Deciding on the pathophysiology guides the Intervention

• Dual defect: insulin deficiency and insulin resistance
• Glucose delivery and disposal abnormalities
• Beta-cell preservation including first phase insulin release

When I was in medical school—"Post receptor defect"
Case 1
• 56 y.o. Hispanic male UBSO
• A. nigricans
• DM x 5 yrs - Tx OSA + Met  A1C 8.5%
• ↑ GGTP, ↑ Alk Phos, ↑ Transaminases
• ↑ Microalbumin/Cr ratio
• Hx CAD, PCI and 1 stent
• C-peptide 2x nl.
• Mixed hyperlipidemia

Comment: Type 2 with lots of IR features

Case 2
• 26 y/o female
• New Sx's of increased Glu
• Glu 386, A1C 12%
• C-peptide high normal
• (+) GAD Ab

Comment: Type 1.5 Diabetes

Heterogeneity of Diabetes Mellitus
Type 1 Diabetes
Type 1.5 Diabetes
LADA - latent autoimmune diabetes in adults
Ab positive type 2 DM
Type 2 Diabetes (how many subtypes?)
Type 3 Diabetes - IR and Insulin deficiency
Overlap Features of Type 1.5 and 2 in UKPDS

3,672 Type 2 patients with diabetes screened for antibodies

6% ICA Positive
10% GADAb Positive
12% ICA or GAD Ab Positive
4% Positive for both

The Normal β-Cell Insulin Response to Intravenous (IV) Glucose Is Biphasic

First-Phase Insulin Response to IV Glucose Is Lost in Type 2 Diabetes

![Graph showing insulin response comparison between normal and type 2 diabetes patients.]


Insulin and Glucagon Dynamics in Response to Meals Are Abnormal in Type 2 Diabetes

![Graph showing glucose, insulin, and glucagon levels in normal and type 2 diabetes patients during a meal.]


More Organs are involved in the Diabetic Disease State

The ominous octet

Proliferation of drugs since the 1990’s
Now there are 13 Classes of FDA Approved drugs for Type 2 DM

- Biguanides
- Sulfonylureas
- TZD’s
- Alpha glucosidase inhibitors
- Meglitinides
- GLP-1’s
- DPP-4’s
- Bromocriptine
- Welchol
- Pramlintide
- Insulin injected
- Insulin inhaled
- SGLT-2’s
- Combos of all sorts
Classes to save $ 

- Sulfonylureas 
- Biguanides 
- Older Insulins – NPH, Regular, 70/30
Classes associated with best A1C lowering

- Sulfonylureas
- Metformin
- TZD’s
- GLP-1’s
- Insulins
- Combinations

Classes associated with weight loss

- GLP-1’s
- SGLT-2’s

Classes you'll likely not use

- Bromocriptine
- Welchol
- Meglitinides
- Alpha glucosidase inhibitors
Controversial class
TZD’s

Controversies within SGLT-2 class
Bone loss
Fracture
Amputations

Classes you may not know exist
• Pramlintide
• Inhaled insulin

CVOT/Renal protection
(may change algorithm)
• GLP-1’s
• SGLT-2’s
Metformin variations
• IR
• XR
• DR – to get gut peptide effect
• Glumetza

Weight Loss
• Behavior interventions
  – Commercial programs
  – Classes
  – One on one
  – Medicare YMCA
  – Accountability

Weight Loss
• Medications
  – Orlistat
  – Phentermine
  – Qsymia
  – Contrave
  – Belviq
  – GLP-1
  – SGLT-2
Weight Loss

- Bariatric procedures
  - Restrictive
  - Malabsorbтив

Back to the Cases

- Treat glucotoxicity. Fasting or any agent that lowers glucose will work
- Treat insulin resistance
- Exogenous insulin may be needed, even if transient. Think long-term if autoimmune markers present
- Watch for drug studies that show Beta cell preservation

Extra Slides
Parallels between all types of DM?

Loss of Beta cell mass

When do you use insulin anyway?

- After everything else has been tried
- Patient already on multiple orals
- Establish who is Insulin deficient / immune disease / LADA
- Symptoms of hyperglycemia, hi A1c
- Glucose toxicity
- Progression and duration of type 2
- Transient or permanent
Medical Literacy

- Goes both ways – patient and caregiver
- Cues to aid history
- Patient does not know what and how to tell caregiver
- Caregiver needs to know what they want in the interview
- Both will have responsibility for disease diagnosis and management in diabetes
- Insulin hygiene, educated use of monitoring and agents for treatment
- Inspection of injection sites
- It’s not just the product

Byetta provides 5 Key Actions that mimic those of GLP-1

- Restores First-Phase Insulin Response
- ↑ Glucose-Dependent Insulin Production
- ↓ Glucagon Production
- Slows Gastric Emptying
- ↓ Food Intake*

*This effect is postulated to be mediated through the central nervous system


See accompanying Prescribing Information and safety information included in this presentation
Mechanism of Action of gut peptides

Ingestion of food

Pancreas

Release of gut hormones — incretins

GLP-1 & GIP

Insulin from beta cells

Glucose-dependent glucose uptake by muscles

Glucose production by liver

Blood glucose

β-cells

α-cells

Blood glucose

GI tract

Active GLP-1 & GIP

Inactive GLP-1 and GIP

DPP-4 Inhibitor

DPP-4 Enzyme

Active incretins physiologically regulate glucose by modulating insulin secretion in a glucose-dependent manner.

GLP-1 also modulates glucagon secretion in a glucose-dependent manner.


Reference: