Is Insulin a Specialty Medication?

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2016 CPFI Annual Conference
“In Christ Alone”
I have no conflict of interest relating in the material covered today

I do not serve on any speaker bureau

I do not have any personal grants concerning the area of discussion today

Some lame jokes included

Lots of brand names mentioned, but no financial interest in any of them

Promise: no Kaplan-Meier Mortality curves
Objectives

- Discuss the history of insulin
- Discuss insulin development and how it laid the framework for drug delivery systems and specialty medications
- Discuss Banting and Best discovery of insulin and the intimate details of involving industry in the process
- Define a specialty medication
Is Insulin a Specialty Medication?

YES!
INSULIN THERAPY

FLAME OF HOPE
A must read!!

ISBN: 987-0-312-64870-1

About Elizabeth Hughes and the Discovery of insulin
A flame of hope was lit by Her Majesty the Queen Mother in 1989 as a tribute to Dr. Frederick Banting and all the people that have lost their lives to diabetes. The flame will remain lit until there is a cure for diabetes. When a cure is found, the flame will be extinguished by the researchers who discover the cure. The flame is located at Sir Fredrick Banting Square in London, Ontario, Canada beside the Banting House National Historic Site of Canada.
Flame of Hope

[Image of Flame of Hope monument]

[Image of a house and statue]
Dr. Frederick Banting

- He was more than a scientist
- He was committed to his country
- He fought in wars
- His life ended during WWII days as he boarded a plane to England on a secret mission to discuss use of chemical weapons
- The plane crashed, he was 49 years old
A Discovery Beyond Discoveries

- It was the first “cure” of a disease (type 1 DM)
- Diabetes connected the industry into academic medicine
- It’s a lesson in compassion and persistence
- On the grave of Eli Lilly
  - “To the glory of God with thanksgiving for the wonder of life.”
Discovery of Insulin Timetable

- Type 1 diabetes in early 20th century carried a diagnosis of poor prognosis.
- After diagnosis, patients had an expected life span of a mere 11 months, filled with suffering and then death.
- The Egyptian papyrus in early 1550 BC describes a treatment of boiling an assortment of bones, wheat, grain and earth for 4 days – yummmm!
Discovery of Insulin Timetable

- The name “diabetes” was coined by a Greek physician (Aretaeus of Cappadocia) in the 2nd century – the word comes from the Greek word *sieve* because of the symptoms of thirst and urination.
- Matthew Dobson of England in the 18th century determined that the sweet sticky substance in diabetic urine was sugar.
- The Father of Physiology was Claude Bernard. He postulated that the problem was the pancreas. This lead to a number of experiments.
An unrecognized discovery in 1889 was a dog surgery by Oskar Minkowski and Joseph von Mering (Germans) – they removed the pancreas and the dog had all the symptoms of diabetes.

Paul Langerhans (German) found the clusters of cells in the pancreas but did not investigate the purpose.

Edouard Laguesse of France suggested that these cells lower blood glucose and he called them islets of Langerhans.
Discovery of Insulin Timetable

- In the early 1900’s Jean de Meyer of Belgium named the mysterious substance from the pancreas “insulin” after the Latin word island (islet) – but all this was speculation.
- It would be years before the insulin was isolated and produced.
- Until then the children were institutionalized and placed on a strict “starvation treatment”
  - Dr. Fredrick Allen
  - 1914-1922 is known as the “Allen years”
  - His hope was to increase life span in hopes of a cure
Dr. Diabetes, as he was known

- The approach was to find the minimal amount of food to sustain life
- “The cure is worse than the disease” fits
- “To starve is to survive”
- “Less food, the more life”
- Dr. Allen tells a family that he can extend their time, the mother’s comments, “at what cost to my daughter”, “is a year of agony better than 2 happy months?”
Physiatric Institute

Before Insulin    After Insulin

Dr. Allen
“To starve is to survive”
Dr. Banting

- He was in the Class of 1917, University of Toronto Medical School
- The class finished a year early to get the students off to war (WWI) at the cry of England
- After the war he opened a practice in London, Ontario
- He made most of his money handing out prescriptions for alcohol to alcoholics during the prohibition. His first month income was $4
It began with a boring article!

- It all started with reading an article that was suggested for him to read from a doctor (Dr. C.L. Starr) in the local hospital.
- Banting was frustrated (does he marry or not?)
- It was 1 AM in the morning on Halloween 1921.
- It was a long paper, 12 pages.
  - “The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis”
  - November issue of Surgery, Gynecology, and Obstetrics.
It persisted with an idea?

- He suffered through the article saying, “I pity the poor %*&*@ in that field” speaking of endocrinology!
- He dozed off only to open his eyes to an idea – he wrote it down
- “Diabetes ligate pancreatic ducts of dogs. Keep dogs alive till acini degenerate leave Islets. Try to isolate the internal secretion of these to relieve glycosurea”
  - Not a new idea, been tried before, but few persisted
  - The idea lead to persistence that lead to the discovery
Write down ideas!
Persistence leads to reality!

- He ended up at University of Toronto with an idea, an opportunity to have a dusty old Frankenstein lab for the Summer and a graduate student Charley Best.
- All under the direction of the department chair Dr. John Macleod (Banting’s arch nemesis).
  - Dr. Macleod introduced Banting at a presentation. Macleod essentially presented the paper in his introduction and use the term “we” in the experiments. The real war began!
- They did many experiments on dogs and removed the pancreas and made an extract they called isletin.
- They intentionally overdosed the dogs to see if the sugar would drop below normal – it did!
A cure was on the way!

- The original paper of the discovery was generated from the Summer work and was accepted for presentation at the 34th Annual Physiological Society in 1921.
- It was the last presentation on a Friday.
- At the presentation was Dr. Elliott Joslin, Dr. Fredrick Allen, Dr. Alec Clowes, research director of Eli Lilly.
Eli Lilly Products of 1920

- Charcoal Lozenges for indigestion
- Cape Aloes for constipation
- Passolaria for insomnia and anxiety
- Liquid Blaud for anemia
- Elixir #63 (catnip and fennel) for colds, headaches, colic and fever

- Eli, the grandson John Lilly said that the future of pharmaceutical manufacturing was in the fundamentals of biologic research
Industry vs. Academia

- For years Dr. Clowes tried to get Dr. Banting and Macleod to let his company manufacture their pancreatic mixture.
- They were very suspicious of the industry in that day – besides University of Toronto had its own manufacturer – Connaught Labs.
- They were very concerned with a patent because they felt it was in direct violation of the Hippocratic oath.
- Best and Collip (chemist) got the patent because they had never taken the oath and then assigned the rights over to University of Toronto for $1.
Industry vs. Academia

- Separation of church and state Boo!!
- Separation of earth and state Yea!!
- Separation of university research and commercial enterprise
- The problem became a moral one – the high ground of separation would be at the expense of children dying – they needed mass production
- Eli Lilly and Company was ready - Dr. Clowes fueled the collaboration
- All Mr. Lilly wanted was a brand name to ensure the public of the quality - he called it Iletin after isletin, the original Banting formula
The Real Hero

- Mr. Austin Brown of Lilly and Company
- He was the one put in charge of finding 2,000 pounds of beef or pork pancreas glands weekly 😊
- He traveled all over America, talking to all farmers and meatpackers
- They got suspicious and had to change some of their procedures to get him the pancreas glands
- He had to tell them that for every pound Lilly got, a child’s life would be saved! He became a salesman!
Dr. Elliott Joslin

- In America as Lilly scaled up production, Mr. Joe Lilly, Sr. allowed Dr. Elliott Joslin of Boston to be the first to administer Lilly insulin in the America
- Dr. Joslin called Ezekiel 37 the “Banting Chapter” of the Bible
  - ....and the valley of the bones came to life
  - p. 196 in book
- Joslin died at the age of 92 – he keep a registry of the patients he treated with diabetes
  - 58,784 names in 80 volumes
The Arch Nemesis…..

- Secret shhhhhhh
  - Dr. Macleod secretly gave the insulin formula to Dr. August Krogh of Copenhagen – his wife had diabetes and he was a Nobel Prize winner for Physiology – he came over to investigate the discovery
  - He is the founder of Nordisk labs in Denmark 😊
  - His partner was Dr. Hagedorn
    - Discovered protamine from fish sperm to slow the action of insulin
    - Cut the shots in half
    - Connaught labs added the zinc which further slowed the action
And the story continues…..

- It still took 2.5 tons of pancreas glands to produce 8 oz of insulin in 1948.
- This paved the way to biotechnology and recombinant insulin in 1982 and the specialty drugs we have today.
- Insulin took 2 years and $2.5 million (in today’s dollars) to get it to market.
- Today it takes 10 to 15 years and $1 billion to get a biologic to market.
It paved the way to this 😊

- Degludec
- Ryzodeg
- Lente
- Toujeo
- NPH
- Lispro
- Humalog
- 75/25 mix
- Novo Nordisk
- 70/30 mix
- Aspart
- Novolog
- 70/30 mix
- Glargine
- Humulin
- Regular
- Aventis
- Detemir
- Glulisine
- Basaglar
The Companies & The Drugs

**Novo Nordisk**
- Novolin
  - Novolin N (NPH)
  - Novolin R (regular)
  - Novolin 70/30
  - Novolog (aspart)
  - Novolog mix 70/30
  - Novolin L (lente)
  - Levemir (detemir)
  - Tresbia (degludec)
  - Ryzodeg 70/30
  - degludec/log

**Lilly**
- Humulin
  - Humulin N (NPH)
  - Humulin R (regular)
  - Humulin 70/30, 50/50
  - Humalog (lispro)
  - Humulin L (lente)
  - Humalog Mix 75/25
  - Humulin U (ultralente)

**Aventis**
- Lantus (glargine)
- Toujeo (glargine, 300 units/ml)
- Apidra (glulusine)

**Wal-Mart**
- ReliOn N (NPH)
- ReliOn R (regular)
- ReliOn 70/30

Yikes---------Basaglar® (glargine)---------
(Lilly/BI) 5-3 ml KwikPen
Insulin Glargine (Toujeo®)

- Basically Lantus in a **300 unit/ml** formulation
- 1:1 conversion from other basal insulin
- Twice daily NPH – use 80% of total daily NPH dose
- Insulin naïve – 0.2 units/kg
- Titrate every 3-4 days
- SoloStar® - 1.5 ml pen (3 for $336) – 450 units
Degludec (Tresiba®)

- **Degludec**
  - Addition of hexadecanedioic acid to lysine at the B29 position allows for the formation of multi-hexamers in subcutaneous tissues and long activity

- **Ultra long-acting**
  - Last 40 hours while Lantus last up to 24 hours
  - May need less dose – can use once daily
  - Can mix with short-acting insulins
    - Ryzodeg® 70/30
    - Not approved by FDA in 2013 – awaiting additional cardiovascular data
Degludec (Tresiba®)

- Any time of day dosing
- Can last 8 weeks out of frig
- Flextouch, each 3 ml pen
- U-100 (5 pens, $460)
  - 1500 units total
- U-200 (3 pens, $550)
  - 1800 units total
- U-200 can deliver up to 160 units at a dose

- There is also a new Humalog 200 units/ml pen
**Monotherapy**
- Efficacy
- Hypoglycemia risk
- Weight
- Side effects
- Costs

**Dual therapy**
- Efficacy
- Hypoglycemia risk
- Weight
- Side effects
- Costs

**Triple therapy**

**Combination injectable therapy**

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**Healthy eating, weight control, increased physical activity, and diabetes education**

**Metformin**
- High efficacy
- Low risk for hypoglycemia
- Neutral to weight loss
- GI/lactic acidosis
- Low costs

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
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</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
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<tr>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Moderate risk</td>
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<td>Low risk</td>
<td>Low risk</td>
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<tr>
<td>Weight gain</td>
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<td>Weight gain</td>
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<tr>
<td>Low</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
</tr>
<tr>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
<td>SGLT2-i</td>
<td>SGLT2-i</td>
<td>Insulin</td>
</tr>
<tr>
<td>SGLT2-i</td>
<td>GLP-1-RA</td>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
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<tr>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
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<tr>
<td>Insulin</td>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i.

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**Diabetes Care 2016;38(S1):52-9**
**Basal insulin**  
(usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine and address cause; ↓ dose by 4 U or 10–20%.

If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin. *(Consider initial GLP-1-RA trial.)*

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**Add 1 rapid insulin injection before largest meal**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.

If not controlled, consider basal–bolus.

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**Add ≥ 2 rapid insulin injections before meals (“basal–bolus”)**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.

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**Change to premixed insulin twice daily**

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.

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If not controlled, consider basal–bolus.
Inhaled Insulin (Afrezza®)

- New inhaled insulin is FDA approved
- MannKind Corp is the maker and is seeking a potential partner to market the drug.
- It has been in development for more than 20 years
- FDA is still concerned about lung function and lung cancer so post-marketing research will be ongoing.
- It is not recommended in smokers, COPD, asthma patients.
Inhaled Insulin (Afrezza®)

- Human insulin
- Similar to “log” insulin
  - Onset 15 to 30 min
  - Peak 1 hour
  - Duration 2.5 hours
- Administer before a meal
- 4 unit (blue), 8 unit (green) cartridges
- NEW – 12 unit cartridge (yellow)

$226.06/90 4-unit cartridges plus 2 inhalers
$252.33/60 4-unit cartridges plus 30 8-unit cartridges plus 2 inhalers
$278.59/30 4-unit cartridges plus 60 8-unit cartridges plus 2 inhalers
# Dosing

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA® Dose</th>
<th># of 4 unit (blue) cartridges needed</th>
<th># of 8 unit (green) cartridges needed</th>
</tr>
</thead>
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<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td>4 units</td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td>8 units</td>
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<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>12 units</td>
<td>+</td>
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<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>16 units</td>
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</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>20 units</td>
<td>+</td>
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<tr>
<td>21-24 units</td>
<td>24 units</td>
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</tr>
<tr>
<td>DOSE/MEAL (3 meals/day)</td>
<td>TOTAL DAY</td>
<td>AFREZZA® NDC/SKU NUMBERS</td>
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</tr>
<tr>
<td>------------------------</td>
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<td>1 4 units</td>
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<td>3 16 units</td>
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