GLP-1 Therapy for Type 2 Diabetes
New Treatment, New Controversy

Peter Butler
Division of Endocrinology
Insulin secretion and glucagon suppression defects in T2DM

- **Butler P Diabetes 1991**

### Graph Details
- **Y-axis**: Glucose (mg/dl), Insulin (µu/ml), Glucagon (pg/ml)
- **X-axis**: Minutes (0-300)
- **Lines**:
  - **Nondiabetic**
  - **“Early” T2D**
  - **“Late” T2D**

### Data Points
- **Glucose**
  - 1300 mg/dl
  - 650 mg/dl
  - 2500 mg/dl
  - 2000 mg/dl
  - 1500 mg/dl
  - 1000 mg/dl

- **Insulin**
  - Nondiabetic: 65 µu/ml, 75 µu/ml
  - “Early” T2D: 250 µu/ml, 200 µu/ml
  - “Late” T2D: 150 µu/ml, 100 µu/ml

- **Glucagon**
  - Nondiabetic: 200 pg/ml, 150 pg/ml
  - “Early” T2D: 200 pg/ml, 150 pg/ml
  - “Late” T2D: 200 pg/ml, 150 pg/ml
The islet in Type 2 Diabetes

Non diabetic

Type 2 diabetes

Medications for Type 2 Diabetes

- Sulfonylurea
- Metformin
- Pioglitazone
- Rosaglitazone
- GLP-1

Life style
Glucagon like peptide 1 (GLP-1)

His \( \text{Ala} \) Gl\( \text{Tyr} \) Thr\( \text{Val} \) As\( \text{Ser} \) Se\( \text{Thr} \) Le\( \text{Glu} \) Gl\( \text{Gly} \) Gl\( \text{Ala} \) Ala Lys Glu Ile Ala Trp Leu Val Lys Gly Arg
Glucagon like peptide 1 (GLP-1)

Sitagliptin (Januvia)

DPP-4

Exenatide (Byetta)
Incretin therapy versus Metformin and Pioglitazone

Russell-Jones D, Diabetes Care (2012)
The Pancreatitis Controversy begins

- Exenatide launched 2005
- Investment advisors searched FDA data base, 2006.
- Label change by Amylin 2006.
- Ahmad S (FDA). NEJM 2008

"According to the FDA's Adverse Event Reporting System (AERS) database, 48 domestic cases of acute pancreatitis in association with exenatide use have been reported from the date of the drug's approval through December 31, 2006".

"On the basis of a review of these cases, the FDA recently asked the manufacturer to strengthen the labeling of acute pancreatitis from the Adverse Reactions section to the Precautions section of the exenatide product label. Health care professionals should be aware of this association and report all serious adverse events to the FDA or the manufacturer".
The Pancreatitis controversy continues

- Exenatide launched 2005
- Investment advisors searched FDA data base, 2006.
- Label change by Amylin 2006.
- Ahmad S (FDA), NEJM 2008
- Garg R Diabetes Care 2010 (retrospective pharmacy claims)

CONCLUSIONS:
“Our study demonstrated increased incidence of acute pancreatitis in diabetic versus nondiabetic patients but did not find an association between the use of exenatide or sitagliptin and acute pancreatitis. The limitations of this observational claims-based analysis cannot exclude the possibility of an increased risk”.

GLP-1 therapy is launched
The Pancreatitis controversy continues

• Exenatide launched 2005
• Case report pancreatitis 2006 Denker P, Diabetes Care.
• Investment advisors searched FDA data base, 2006.
• Label change by Amylin 2006.
• Ahmad S (FDA), NEJM 2008
• Garg R Diabetes Care 2010
• Sing S JAMA Int Med 2013

METHODS A retrospective cohort study of a large medical and pharmacy claims database was performed. Data for 786,656 patients were analyzed.

CONCLUSIONS AND RELEVANCE:
“In this administrative database study of US adults with type 2 diabetes mellitus, treatment with the GLP-1-based therapies sitagliptin and exenatide was associated with increased odds of hospitalization for acute pancreatitis”
• Is the risk of acute pancreatitis increased with incretin therapy?
Effects of Sitagliptin in the HIP rat model of Type 2 Diabetes

Study design:

Humans

Rats

Wild Type 60% HFD
HIP rat 60% HFD
HIP+SIT 60% HFD + SITAGLIPTIN
HIP+MET 60% HFD + METFORMIN
HIP+SIT+MET 60% HFD SIT+ MET

12 weeks treatment

Impact of GLP-1 therapy in rodents in-vivo

Matveyenko et al., Diabetes (2009)
Pancreatitis in a HIP rat treated with Sitagliptin

Untreated

HIP rat (12 weeks Sitagliptin)

Matveyenko et al., Diabetes (2009)
Acinar to ductal metaplasia in HIP rats treated with Sitagliptin

Matveyenko et al., Diabetes (2009)

Impact of GLP-1 therapy in rodents in-vivo
Ductal replication in HIP rats treated with Sitagliptin

Impact of GLP-1 therapy in rodents in-vivo

Matveyenko et al., Diabetes (2009)
Because the apparent adverse effects of GLP-1 mimetic therapy are at least to some extent offset by concurrent use of metformin, it is perhaps judicious to use GLP-1 mimetic therapy (including DPP-4 inhibitors) only in addition to metformin until potential long-term adverse effects of GLP-1–based therapy on exocrine pancreas can be ruled out in humans with diabetes.
Effects of Exendin-4 treatment in Sprague Dawley rats

Study design:

Wild Type Chow diet

- Saline
- Exendin-4

12 weeks treatment

Tissue and blood collection

Impact of GLP-1 therapy in rodents in-vivo
Proliferation of PDGs in Exendin-4 treated rats

Impact of GLP-1 therapy in rodents in-vivo
Anatomy of the pancreas

Introduction

Pancreatic duct glands (PDGs)

Main duct with PDGs

Strobel et al., Gastroenterology (2010)

Cross-section of a PDG (H&E stain)

Gall bladder
Bile duct
Main pancreatic duct
Tail of pancreas
Duodenum
Head of pancreas

Acinar cell
Duct cell
Proliferation of PDGs in Exendin-4 treated rats

Impact of GLP-1 therapy in rodents in-vivo
Impact of GLP-1 therapy in rodents in-vivo

Proliferation of PDGs in Exendin-4 treated rats

Ki-67+ Duct Cells (%)

- PDGs
- Main duct
- Tail

Exendin-4 vs Control

*, statistically significant difference

Gier B, Diabetes (2012)
“Collectively, these studies imply that GLP-1 induced proliferation within the exocrine pancreas is focal and may accelerate the development of dysplastic lesions when present.”
Type 2 Diabetes and Cancer risk

Meta-analyses 2005-2008

Breast (Larsson, Int J Can, 2007); N=20

Pancreas (Huxley, Br J Cancer, 2005); N=36

Bladder (Larsson, Diabetologia 2006); N=16

Colorectal (Larsson, J Natl Can Inst 2005); N=15

Endometrial (Friberg, Diabetologia 2007); N=16

Prostate (Kasper. Cancer Epi 2006); N=19

OR:

Reduced Risk

0.6 0.9 1.0 1.3 1.6 1.9 2.1 3.0 3.5

Increased Risk

0.84 1.20 1.24 1.30 1.82 2.10

(Courtesy of EA Gale)
Cellular progression to pancreatic cancer

Normal  ➔  Premalignant lesions  ➔  Cancer
(PanIN)

Nestin  ➔  Telomere shortening  ➔  p16/CDKN2A  ➔  TP53

SMAD4  
BRCA2

increased duct cell proliferation

Effects of GLP-1 Rx in a model of chronic pancreatitis

Study design:

C57/BL6 Pdx1-Kras\textsuperscript{G12D} → \text{Saline} → \text{12 weeks treatment} → \text{Exendin-4} → \text{Tissue and blood collection}

Gier B, Diabetes (2012)

Impact of GLP-1 therapy in Chronic Pancreatitis prone rodents in-vivo
Effects of GLP-1 Rx in a model of chronic pancreatitis

Untreated

Exendin-4 treated

Impact of GLP-1 therapy in Chronic Pancreatitis prone rodents in-vivo
Conclusions

“Exendin-4 treatment increased duct cell replication, increased the formation of dysplastic mPanIN lesions, and accelerated the development of chronic pancreatitis. These data are consistent with the hypothesis that PanIN lesions contribute to the development of pancreatitis by the obstruction of ductal outflow, with the resulting chronic pancreatitis fostering further development of PanINs”

Gier et al., Diabetes (2012)
Impact of GLP-1 therapy in human pancreas

GLP-1 signaling in human pancreas duct cells?

Gier B, Diabetes (2012)
• Is the risk of acute pancreatitis increased with incretin therapy?

• Does incretin therapy accelerate chronic (asymptomatic) pancreatitis?

• Does incretin therapy increase the risk of pancreatic cancer?
Question

Is the use of Exenatide (*Byetta*) or Sitagliptin (*Januvia*) associated with increased reports of pancreatitis or pancreatic cancer?

*Elashoff M., Gastroenterology (2011)*
Advantages

• Large sample size
• Independence from marketing companies
• Real world use of drug
• Open access
• History of success detecting unexpected side effects

Limitations

• Limited data entry
• Subject to Confounding Variables

Elashoff M., Gastroenterology (2011)
**FDA Adverse Events Reporting System**

**Controls**

(1) Other Type 2 Diabetes medications: 
Rosiglitazone, Nateglinide, Repaglinide, Glipizide

(2) Control events: 
back pain, UTI, chest pain, cough, syncope

**Analysis**

First quarter 2004 – third quarter 2009

Events of interest in test drug compared to control drugs and control events 2 x 2 tables

Fisher’s exact test null hypothesis that the OR = 1

_Elashoff M, Gastroenterology (2011)_
Pancreatitis with GLP-1 therapies (FDA database)

Exenatide vs. controls
- Odds Ratio: P=2x10^{-16}

Sitagliptin vs. controls
- Odds Ratio: P=2x10^{-16}

2006 and prior

Exenatide vs. controls
- Odds Ratio: P=8x10^{-7}

Sitagliptin vs. controls
- Odds Ratio: P=.37

Impact of GLP-1 therapy in humans
Pancreatic cancer with GLP-1 therapies (FDA database)

Exenatide vs. controls  
P = 9 \times 10^{-5}

Sitagliptin vs. controls  
P = 0.008

In agreement.
Monitoring MedWatch Reports, QuarterWatch (2011)
AKdÄ Drug Safety Mail, Deutsches Ärzteblatt (2011)
Monitoring MedWatch Reports, QuarterWatch (2013)
DuMouchel W, Oracle (2013)
Butler P, Diabetes Care (2013)
Cohen D, BMJ (2013). EMA, FDA and WHO.

Elashoff M, Gastroenterology (2011)

Impact of GLP-1 therapy in humans
“For now this analysis of the FDA database does not establish that pancreatitis, pancreatic and thyroid cancer are caused by GLP-1 based therapy. It simply raises the level of concern that they may be and that the appropriate prospective studies are required to rule them out.”

Elashoff M, Gastroenterology (2011)
Human pancreas, brain dead organ donors

JDRF network for Pancreatic Organ Donors with Diabetes (nPOD) University Florida.

T2DM (n=20),
   Incretin (n=8, age 58±4)
   Other Rx (n=12, age 40±4)
   Non diabetic (n=14, age 45±5).

Incretin; 7 Sitagliptin 1 Exenatide.

Butler A, Diabetes (2013)
Incretin treatment in humans, pancreas mass

Pancreas mass increased in incretin Rx group

Pancreas mass declines in from age 40 yrs

Butler A, Diabetes (2013)

Pancreas Weights

A

B

Pancreas Weight (g)

No diabetes  T1D  T2D  T2D Incretin

Weight (g)

No Diabetes Head  No Diabetes Body  No Diabetes Tail  T1D Head  T1D Body  T1D Tail  T2D Head  T2D Body  T2D Tail  T2D Incretin Head  T2D Incretin Body  T2D Incretin Tail

*  **  *  NS  NS  NS  *  NS  NS  *  #  *
Incretin treatment in humans, proliferation and dysplasia

Butler A, Diabetes (2013)

nPOD Human studies
Incretin treatment in humans, proliferation and dysplasia

nPOD Human studies

Butler A, Diabetes (2013)
Incretin treatment in humans, glucagon hyperplasia

Butler A, Diabetes (2013)
Incretin treatment in humans, glucagon hyperplasia

Exenatide Rx

Butler A, Diabetes (2013)
Controversies

• Is the risk of acute pancreatitis increased with incretin therapy?

• Does incretin therapy accelerate chronic (asymptomatic) pancreatitis?

• Does incretin therapy increase the risk of pancreatic cancer and/or neuroendocrine tumors?

• Does incretin therapy increase the risk of thyroid cancer?

• Will there be any proven superior outcome benefits of incretin therapy, and if so, will those benefit(s) outweigh the cost and adverse effects?
Medications for Type 2 Diabetes

GLUCOSE

INSULIN

+ Metformin

+ Pioglitazone

+ Rosaglitazone

GLP-1

BMS (Amylin)

Merck

Novo Nordisk

Eli Lilly

Astra Zenica

Boehringer Ingelheim

Novartis

Takeda

(Glaxo)

(Pfizer)

Market

20-40 billion dollars per year

Don’t forget lifestyle and vascular protection!
As of last week...

The EMA's Committee for Medicinal Products for Human Use said that the study had a number of methodological limitations and potential sources of bias, with "important differences" in age, gender, disease duration, and treatments that "preclude a meaningful interpretation of the results," according to the EMA release.

The committee said it also reviewed "all available nonclinical and clinical data" and found "no change in evidence regarding the risks of pancreatic adverse events associated with the use of GLP-1 based therapies."

In response to the EMA announcement, the American Diabetes Association issued a statement acknowledging that "at this time, there is insufficient information to modify current treatment recommendations."
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