Insulin Therapies for T2DM
Defects in T2DM

- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscles)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increase in free fatty acids (FFA) production
- Neurotransmitter dysfunction
- Increased renal glucose reabsorption
Dashed line shows extrapolation forward and backward from years 0 to 6 from diabetes diagnosis, based on Homeostasis Model Assessment (HOMA) data from UKPDS.

The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.

T2DM = Type 2 Diabetes Mellitus; OAD = oral anti-diabetic; UKPDS = United Kingdom Prospective Diabetes Study Group.

UKPDS: Over Time, Need for Exogenous Insulin Increases

Patients Requiring Additional Insulin (%)

By 6 years, more than 50% of UKPDS patients required insulin therapy

UKPDS=United Kingdom Prospective Diabetes Study Group.

Antihyperglycemic Monotherapy
Maximum Therapeutic Effect, Dependent Upon Initial A1C

Baseline A1C

- Acarbose: 8.5¹
- Nateglinide: 8.3–8.5²
- Sitagliptin: 7.7³
- Bromocriptine: 7.8–12.5⁴
- Liraglutide: 8.2–8.5⁵
- Exenatide: 8.0⁶
- Pioglitazone: 10.0–10.3⁷
- Repaglinide: 8.8–9.0⁸
- Glimepiride: 7.7⁹
- Glipizide GITS: 8.3–8.8¹⁰
- Metformin: 9.7–10.1¹¹
- Canagliflozin: 7.8–8.3¹²
- Insulin

Reduction in A1C Level (%)

A1C=glycated hemoglobin

When To Start Insulin in T2DM

• When combination oral/injectable agents become inadequate
• Unacceptable side effects of oral/injectable agents
• Patient wants more flexibility
• Special circumstances (i.e. steroid use, infection, pregnancy)
• Patients with hepatic or renal disease,
• Patients with CAD, ↑TG

CAD=coronary artery disease; T2DM=type 2 diabetes mellitus; TG=triglycerides.
### Comparison of Available Insulins
(Per Prescribing Information)

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin (R)</td>
<td>30-60 min</td>
<td>2-5 hrs</td>
<td>5-8 hrs</td>
</tr>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin lispro U-200</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10-20 min</td>
<td>40-50 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>20-30 min</td>
<td>30-90 min</td>
<td>1-2.5 hrs</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hrs</td>
<td>4-12 hrs</td>
<td>18-24 hrs</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1-1.5 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>6 hrs</td>
<td>flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1-2 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insuline degludec</td>
<td>1 hr</td>
<td>3-4 days</td>
<td>up to 42 hours</td>
</tr>
<tr>
<td><strong>Premixed Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular/NPH insulin 70/30</td>
<td>30 min</td>
<td>2-12 hrs</td>
<td>14-24 hrs</td>
</tr>
<tr>
<td>Lispro protamine 75/25, 50/50</td>
<td>15 min</td>
<td>0.5-2.5 hrs</td>
<td>16-20 hrs</td>
</tr>
<tr>
<td>Biphasic insulin aspart 70/30</td>
<td>10-20 min</td>
<td>1-4 hrs</td>
<td>up to 24 hrs</td>
</tr>
</tbody>
</table>

NPH=Neutral Protamine Hagedorn
Insulin Therapy in Type 2 Diabetes

Current Strategies

• **Basal insulin therapy**
  - Long-acting insulin analog once daily
  - Intermediate-acting NPH at bedtime

• **Human or analog insulin (prandial or premixed w/ intermediate)**
  - Once daily at largest meal
  - Twice daily (breakfast and dinner)
  - Three times daily (with each meal)

• **Intensive insulin therapy**
  - Basal +
  - rapid-acting analog insulin
    - Once daily at largest meal
    - Twice daily at meals
    - Three times daily (with each meal)

• **Insulin pump therapy**

NPH=Neutral Protamine Hagedorn.

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (long-acting insulin)

A1c < 8%
TDD 0.1–0.2 U/kg

A1c > 8%
TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 Unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

INTENSIFY (prandial control)

Add GLP-1 RA
or SGLT-2i
or DPP-4i

Add Prandial Insulin
TDD 0.3–0.5 U/kg

- 50% Basal Analog
- 50% Prandial Analog
- Less desirable: NPH and regular insulin or premixed insulin

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between-meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

**Glycemic Goal:**
- <7% for most patients with T2DM; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1c and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk
Insulin Analogs More Closely Match the Physiologic Insulin Profile Than Human Insulin

• **Bolus (meal-related) insulin analogs**
  
  – Rapid absorption
  
  – Peak action coincides with peak carbohydrate absorption

• **Basal insulin analogs**
  
  – Slow and steady rate of absorption
  
  – Protracted action

Long-Acting Insulin Analogs vs NPH In Type 2 Diabetes

A Meta-Analysis

• Long-acting analogs provide comparable glycemic control to NPH

• Reduced risks of nocturnal and symptomatic hypoglycemia

• May be associated with less weight gain than NPH

NPH=Neutral Protamine Hagedorn.

Hypoglycemic events per patient per year

NPH=Neutral Protamine Hagedorn; OAD=oral antidiabetic drug.

## Pitfalls and Caveats In the Use of Basal Insulin (BI)

<table>
<thead>
<tr>
<th>The Challenge</th>
<th>The Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptitrating dose based on elevated pre-supper blood glucose → nocturnal hypoglycemia</td>
<td>• Post-lunch hyperglycemia is the culprit; only titrate BI based upon fasting blood glucose</td>
</tr>
<tr>
<td>Over-reliance on BI to control PP hyperglycemia when added to non-prandial agents (eg, metformin, thiazolidinediones)</td>
<td>• As both fasting and PP hyperglycemia are present, consider use of a prandial agent before/at time of BI addition</td>
</tr>
<tr>
<td>Delay in down-titration of BI with improved glycemia → hypoglycemia and pre-emptive eating</td>
<td>• Discuss this scenario with patient as glycemic control is re-established: “Less insulin is needed to maintain control than establish control”&lt;br&gt;• Reduction of OHAs, such as SUs or glinides, may also be required</td>
</tr>
</tbody>
</table>

PP=postprandial; BI=basal insulin; OHA=oral hypoglycemic agents; SU=sulfonylurea.
At Some Point, Raising Basal Dose Alone Will Be Inadequate, Failing to Address PPG

![Graph showing plasma insulin levels over time with mealtime peaks and basal insulin.]

- **Breakfast**
- **Lunch**

**Mealtime insulin response is missing; high postprandial readings every meal**

**This may lead to hypoglycemia if food changes or meals are missed**

Plasma insulin (µU/mL)

- 75
- 50
- 25
- 0

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

**Time**

**Basal insulin**

PPG = post prandial glucose; µU= micro units; mL=milliliter.

Options When Not at Goal with 1 Injection of Basal Insulin

- Basal Plus
  
  Add prandial insulin at main meal

  *or*

- Switch to Premixed Insulin (if regular meal schedule)

  *or*

- Switch to Basal/Bolus

  *or*

- Add an incretin-based therapy (DPP-4 inhibitor or GLP-1 RA, if patient is not already on incretin therapy)

DPP-4=dipeptidyl peptidase-4;  
GLP-1=glucagon-like peptide-1;  
RA=receptor agonist

Basal Insulin Therapy

Plasma Insulin

Time

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00

Glargine or Detemir

Meal Insulin
Rapid-Acting Analogs (Aspart, Glulisine, Lispro) vs Regular

Effect of Adding 1, 2, or 3 Pre-meal Rapid-acting Insulin Injections To a Background of Basal Insulin Analog Therapy in Patients Requiring Therapy Intensification

<table>
<thead>
<tr>
<th>Patients (%) Achieving A1C &lt;7.0% at Week 24</th>
<th>1 Injection</th>
<th>2 Injections</th>
<th>3 Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C &lt;7.0%</td>
<td>30</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Hypo (%)</td>
<td>7</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

A1C=glycated hemoglobin.

Biphasic Analog Insulin (Premixed Insulin)

Premixed (Biphasic) Analog Insulin

- **Initiation**

  - Divide basal dose in half and administer before breakfast and supper; subsequent titration may be required
    - Titrate: Add 1 to 2 units to prebreakfast or presupper dose to reach blood glucose targets, continue to increase daily until targets are met

- **Premixed insulin may be appropriate**
  - When basal/bolus cannot be used
    - and
  - For those with regular lifestyles, who eat similar amounts at similar times each day
    - and
  - Those who wish only 2 injections/day

Basal-Bolus Insulin Treatment with Insulin Analogs

Lispro, glulisine, or aspart

Glargine or Detemir

Normal pattern

Insulin (µU/mL)

0600 0800 1200 1800 2400 0600

Time of day

µU=milli units; mL=milliliters; B=breakfast; L=lunch; D=dinner.

Starting Basal/Bolus Therapy

• **Starting insulin dose** is based on weight
  = 0.3-0.5 units/kg

• **Basal dose** (glargine/detemir/NPH)
  = 50% of starting dose at bedtime

• **Bolus dose** (meal dose)
  = 50% of starting dose divided between meals
  (rapid-acting analog or Regular insulin)

kg=kilogram; NPH=Neutral Protamine Hagedorn.

Example: Starting Multiple Daily Injections in 100-kg Patient with Moderate Insulin Resistance

• **Starting dose** = 0.5 x weight in kg
  - 0.5 x 100 kg = 50 units

• **Basal dose** = 50% of starting dose at bedtime
  - 50% of 50 units = 25 units at bedtime

• **Total bolus dose** = 50% of starting dose evenly distributed 1/3 at each meal
  - 25 units ÷ by 3 meals = 8 units before meals (TID)

kg=kilogram; wt=weight; TID= three times daily.
Inhaled Human Insulin

• Approved July 2014
• Dry powder, human regular insulin
• Adsorbed onto technosphere microparticles
• Dissolves immediately when inhaled
• Ultra-rapid acting: peak concentration at 12-15 minutes, back to baseline at 180 minutes
• Bioavailability: 21-30% of subcut. dose
• Mealtime glycemic control
• Need to use with basal insulin in type 1 DM
Inhaled Human Insulin

- Supplied: 4 or 8 unit cartridges
- Dosing: Insulin naïve: 4 units AC
- Using sc prandial insulin: Conversion

<table>
<thead>
<tr>
<th>subcut (units)</th>
<th>inhaled (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5-8</td>
<td>8</td>
</tr>
<tr>
<td>9-12</td>
<td>12</td>
</tr>
<tr>
<td>13-16</td>
<td>16</td>
</tr>
<tr>
<td>17-20</td>
<td>20</td>
</tr>
<tr>
<td>21-24</td>
<td>24</td>
</tr>
</tbody>
</table>
Inhaled Human Insulin

• Clinical Trials:
  • Non-inferior to sc basal bolus when given with basal insulin in type 1 diabetes (Affinity 1 Study; B.W. Bode et al, Diabetes Care 2015)
  • More patients achieved HbA1c <7% when added to oral agents w/o basal insulin in type 2 diabetes: 38% vs 19%, \( P = 0.002 \), (Affinity 2 Study; J. Rosenstock et al, Diabetes Care 2015)
Inhaled Human Insulin

• Adverse Effects/Contraindications
  – Hypoglycemia: similar or lower than sc insulin
  – Decreased FEV1: small, occurs w/i first 3 months, potentially reversible with discontinuation
  – Lung cancer: 2 cases in clinical trials-both heavy smokers
  – Not recommended in smokers or recent stoppers
  – Contraindicated in COPD, asthma
  – REMS: baseline, 6 mo. and annual spirometry
    5 year monitoring to assess risk of lung cancer, change in PFTs
<table>
<thead>
<tr>
<th>Name</th>
<th>Approved</th>
<th>Conc</th>
<th>Volume</th>
<th>Supplied</th>
<th>#units</th>
<th>Admin.</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U-300</td>
<td>February 2015</td>
<td>3X</td>
<td>1/3</td>
<td>Prefilled Pen</td>
<td>450</td>
<td>QD</td>
<td>More compact sc depot with smaller surface area; “Flatter” insulin</td>
</tr>
<tr>
<td>Lispro U-200</td>
<td>May 2015</td>
<td>2X</td>
<td>1/2</td>
<td>Prefilled Pen</td>
<td>600</td>
<td>AC TID</td>
<td>Bioequiv. to Lispro U-100; Similar time to max. conc.</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>1952 (Beef)</td>
<td>5X</td>
<td>1/5</td>
<td>Vial (20 mL)</td>
<td>10,000</td>
<td>AC BID-TID</td>
<td>Prefilled pen in develop.</td>
</tr>
</tbody>
</table>
Incretin-Based Therapy in Combination With Basal Insulin
A Promising Tactic for the Treatment of Patients With T2DM

- Consider non-insulin options with synergistic mechanisms of action and low hypoglycemia risk when intensifying regimens beyond basal insulin
  - DPP-4 inhibitors when A1C reductions of <1.0% are needed
  - GLP-1 receptor agonists when A1C reductions ≥1.0% are needed (and patients may benefit from possible weight loss)
  - Insulin doses may be able to be – or may need to be – lowered
- Targets insulin deficiency and glucagon excess

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; A1C=glycated hemoglobin; T2DM=type 2 diabetes mellitus.
Reasons Patients Avoid Insulin

- Lack of knowledge
- Cultural taboos and family beliefs
- Fear of needles or injection pain
- Fear of hypoglycemia and/or weight gain
- Inconvenience
- Sense of personal failure

- Diabetes seen as worse or more serious once insulin is initiated
- Fear that insulin causes complications and/or that insulin will impose constant demands on patient
Strategies to Overcome Patient Barriers To Insulin Use

• **Starting insulin** – get help from Certified Diabetes Educators, dietitians, pharmacists; consider group instruction

• **Needle phobia** – show fine needles, pens, demonstrate technique

• **Convenience** – use pens or other devices

• Begin therapy with **simple regimen** – detemir or glargine pen at bedtime

Insulin Pens

• More convenient than traditional vial and syringe
• More accurate, repeated doses
• Easier to use for those with visual or fine motor skill impairment
• Less injection pain
  – Polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin

Real-world Choices Depend On the Patient

• Injection frequency preference
  – Some patients may prefer premix
• Frequency of self-monitoring of blood glucose
• Variability of lifestyle, including meal timing and carbohydrate content of meals
• Presence of postprandial hyperglycemia
• Patient’s ability to follow the prescribed regimen
• Educational and emotional support available to patient
• Cost of analogue insulin options may be nearly double that of NPH or regular insulin

Key Points: Insulin Initiation

• Diabetes is a progressive disease and many individuals with T2DM eventually need insulin to control their blood glucose.

• There are cultural taboos and misconceptions regarding insulin therapy; it is important to understand and acknowledge patients' specific concerns and design individualized treatment plans that fit their needs.

• Start with a simple regimen, such as a once-daily basal insulin analog, and up-titrated the dose based on FPG; if A1C remains high when FPG is in the target range, add a DPP-4 inhibitor, a GLP-1 RA, or mealtime insulin.

T2DM=type 2 diabetes mellitus; FPG=fasting plasma glucose; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; RA=receptor agonist; A1C=glycated hemoglobin.

2. Peragallo V. Diabetes Educ. 2007;33:60S–65S.
Key Points: Insulin Initiation

• Allow patients to give the first injection during the office visit (because the first injection is often the biggest hurdle)

• Alternately, to help diminish fear, give patient a mock shot as soon as insulin is discussed (this can be done before insulin is initiated)

• Insulin pens facilitate the initiation and acceptance of insulin

• PCP and/or nurse educator should provide ongoing, enthusiastic support, advice, and trouble-shooting

PCP=primary care provider.
Summary

• Many patients on basal insulin therapy will ultimately require treatment intensification

• Current options include:
  – Addition of mealtime control via addition of prandial insulin, leading to multiple daily insulin therapy
  – Switch to premix insulin
  – Add a DPP-4 inhibitor or a GLP-1 agonist

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

Insulin Therapies for T2DM

Thank You!