenko et al., 2009 (7)	HIP rats 2 months	Sitagliptin 200 mg/kg, 12 weeks	↑	NR	Pancreatitis (1/8) and acinar to ductal metaplasia (3/16)	↑ Ducts, Ki67
Nachnani et al., 2010 (12)	Rats 8 weeks	Exenatide 10 μg/kg, 11 weeks	NR	↑ Amylase	Exocrine inflammation	NR
Tatarkiewicz et al., 2010 (11)	Mice 10 weeks	Exenatide 7.2 nmol/kg, 4 weeks	→	→	No pancreatitis	→ Ducts Ki67
Vrang et al., 2012 (9)	ZDF rats 7 weeks	Exenatide 0.25 mg/kg, 13 weeks	→	↑ Amylase	1/12 death pancreatic necrosis; focal acinar hyperplasia;	→ Ducts Ki67*
		Liraglutide 1.0 mg/kg, 13 weeks	→	→	3/12 death by overdose, unexplained; increased ductal proliferation and acinar to ductal metaplasia	→ Ducts Ki67*
Nyborg et al., 2012 (13)	Cynomolgus monkeys age NR	Liraglutide 5 mg/kg, 87 weeks	NR	NR	Normal	NR
	Rats age NR	Liraglutide 1 mg/kg 26 weeks	NR	NR	Normal	NR
	Mice age NR	Liraglutide 3 mg/kg, 104 weeks	NR	NR	Normal	NR
Gier et al., 2012 (8)	Rats 10 weeks	Exenatide 10 μg/kg, 12 weeks	↑	→	PDG hyperplasia;	↑ PDG and ducts Ki67
	Pdx-1 Kras mice 6 weeks	Exenatide 5 nmol/kg, 12 weeks	↑	↑ Lipase	chronic pancreatitis and advanced PanINs	↑ Ducts Ki67
Tatarkiewicz et al., 2012 (10)	ZDF rats 8 wks	Exenatide 250 μg/kg, 12 weeks	→	↑ Amylase	Normal	→ Ducts Ki67*

Butler PC, et al. Diabetes Care 2013

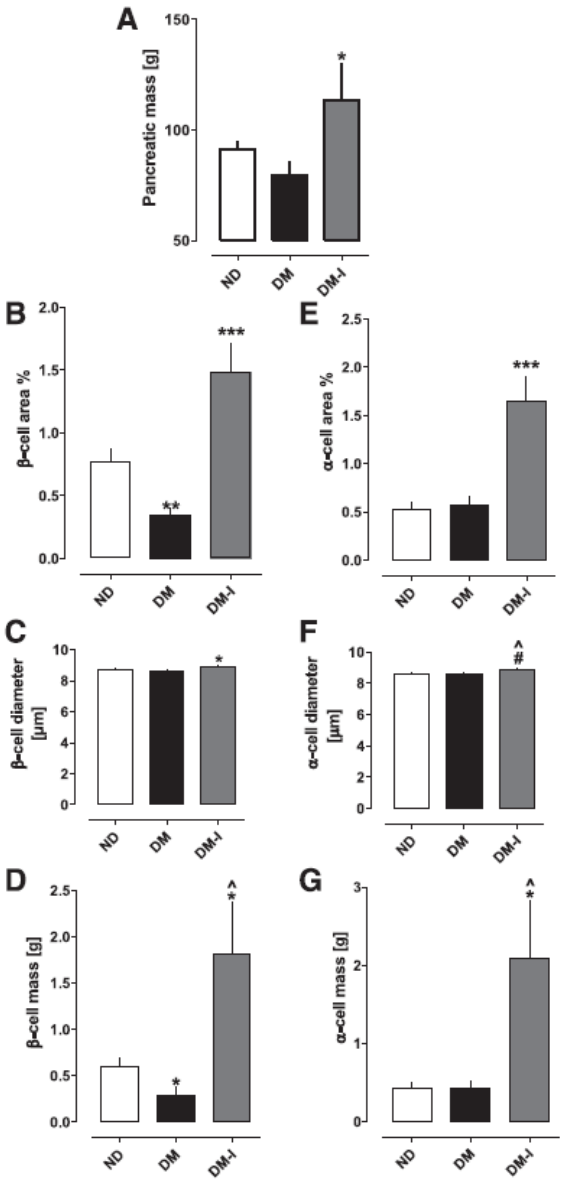
Human study

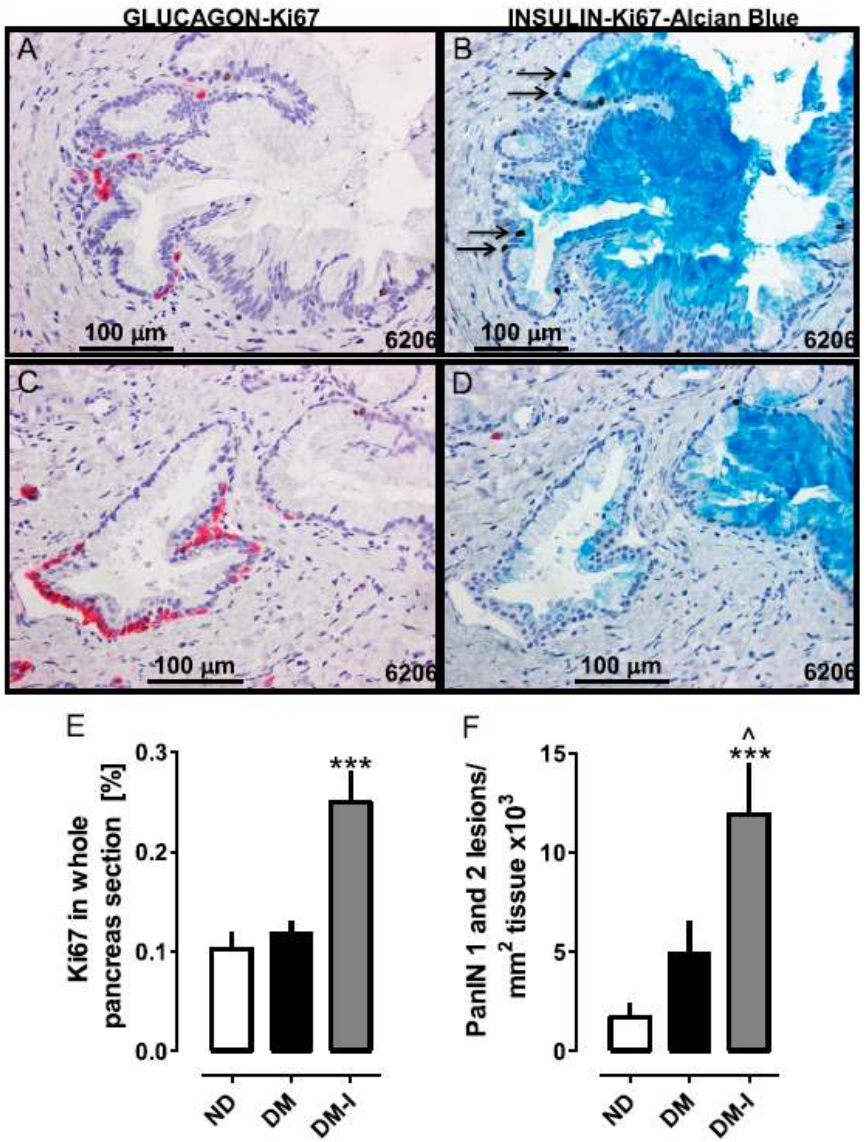
Clinical characteristics of brain-dead organ donors

Case	Age (years)	Duration of DM (years)	Sex	BMI (kg/m^2)	Treatments	Cause of death
DM-I						
6157	74	1	F	39	Januvia	ICH/stroke
6185	46	15	M	41	Januvia, metformin	Anoxia
6186	68	5	M	21	Januvia, metformin	ICH/stroke
6189	49	26	F	36	Byetta, metformin, glipizide	Stroke
6199	53	20	M	30	Januvia, insulin pen	ICH/stroke
6194	47	13	M	24	Humulin, NovoLog, Januvia	ICH/stroke
6203	68	5	M	33	Januvia, metformin	Stroke
6206	59	10	M	42	Januvia, metformin	Stroke
Mean (SEM)	58 (4)	12 (3)		33 (3)		
DM						
6028	33	17	M	30	Insulin	Gunshot wound to head
6059	18	0.3	F	39	None	Cardiovascular
6108	57	2	M	30	Metformin	ICH/stroke
6110	20	0.2	F	40	None	ICH/stroke, DKA
6109	48	—	F	33	None	ICH/stroke, DKA
6114	42	2	M	31	Metformin, noncompliant	Asphyxiation
6124	62	3	M	34	Metformin	ICH/stroke
6127	44	10	F	30	Insulin	ICH/stroke
6133	45	20	F	40	Insulin	Cardiovascular
6139	37	1.5	F	45	None	Seizure
6142	29	14	F	34	None	Bacterial meningitis
6149	39	20	F	29	Insulin	ICH/stroke
Mean (SEM)	40 (4)	8 (3)		35 (2)		
ND						
6009	45		M	31		Anoxia
6015	39		F	32		Anoxia
6012	64		F	31		Cerebrovascular/stroke
6016	42		M	31		Cerebrovascular/stroke
6019	68		F	24		Head trauma
6020	60		M	30		Cerebrovascular/stroke
6022	75		M	31		Cerebrovascular/stroke
6034	32		F	25		Head trauma
6060	24		M	33		Head trauma
6097	43		F	36		Cerebrovascular/stroke
6099	14		M	30		Head trauma
6102	45		F	35		Cerebrovascular/stroke
6158	40		M	30		Head trauma
6165	45		F	25		Cerebrovascular/stroke
Mean (SEM)	45 (5)			30 (1)		

Butler AE, et al. Diabetes 2013

Human study





Butler AE, et al. Diabetes 2013

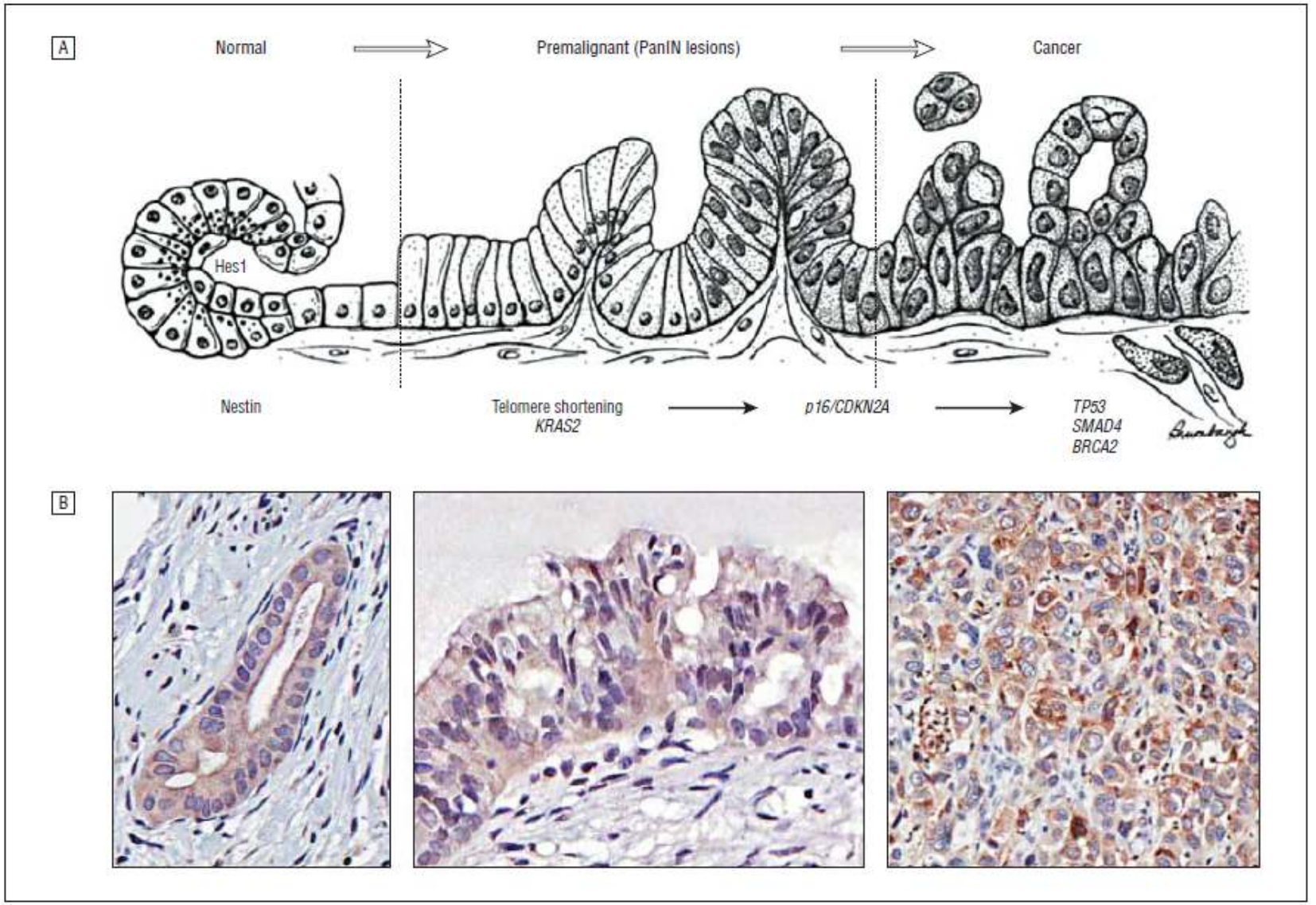
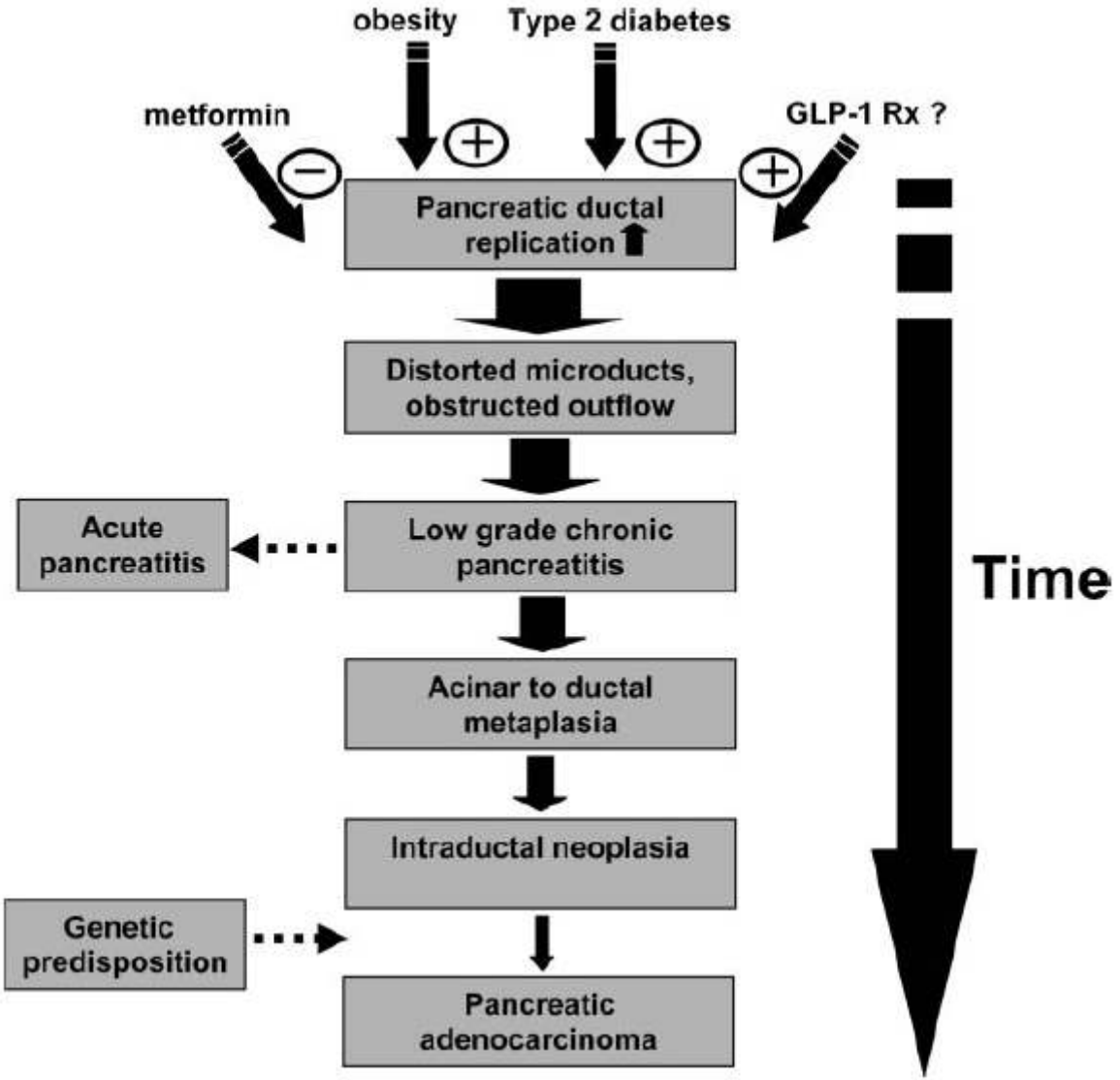
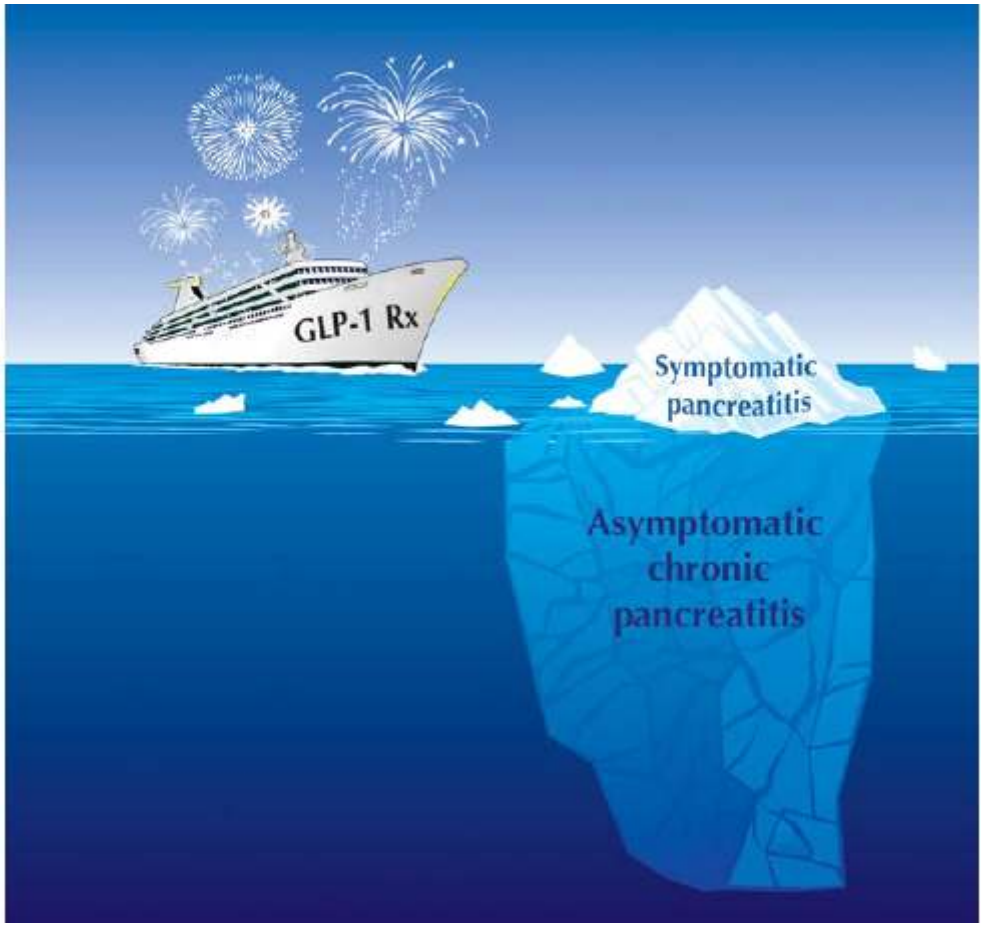


Figure. Human expression of glucagonlike peptide 1 (GLP-1) receptor in healthy tissue and malignant disease. A, Morphological stages in the transition from normal healthy ducts through intermediate premalignant pancreatic intraepithelial neoplasia (PanIN) lesions and invasive pancreatic cancer. Modified from Hruban et al.[7] B, Corresponding immunohistochemical labeling[8,9] of human tissue for GLP-1 receptor (brown) in normal pancreatic ducts, premalignant PanIN lesions, and pancreatic cancer.

Theoretical model



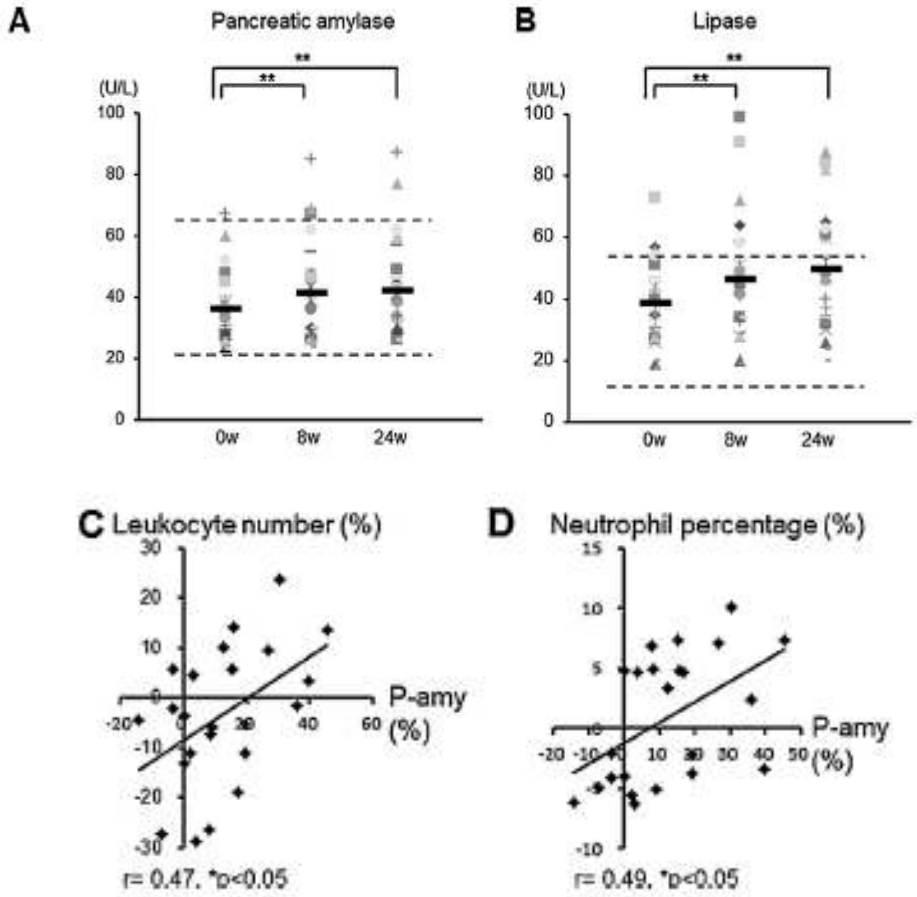
Butler PC, et al. Diabetes Care, 2010



Butler PC, et al. Diabetologia, 2010

Low-grade increase of pancreatic exocrine enzyme levels

DPP-4i potentially cause a low-grade subclinical asymptomatic inflammatory change with the pancreas



Tokuyama H, et al. DRCP, 2013

Summary

- The reporting rate for pancreatitis/pancreatic cancer with incretin-based therapies are dramatically increasing.
- Although this does not establish the causal relationship, it does raise the level of concern.
- Some preclinical studies offer a plausible mechanism for the occurrence of pancreatitis/pancreatic cancer in patients exposed to incretin-based therapies.
- Asymptomatic low-grade chronic pancreatitis might be more common than expected.


Thank you for
your attention.
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