Intensive Diabetes Management in Type 2 Diabetes
Disclosures

Member of NovoNordisk, Lilly Diabetes, Metavention, Sanofi, and Janssen Advisory Boards
Effects of Type 2 Diabetes on Glucose Metabolism

Liver
- Glycogenolysis
- Gluconeogenesis
- Glycogen
- Lactate
- CO₂
- Glycerol
- Lactate
- Alanine
- Glutamine

Brain
- Glycogen
- Lactate
- CO₂

Muscle
- FFA
- Glycogen

Fat
- FFA

Kidney
- Glycerol
- Lactate
- Alanine
- Glutamine
<table>
<thead>
<tr>
<th>The Ideal Therapy</th>
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<tbody>
<tr>
<td><strong>Glucocentric:</strong></td>
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<tr>
<td>• Normalize preprandial, postprandial, and intraprandial glucose concentrations</td>
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<td><strong>Holistic:</strong></td>
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<td>• Normalize everything</td>
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<td><strong>In a manner that is convenient, comfortable, and affordable</strong></td>
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Premise for Intensive Management of Type 2 Diabetes

Appropriate use of agents whose mechanism(s) of action are complimentary and suitable for a given individual is required to achieve optimal glycemic control in people with type 2 diabetes.
Lifestyle Modification

Not only may improve survival, but also improves the effectiveness of:

- Glucose lowering medications
- Blood pressure lowering medications
- Lipid lowering medications
- Sleep apnea treatments

And it makes you feel better
• Epidemiologic studies suggest that it decreases both micro- and macrovascular complications

• One randomized controlled trial (UKPDS) indicates it reduces both microvascular and macrovascular complications in obese people with short duration of diabetes

• However, in that study, addition of metformin to a sulfonylurea resulted in an increase in mortality in obese individuals
How Does Metformin Lower Glucose Concentrations?

Effect on HbA1c: -1.0 to -1.5%

- Increases insulin action?
- Reduces glucose production by inhibiting gluconeogenesis?
- Increases muscle glucose uptake?
- Increases insulin secretion by stimulating release in incretins (e.g. GLP-1)?
Effects of Metformin on Glucose Tolerance

**Glucose**
- Pre-Metformin
- Post-Metformin

**Insulin**
- Pre-Metformin
- Post-Metformin

DeFronzo R, JCEM 1991
Effects Three Months of Treatment With Metformin

Glucose Production

- Basal
- Clamp

µmol/kg/min

Pre treatment
Post treatment

Glucose Disappearance

- Basal
- Clamp

µmol/kg/min

Basu, R, Diabetes 2008
Effects Three Months of Treatment With Metformin

Glucose Production

- Basal
- Clamp

Pre treatment
Post treatment

µmol/kg/min

Glucose Disappearance

- Basal
- Clamp

Pre treatment
Post treatment

µmol/kg/min

Basu, R, Diabetes 2008
Sulfonylureas

- Epidemiologic studies suggest use associated with increased mortality
- Reduced overall mortality over the long term in the follow up of the UKPDS
- Implications of selectivity for pancreatic and extra-pancreatic channels unclear
- Long-term effects on beta cell mass and function not known
<table>
<thead>
<tr>
<th>How do Sulfonylureas Lower Glucose Concentrations?</th>
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<tr>
<td><strong>Effect on HbA1c: -1.0 to -1.5%</strong></td>
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<tr>
<td>• Stimulate insulin secretion in a non-glucose dependent manner</td>
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<tr>
<td>• Increase overall insulin availability but do not restore early postprandial insulin secretion</td>
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<tr>
<td>• Do not directly alter insulin action</td>
</tr>
<tr>
<td>• Do not directly suppress glucagon</td>
</tr>
</tbody>
</table>
Effects of Tolazamide Glucose Tolerance and Insulin Secretin

Firth R et al: Diabetes, 1987
Effects of Sulfonylureas on Pre-ischemic Conditioning in Type 2 Diabetes

Chest Pain

GLP-1 Agonists

- No long term outcome studies showing reduced micro- or macrovascular events
- Consistently results in modest weight loss
- Short term studies indicate GLP-1 agonist may have a favorable effect on endothelial function
- May increase the risk of pancreatitis and possibly may increase the risk of pancreatic cancer
How do GLP-1 Agonists Lower Glucose Concentrations?

Effect on HbA1c: -1.0 to -1.5%

- Stimulate insulin secretion in a glucose dependent manner
- Suppresses glucagon
- Increases satiety
- May improve insulin action
Effects of GLP-1 On Insulin and Glucagon Secretion in Type 2 Diabetes

Nauck M, Diabetologia 1993

Glucose

Insulin

Glucagon

Nauck M, Diabetologia 1993
Question

Does inhibition of glucagon reduce postprandial glucose concentrations control?
**Glucagon**

**Non-Diabetic Insulin Profile**

- Suppressed glucagon
- Non-suppressed glucagon

**Diabetic Insulin Profile**

- Suppressed glucagon
- Non-suppressed glucagon

Minutes:
-30  0  60  120  180  240  300  360

NG/L:
-200  100  0  100  200

Shah P: AJP, 1999
Shah P: AJP, 1999

**Insulin**

**Non-Diabetic Insulin Profile**
- Suppressed glucagon
- Non-suppressed glucagon

**Diabetic Insulin Profile**
- Glucagon levels are suppressed compared to non-diabetic profile.
Shah P: AJP, 1999

**Glucose**

**Non-Diabetic Insulin Profile**

- mmol/L vs Minutes
- Glucose levels for non-diabetic individuals
- Suppressed glucagon
- Non-suppressed glucagon

**Diabetic Insulin Profile**

- mmol/L vs Minutes
- Glucose levels for diabetic individuals
- Suppressed glucagon
- Non-suppressed glucagon

Shah P: AJP, 1999
**DPP-4 Inhibitors**

- No long term outcome studies showing reduced micro- or macrovascular events
- Do not alter weight
- Do not have an effect on endothelial function
- May increase the risk of pancreatitis and possibly may increase the risk of pancreatic cancer
- May modulate immune function and inflammation
How do DPP-4 Inhibitors Lower Glucose Concentrations?

Effect on HbA1c: -0.7 to -0.9%

- Stimulate insulin secretion in a glucose dependent manner
- Minimal suppression of glucagon
- Do not alter satiety
Effects DPIV Inhibitors on Glucagon Secretion in Type 2 Diabetes

- **Glucose**
  - Placebo: 18 mmol/L
  - Vildagliptin: 9 mmol/L

- **Insulin**
  - Placebo: 500 pmol/L
  - Vildagliptin: 250 pmol/L

- **Glucagon**
  - Placebo: 110 ng/L
  - Vildagliptin: 55 ng/L

*Vella A, Diabetes, 2007*
Pioglitazone

- May decrease cardiovascular events
- Increases body fat
- Increases risk of congested heart failure
- Decreases bone density and increases risk of fractures
- May increase risk of bladder cancer
How Does Pioglitazone Lower Glucose Concentrations?

**Effect on HbA1c: -0.7 to -0.9%**

- Improves insulin action primarily by enhancing insulin induced suppression of gluconeogenesis
- Increases insulin secretion
- Does not alter glucagon secretion
Effects Three Months of Treatment With Either Pioglitazone or Metformin

**Pioglitazone**

**Glucose Production**

- Basal: Pre treatment
- Clamp: Post treatment

**Glucose Disappearance**

- Basal: Pre treatment
- Clamp: Post treatment

**Metformin**

- Basal: Pre treatment
- Clamp: Post treatment

Basu, R, Diabetes 2008
Effects Three Months of Treatment With Either Pioglitazone or Metformin

Pioglitazone

Gluconeogenesis

Metformin

Glycogenolysis

Basu, R, Diabetes 2008
Effects Three Months of Treatment With Either Pioglitazone or Glipizide on Insulin Secretion

Pioglitazone

Glipizide

Basu, A, (unpublished)
How do SGLT2 Inhibitors Lower Glucose Concentrations?

Effect on HbA1c: -0.7 to -1.0%

- Increases glucose disposal by inhibiting renal glucose absorption
- Depending on threshold, could increase risk of hypoglycemia
- If also inhibits SGLT1, could decrease intestinal glucose absorption
- Effects in other tissues?
Insulin

- Epidemiologic studies suggest use associated with increased mortality
- Reduced overall mortality over the long term in the follow up of the UKPDS
- Results in systemic hyperinsulinemia
- Increases the risk of hypoglycemia
How Does Insulin Lower Glucose Concentrations?

**Effect on HbA1c: -1.0 to -1.5%**

- Reduces glucose production by inhibiting glycogenolysis and gluconeogenesis
- Increases muscle glucose uptake
Effects of Six Weeks of Treatment With Either Ultralente or Ultralente Plus Regular

McMahon, in et al: Diabetes, 1989

Glucose

Insulin

McMahon, in et al: Diabetes, 1989
How to Successfully Implement Intensive Management of Type 2 Diabetes

In order to achieve optimal glycemic control in people with type 2 diabetes:

• Use agents whose mechanism(s) of action are complimentary
• That are given at the appropriate time and in an appropriate doses
• Whose benefits outweigh risks in the individual in whom they are being used