Questions To Address

- Who are candidates for insulin?
- When do we start insulin?
- How do the different types of insulin compare?
- How do we decide which type to use?
- How do we initiate and titrate insulin?
- What prevents us from starting insulin sooner?
Candidates for Insulin

- All Type 1’s
- Gestational Diabetes

**Type 2’s:**
- Unable to control BG with orals/diet/exercise
- Newly diagnosed and in poor control
- Oral meds and/or incretin-based therapy not an option due to contraindications (comorbid conditions)
Reducing Complications of Diabetes

- Early diagnosis and treatment
- Achieving and maintaining A1C level < 7%
- A1C < 7% requires controlling post-prandial and fasting hyperglycemia
- Progressive disease requires progressive treatment
The Price Patients Pay…

‘avoidable glycemic burden’

Hormone Replacement Therapy?

- **Basal**: Secreted constantly at slightly varying rates to maintain glucose balance
  (Also known as background insulin)

- **Bolus**: Rapid release to offset rising glucose levels due to carbohydrate intake
  (Also known as prandial or mealtime insulin)
Actions/Uses of Exogenous Insulin

Basal Insulin (Background insulin)

• Examples: NPH, insulin glargine and detemir
• Controls fasting and between-meal glucose
• Ideally released at nearly constant level throughout the day

Bolus Insulin (Prandial insulin, Mealtime insulin)

• Examples: Regular insulin, insulin lispro, aspart and glulisine
• Rapid-acting or short-acting insulin
  - Controls mealtime glucose proactively ("covers" food you eat)
  - Corrects hyperglycemia reactively ("correction bolus")
Goals of Insulin Therapy

To mimic Mother Nature

Match insulin need to:

- Carbohydrate intake
- Physical activity
- Stress
- “Dawn phenomenon”
- Other physiological processes
Basal-Bolus Concept

- Physiological Insulin Administration
  - Approx. 50% of the dose from basal insulin and 50% from short- or rapid-acting insulin (typical for T1 patients)
  - Basal (NPH, detimer, and glargine)
  - Bolus (regular, lispro, aspart, and glulisine; divided over 3 meals)

1. Insulin Therapy for Type 2 Diabetes: Making It Work. JFPONLINE.com Vol 59, Apr 2010
2. Insulin Regimens for Type 2 Diabetes Mellitus. JFPONLINE.com (December 2006-Supplement)
## Insulin Pharmacokinetics: Quick Summary

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog®)</td>
<td>10-20 min.</td>
<td>1-3 hours</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Lispro (Humalog®)</td>
<td>&lt; 15 min.</td>
<td>30-90 minutes</td>
<td>&lt; 5 hours</td>
</tr>
<tr>
<td>Glulisine (Apidra®)</td>
<td>10-15 min.</td>
<td>30-90 minutes</td>
<td>&lt; 5 hours</td>
</tr>
<tr>
<td><strong>Regular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin® R</td>
<td>30-60 min.</td>
<td>2-3 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Novolin® R</td>
<td>30 min.</td>
<td>2.5-5 hours</td>
<td>8 hours</td>
</tr>
<tr>
<td><strong>NPH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin® N</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
<td>14-18 hours</td>
</tr>
<tr>
<td>Novolin® N</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
<td>14-18 hours</td>
</tr>
<tr>
<td><strong>Peakless Basal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus®)</td>
<td>1-4 hours</td>
<td>Minimal</td>
<td>24 hours</td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>1-4 hours</td>
<td>Minimal</td>
<td>Up to 24 hours</td>
</tr>
</tbody>
</table>

Basal Analogs versus NPH

- Less variability
- Able to achieve a lower FPG vs. NPH
- Reduced risk of nocturnal hypoglycemia vs. NPH
- Reduced risk of weight gain vs. NPH

Regular Insulin Limitations

• Doesn’t fit the way we live
  - Slower onset means injecting 30-45 minute before a meal
  - For unknown quantity and amount of food
  - Late postprandial peaks in insulin concentration
Rapid-Acting Insulin Analogs versus Regular Insulin

• Rapid Acting Insulin Analogs (RAIs) have more convenient administration (immediately before meals)

• Rapid onset reduces postprandial hyperglycemia

• Shorter duration of action reduces the likelihood of between-meal or nocturnal hypoglycemia

## Premixed (Biphasic) Insulin Analogs

**Dual-release formulations:**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novolog ® Mix (70/30)</td>
<td>5-15 min</td>
<td>Biphasic</td>
<td>10-16 hours</td>
</tr>
<tr>
<td>Humalog ® Mix (75/25)</td>
<td>5-15 min</td>
<td>Biphasic</td>
<td>10-16 hours</td>
</tr>
<tr>
<td>Humalog ® Mix (50/50)</td>
<td>5-15 min</td>
<td>Biphasic</td>
<td>10-16 hours</td>
</tr>
</tbody>
</table>

[http://www.ttdiabetesguide.org/medications/glucose-lowering/full_pre-mixed_insulin_preparations.html](http://www.ttdiabetesguide.org/medications/glucose-lowering/full_pre-mixed_insulin_preparations.html)
### Common Insulin Regimens in Primary Care

<table>
<thead>
<tr>
<th>Basal Insulin + Oral Agents</th>
<th>Biphasic Alone + Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fasting hyperglycemia</td>
<td>• Not prepared to do multiple daily injections (MDI)</td>
</tr>
<tr>
<td>• Bedtime BG &lt; fasting BG</td>
<td>• Elevated fasting &amp; postprandial glucose</td>
</tr>
<tr>
<td></td>
<td>• Regimented schedule (i.e., meals at fixed time)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basal Insulin + Short/RAI</th>
<th>Complete Basal/Bolus Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fasting hyperglycemia</td>
<td>• Elevated fasting &amp; postprandial glucose</td>
</tr>
<tr>
<td>• Problem meals</td>
<td>• Flexible schedule</td>
</tr>
<tr>
<td></td>
<td>• Insulin pumps or 4 injections per day</td>
</tr>
<tr>
<td></td>
<td>• Willing and able to do MDI and SMBG ≥4-times daily</td>
</tr>
</tbody>
</table>

RAI = Rapid-acting insulin
Premix (Biphasic) Insulin Combinations

• Can be regular/NPH or analog/extended release
• Usually given before breakfast and supper
• Advantages
  - Convenient, easy to use, no mixing errors
• Disadvantages
  - Fixed amount of carbs and more predictive lifestyle
  - Fixed combinations don’t allow for fine tuning
Which would be the *an* appropriate candidate for a regimen of 70/30 insulin am and pm?

A. A 19 year old with T1DM  
B. A 29 year old executive newly diagnosed with T2DM  
C. A 70 year old retired teacher with T2DM  
D. All would be appropriate candidates
The Most Appropriate Candidate?

- A 19 year old with T1DM
- A 29 year old executive newly diagnosed with T2DM
- A 70 year old retired teacher with T2DM
- All would be appropriate candidates
Dealing With Patient Barriers and Resistance to Insulin Injections

Psychological Insulin Resistance (PIR)

Getting Patients on Insulin Sooner

- Explain natural progression of type 2 diabetes
- Emphasize that the “goal is control”
- “This is not your grandmother’s insulin”
- New insulin delivery devices
Barriers to Using Insulin

**Patients** resistance

- Fear of needles
- Fear of complications of insulin
- Feelings of failure and guilt
- Complexity of regimen
- Cost

Meece, J., Dispelling Myths and Removing Barriers About Insulin in Type 2 Diabetes. The Diabetes Educator January/February 2006 32: 9S-18S
Most patients’ perception of insulin injection...
Perception: Insulin Injections Are Painful

Today’s needles are:

• Finer
• Laser sharpened
• Silicone coated
• Very short!
Some cultures believe that insulin is the beginning of the end or that it is actually toxic.
Perception: Hypoglycemia is to be Avoided at All Costs

- Older insulin products are associated with more hypoglycemia
- Explain that “tight” control may increase the likelihood of hypoglycemia
- Fear of hypoglycemia may be just as much of a barrier to good control as actual hypoglycemia

Meece, J., Dispelling Myths and Removing Barriers About Insulin in Type 2 Diabetes. The Diabetes Educator January/February 2006 32: 9S-18S
Provide Hypoglycemia Education

• What is patient’s individual first sign of hypoglycemia?

• Avoid missing meals

• Inject insulin at the right time
  – (30 minutes prior to meals for short-acting regular insulin, mealtime injection for rapid-acting analogs and premixed insulin)

• Plan physical activity

• Limit alcohol consumption
Overcoming Fear of Weight Gain

• Discuss potential weight gain: one of most common side effects of insulin therapy

• Etiology of weight gain:
  - Reduction of glucosuria
  - Increased caloric intake to prevent/treat hypoglycemia

• Emphasize proper eating habits and benefits of exercise
Why Leave Metformin in Place When Adding Insulin to Regimens?

- Metformin + insulin results in less weight gain than insulin therapy alone or insulin plus other oral agents.
- Metformin has also been shown to lower cholesterol and triglyceride levels.

Barriers to Using Insulin

Providers resistance

• Fear of patients “non-compliance”
• Perception of higher cost
• Hypoglycemia
• Weight gain
• Lack of time and resources to start
• Too complicated for patient and too time consuming
The Reality of Insulin Dosing

We now have more clear-cut guidelines from clinical trials concerning insulin initiation and titration

- *Treat-to-Target and other stepwise methods* provide guidelines for dosing basal insulin analogs\(^1\)

- *INITIATE* study provides guidelines for twice-daily initiation of premixed insulin analog (aspart premix 70/30)\(^2\)

---

Titration and Adjustment of Basal Insulin in T2DM: Methods and Algorithms

(Usually starting at 10 U/day of basal analog based on morning fasting BG’s)

• PREDICTIVE 303
  - 3 Units every 3 days until target of 100

• Increase by one unit per day

• Treat-to-Target
  - Per dosing chart weekly


Once-Daily Dosing for Glargine

Start with 10 U once daily basal insulin dose and adjust weekly

<table>
<thead>
<tr>
<th>Self-monitored FPG (mg/dL) from preceding 2 days with no episodes of severe hypo or PG ≤ 72 mg/dL</th>
<th>Titration: Increase in insulin dose (Units per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 mg/dl</td>
<td>(Decrease 2 U)</td>
</tr>
<tr>
<td>100–120 mg/dL</td>
<td>2 U</td>
</tr>
<tr>
<td>120–140 mg/dL</td>
<td>4 U</td>
</tr>
<tr>
<td>140–180 mg/dL</td>
<td>6 U</td>
</tr>
<tr>
<td>≥ 180 mg/dL</td>
<td>8 U</td>
</tr>
</tbody>
</table>

Initiate: 70/30 Mix Can Also Be Started Twice Daily

Start with 6 U BID if FPG is ≥ 180 mg/dL or 5 U BID if FPG is < 180 mg/dL

<table>
<thead>
<tr>
<th>Self-monitored FPG (mg/dL)</th>
<th>Titration: Increase in insulin dose (U/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80 mg/dL</td>
<td>(Decrease 2 U)</td>
</tr>
<tr>
<td>80–110 mg/dL</td>
<td>None</td>
</tr>
<tr>
<td>111–140 mg/dL</td>
<td>2 U</td>
</tr>
<tr>
<td>141–180 mg/dL</td>
<td>4 U</td>
</tr>
<tr>
<td>&gt; 180 mg/dL</td>
<td>6 U</td>
</tr>
</tbody>
</table>

Unit-to-unit transfer for patients already using human premixed 70/30

Patient Empowerment

As a clinician, how do you perceive insulin and the patient who needs it?

“What are your biggest concerns about starting insulin?”

“What do you think about insulin?”

(Then Listen)
How Do We Adjust Insulin for High Blood Glucoses and for Meals?

Correction Factor (Sensitivity Factor)

And

Insulin to Carbohydrate Ratio
1800/500 Rules

1800 ÷ by TDD = **Insulin Sensitivity Factor (ISF)**
(How much does 1 unit of insulin drop blood glucose)

500 ÷ by TDD = Insulin to Carb Ratio (**I:C**)
(How many grams of carbohydrate does one unit of insulin cover)


Correcting for High BG: Sensitivity Factor and the 1800 Rule

- Based on all units of insulin taken in a day
- To be applied to patients on rapid acting insulin
- Divide TDD of insulin into 1800 to find out how much 1 unit will decrease blood glucose.
  - Example: Patient is on 60 units a day of glargine lispro: 10u for breakfast, 6u lunch, 12u dinner

  \[ ISF = 1:20 \]
Insulin to Carb Ratio and the 500 Rule

• Grams of carbohydrate that are approximately covered by 1 unit of insulin.

• Most accurate for:
  - Those who make no insulin of their own
  - Receive 50-60% as basal insulin
  - On rapid-acting insulin

• Based on TDD of insulin for a person with type 1 diabetes in reasonable glycemic control
  - Example: patient is on 20 units a day of lispro and 30 units of glargine

I:C ratio = 1:10

SD takes an average of 24 units per day of insulin aspart with meals along with 30 units of insulin glargine at 10 PM each night. He is setting down to a meal of a baked potato, ham sandwich, salad and a small piece of chocolate cake.

Total carbohydrate content: 90 gms
His SMBG check shows: 220 mg/dL

How many units should he inject before his meal?
Total carbohydrate content: 90 gms
His SMBG check shows 220 mg/dL

ISF = 1800/54 = 33.3
I:C ratio = 500/54 = 9.25 = (10) = 1:10

How many Units should he inject before his meal?

A. 3.5
B. 9
C. 12.5
D. 15
ISF = \frac{1800}{54} = 33.3

I:C ratio = \frac{500}{54} = 9.25 = (10) = 1:10

220 - 100 = 120 \div 35 = \text{3.5 units (To correct)}

90 \text{ gm/10} = \text{9 units (For food)}

\text{Total=} \text{?}
Total carbohydrate content: 90 gms  
His SMBG check shows 220 mg/dL  

How many Units should he inject before his meal?

A. 3.5  
B. 9  
C. 12.5  
D. 15
Injection Site Complications

• **Lipoatrophy** (Rare)
  - Atrophy of subcutaneous fat
  - Caused by repeated injections at the same site

• **Lipohypertrophy** (Not that uncommon)
  - A buildup of subcutaneous fat

http://medical-dictionary.thefreedictionary.com/lipoatrophy
http://medical-dictionary.thefreedictionary.com/lipohypertrophy
Summary: Insulin Therapy

• Replaces complete lack of insulin in type 1 diabetes
• Supplements progressive deficiency in type 2 diabetes
• Regimens to initiate insulin can be straightforward and relatively easy to implement
• Main side effects of insulin therapy: Hypoglycemia and weight gain
• New insulin analogs and injection devices facilitate initiation and adherence
Thank you!

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