Clinical Diabetes
Basic Training

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Global Prevalence of Diabetes Projected to More Than Double to almost ½ billion by 2030

The Americas
2000: 33 million
2030: 67 million

Europe:
2000: 33 million
2030: 48 million

Africa and Middle East
2000: 22 million
2030: 61 million

Asia and Australia
2000: 83 million
2030: 190 million

Nationwide Diabetes Prevalence Categories

A changing Landscape?

- Obesity Rates in the United States Among Children are starting to plateau

- Recent announcement that in 2014 the incidence of Diabetes declined for the first time in 10 years

- Still the Vast Majority of Americans and those world wide have not met targets for glucose management, and several unaware they have diabetes

- The message is getting out but there is still a long way to go
What is Diabetes?

An impairment of the body’s ability to effectively transport glucose into the cell so it may be utilized for fuel.

*Diabetes is a Dual Hormone Disease*

Insulin, the body hormone responsible for the transport of glucose, is either less potent, decreased, or absent in a diabetic individual.

Glucagon, the counter regulatory hormone to insulin is increased and often unopposed.
Natural History of Type 2 Diabetes

- Incretin effect
- $\beta$-Cell function
- Insulin resistance
- Insulin secretion
- Postprandial glucose
- Fasting glucose

Years from diagnosis:
- -10
- -5
- 0 (Onset)
- 5
- 10
- 15

Microvascular complications

Macrovascular complications

Prediabetes

Type 2 diabetes

Figure courtesy of CADRE.
A Touch of Sugar
(fasting serum)

• Glucose intolerance: 105-113

• Pre diabetes: 114-125 (annually 5-10% of individuals progress to diabetes)

• Diabetes: 126 or greater
Ominous Octet

- Islet beta cell: Impaired insulin secretion
- Islet alpha cell: Increased glucagon secretion
- Decreased incretin effect
- Increased lipolysis
- Increased glucose reabsorption
- Increased hepatic glucose production
- Neurotransmitter dysfunction
- Decreased glucose uptake

• Addition of Gut Microbiota

• Increased Glucose Absorption in Stomach/ Small intestine

• Immune Dysregulation/ Inflammation

Look for the publication in Diabetes Care February 2016
3B. β-Cell-Centric Construct: Egregious Eleven
Targeted Treatments for Mediating Pathways of Hyperglycemia

1. Pancreatic β-cells
   - ↓ β-Cell function
   - ↓ β-Cell mass
   - ↓ Insulin

2. ↓ Incretin effect
   - ↑ Glucagon
   - Incretins

3. α-cell defect
   - ↓ Amylin
   - Incretins
   - Pramlintide

HYPERGLYCEMIA

11. Kidney
   - SGLT2 inhibitors

10. Stomach/Small intestine
   - GLP-1 Agonists
   - Pramlintide
   - AGI

9. Immune Dysregulation/Inflammation
   - Incretins
   - Anti-Inflammatories
   - Immune modulators

8. Colon/Biome
   - Probiotics
   - Incretins
   - Metformin

7. Brain
   - Incretins
   - Dopamine agonist-QR
   - Appetite Suppressants

6. Liver
   - Metformin
   - TZDs

5. Muscle
   - TZDs
   - Metformin

4. Adipose
   - TZDs
   - Metformin

FINAL COMMON DENOMINATOR

INSULIN RESISTANCE
Hemoglobin A1C, its just an average

**What is it**- the measured percentage of glucose attached to a red cell. It is a representative of the average blood sugars over a 2-3 month period.

**Why 3 months**- the body replaces the blood volume every 3 months.

**Why measure**- it may assist in the diagnosis of diabetes. Typically used to monitor overall diabetes control. Often a measure used in research.

Level is Independent of Hypoglycemic risk
A1C what should it be?

- A.D.A. - less than 7%
- A.C.E. - less than 6.5%

What does that percentage mean in terms of numbers.

- 6%-135
- 7%-170
- 8%-205
- 9%-240
- 10%-275
- 11%-310
- 12%-345
Glucose Fluctuations Are Not Adequately Measured by A1C

Mean A1C = 6.7%

Type 1 diabetes, N = 9
24-h CGMS glucose sensor data
Data on file, Amylin Pharmaceuticals, Inc.
Relative Contribution of Postprandial Glucose Increases as A1C Approaches Target

N = 290; Percentages are approximations
Adapted from Monnier L, et al. Diabetes Care 2003; 26:881-885
The Pathogenesis of Type 2 Diabetes
Beta-Cell Workload Outpaces Beta-Cell Response

- Healthy Subjects (n = 14)
- Type 2 Diabetes (n = 12)

Mean (SE) 
Medication used for DM II

- **Glucophage** (Metformin)  
  Action is on the liver to decrease extra glucose

- **Sulfonylureas** (Glipizide, Glyburide, Glimiperide)  
  release of insulin

- **SGLT2 Inhibitors**  
  (Invokana, Jardiance, Farxiga)  
  Glucouretic, Kidney release of glucose

- **Glitizones** (Actos and Avandia)  
  mRNA propagation of insulin receptors on cellular surface

- **GLP1 Incretin Family** –  
  (Byetta, Bydureon, Victoza, Tanzium, Trulicity)  
  mimics hormone naturally found in the body

- **DPP4 inhibitors** (Januvia, Tradjenta, Onglyza)  
  prevent native GLP 1 breakdown.
Metformin (Glucophaghe)

• Biguanide

• Dosed 500mg – 1000mg Dosed QD or BID

• Prevents the conversion of glycogen to glucose in the liver

• First Line Treatment for Diabetes

• Limitations Side effects GI and renal function/clearance

• Rarely Metabolic Acidosis since not metabolized in the liver
Sulfonylureas

- Glipizide 2\textsuperscript{nd} Generation (Glucotrol) 2.5m-10mg
- Glyburide 2\textsuperscript{nd} Generation (Micronase)
- Glimiperide 3\textsuperscript{rd} Generation \textit{Pancreatic Specific} (Amaryl) 2mg, 4mg and 8mg only in US

By Blocking potassium channels the opening of voltage dependent gates causing calcium influx and insulin degranulation and release. Also may inhibit glucagon and potentiate insulin action at peripheral tissue. Mainly fasting glycemic effect.
Meglitinides

• Starlix – nateglinide 60-120mg daily

• Prandin – repeglinide .5mg, 1mg and 2mg once daily

• Secretagog like but less affinity with the ATP channels and thus a greater disassociation with the receptor when may lessen the rapid out flow of pro-insulin

• Both Fasting and PPG effect
Glitizones (Sensitizers)

- Pioglitizone (Actos)
  - Dosed 15-45 mg QD
  - Beneficial CV and Lipid effects
  - Non-hypoglycemic
  - Edema due to sodium reabsorption in Nephron

- Rosiglitizone (Avandia)
  - Dosed 2-8 mg QD
  - Data Conflicting on CV effects
  - Non-hypoglycemic
  - Edema sodium reabsorption
DPP-4 Inhibitors

Dipeptidyl peptidase-4 inhibitor

Sitagliptin – Januvia
Typical Dose 100mg daily with or without food
Secondary doses of 50mg GFR 30-50 and 25mg for GFR<30

Saxagliptin- Onglyza
Dosing 2.5mg and 5mg if GFR <50 then 2.5mg

Linagliptin-Tradjenta
5mg single dosing irrespective of GFR
GLP1-Incretins

- Byetta (Exenatide) BID dosing 5mcg and 10mcg
- Victoza (Liraglutide) QD Dosing .6mcg-1.8mcg
- Bydureon (Exenatide LAR) Q weekly Dosing 2mg GFR>30
- Tanzium (Albiglutide) Q weekly Dosing 30mg and 50mg
- Trulicity (Dulaglutide) Q weekly Dosing .75mg and 1.5mg
GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Glucose-dependent postprandial glucagon secretion

Beta cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Incretins for Improved Glucose Control

Two Approaches to Prolonging Incretin Activity

<table>
<thead>
<tr>
<th>DPP-4 Inhibitors</th>
<th>Incretin Mimetics</th>
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<tbody>
<tr>
<td>Modest HbA(_1c) reduction</td>
<td>Significant HbA(_1c) reduction</td>
</tr>
<tr>
<td>Weight neutral</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Oral administration</td>
<td>Injection</td>
</tr>
<tr>
<td>Almost no GI side effects</td>
<td>Higher rate in GI side effects</td>
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<tr>
<td>Very low rate of hypoglycemia</td>
<td>Low rate of hypoglycemia</td>
</tr>
<tr>
<td>Multiple targets (Preservation of GLP1 activity and GIP activity)</td>
<td>Single target (GLP-1)</td>
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SGLT2 (Glucouretics)

- Invokana-(Canagliflozin) 150mg GFR>45 300mg GFR>60

- Farxiga-(Dapagliflozin) 5mg or 10mg GFR>60

- Jardiance-(Empagliflozin) 10mg or 25mg GFR>45

Lower the renal glucose threshold by inhibiting SGLT2 receptors in the Kidney causing renal glucose excretion up to 120 grams of glucose. Recent CV data for Empagliflozin
SGLT2 Blockade
Atypical Orals

- **Precose**- Acarbose alpha glucosidase inhibitor 25-100mg TID prior to meals

- **Bromocriptine**-Parlodel dopamine agonist 1.6mg-4.8mg daily

- **Welchol**- Colesevelam bile acid sequestrant doses 6 tablets daily or one packet daily
A Process of Matching the Right Drug to Right Patient
When to cross over to insulin.

- No more non-insulin medication to add.
- Rising post-meal blood sugars
- Increasing hemoglobin A1C (this occurs later)
- Very high blood sugars either early on in the disease or later in the advanced disease.
- A large percentage of diabetics will require Insulin within 10-15 years after diagnosis.
- Insulin Deficiency by laboratory or Disease progression
DON’T BE AFRAID OF INSULIN
It’s natural!
Modification of Oral when transitioning to Insulin

• No need for secretagogues (Sulfonylureas) personal opinion
• May continue sensitizers but may increase risk of edema
• Metformin may always be continued as long as appropriate (pts. still have livers)
• GLP1 should always be considered if possible (Fortified with Insulin in Europe)
• SGLT2 (Kidney dependent) able to be added at any time to insulin
Strive for Ideal: Insulin Regimen

- Mimic normal physiology with insulin therapy that addresses
  - Mealtime needs
  - Basal needs

- Theoretical representation of rapid-acting insulin
- Theoretical representation of basal insulin
- Expected insulin changes during the day for healthy individuals

Insulin effect images are theoretical representations and are not derived from clinical trial data.
Types of Insulin Commonly Used

- Once-a-day long-acting Lantus U100/U300 Toujeo or Levemir or BID NPH Tresiba (Degludec) U100/U200

- 75/25 mix insulin, Novolog 70/30, or Humalog 50/50

- Short-acting at meal time Bolus (Humalog, Novolog, Apidra, or Inhaled Afrezza)

- Complete transition to insulin using long-acting/short-acting with multiple injections termed Basal/Bolus

- Continuous Insulin Infusion using Pumps
Basal Insulin

- Glargine (Lantus) U100
  - QD approved but used BID
- Glargine U300 (Toujeo)
  - Dose QD Use same units as U100
  - 3 times concentrated U100; the pen makes the volume adjustment
  - PK/PD flatter than U100
- Detemir (Levemir)
  - Dosed QD and BID
  - Bound to Albumin, Fairly flat basal
- NPH (Neutral Protamine Hagedorn)
  - Dose BID
  - Duration 12 hours Peak at 6-8 hrs
- Degludec (Tresiba) U100/U200
  - 48-72 hours activity but dosed QD
Basal only; advantages and disadvantages

**Yeas**
- Ideal for *needle scared* patients
- Less brain cell usage to administer
- Overall Less Hypo than Prandial Insulin

**Nays**
- Frequently relied upon for too long
- Difficult to titrate Fasting Glucose is limiting factor
- Not quite physiologic, after all it is a basal
- No meal time or post prandial coverage
Premixed Insulin Preparations

Lispro (Humalog) 75/25  Aspart (Novolog) 70/30
- 70%-75% 12 hour long acting and 25%-30% rapid meal time insulin.
- Better total day coverage and can be given initially once daily or increased to two times daily.
- A more physiologic (better fit) than older 70/30 with Regular. Don’t be stuck in the time warp of the past.

Lispro (Humalog) 50/50
- 50% long 50% rapid Dosed QD-TID
- Basal/Bolus in a Pen
- “High Mix”
Dosing Low Premix

• QD initiation begin with Dinner 15-20 units

• Monitor Pre meals or 2 hour post prandial for titration

• AM fasting elevation will also indicate need for increase dinner dose and PM pre Dinner Blood sugar to increase Breakfast Dose

• Augment with rapid with Lunch if Gaps in insulin coverage or transition to 50/50 or Basal/Bolus
High Mix Insulin

- Lispro (Humalog 50/50)
  - Only high mix available in US
  - Dose calculations based on TDD if reasonable or .5-.8 unit Kg/Day
  - Can be dosed QD-TID
  - Limitations Over Night Basal Units Frequently not sufficient
  - Basal Bolus in a Pen
  - Limited by fixed dose
  - Titration based on Premeal CBG adjustment made to Insulin dose preceding the CBG
Scope of Premix Insulin

- Advantages
  - More physiologic in addressing meal time as well as basal
  - Can start as once daily and work up from there
  - Titration is possible
  - Augmenting with rapid acting at lunch for Low Mix

- Disadvantages
  - Fixed Dosing
  - More awareness needed due to rapid acting
  - Lunch time can be uncovered in patients who need more comprehensive insulin coverage
  - Addition of Basal to High Mix users
Rapid Acting Insulin

- Lispro (Humalog)  
  - DOSED MEALS AND HIGHS
- Aspart (Novolog)  
  - VERY SIMILAR PK/PD
- Glulisine (Apidra)

- Insulin Human (Afrezza)
  - Inhaled
  - PFT required
  - Bolus Unit packets 4, 8, 12 unit
  - Very Rapid Onset 30 mins
  - Sanofi Recently Returned Drug to Mankind
Intensive Insulin Management
Basal Bolus
More Advanced Insulin Plan

• QD or BID long-acting Basal
• Short-acting Prandial insulin for Meals and Highs

1. Calculate using CBG levels: start at 1 unit per 50 blood sugar greater than 100 (glucose correction factor)
2. Grams of carbohydrate: begin with 1 unit per 15 gram of carb. (insulin to carbohydrate ratio)
3. Testing is the key to being successful
4. Get assistance from your local CDE’s they are invaluable
Basal-Bolus Insulin Regimen: MDI

- 3-4 injections/day
- 5-7 blood sugars/day
- Adjust mealtime dose with carbohydrate content
- Rapid-acting insulin such as lispro used with a basal insulin closely mimics normal pancreatic secretion of insulin

See Important Safety Information included in this presentation.
*Insulin effect images are theoretical representations and are not derived from clinical trial data.
Insulin Delivery Systems

- Insulin Infusion Pumps
  - Omni pod, T-Slim, Animas, Medtronic, and Accu-chek
Glucose Sensing

- Dex Com G5
- Medtronic Enlite
- Libre pro
- Contact Lens
Parting thoughts

• The treatment of diabetes is changing rapidly, with new information and insights yearly.

• It’s a struggle for even the most enthusiastic of providers to stay current on treatment options.

• Remember this is a team approach, your education and input is critical for effective treatment.