Safe and Effective Insulin Use (in Type 2 Diabetes)

Disclosures

**Advisor / Consultant**
- Merck
- BMS/AstraZeneca
- Sanofi/Regeneron
- Janssen
- TransTech Pharma
- Poxel

**Clinical Trial Steering Committees**
- Boehringer Ingelheim
- Lexicon
- Eisai

**Clinical Trial DSMB/DMCs**
- Novo Nordisk
- Intarcia

**Research Support**
- NIDDK
- NINDS
- Takeda*

* study drug & placebo

Human Pancreas
Human Islet

Insulin

Insulin Hexamer
Normal Secretory Pattern of Insulin

- **Prandial** Insulin ≈ 50%
- **Basal** Insulin ≈ 50%

Breakfast Lunch Dinner Sleep

Insulin Level

Absent Absent Insulin Secretion in T1DM

Insulin Secretion in T1DM Early-Stage Diabetes (< 5 years)

Absence in T1DM

Insulin Secretion in T2DM Early-Stage Diabetes (< 5 years)

Insulin Secretion in T2DM
When To Start Insulin in T2DM

- When hyperglycemia is severe, especially if catabolic features are present
  - When combination oral / non-insulin injectable agents become inadequate to control glucose
  - Unacceptable side effects of other agents
  - Patient wants more flexibility.
  - Patient with advanced hepatic or renal disease
  - Special circumstances (i.e. steroids, infection, pregnancy)
  - Patient with hyperglycemia in the hospital

Insulin

- Remains the most powerful & versatile tool we have to control blood glucose.
- Dosing potential and A1C reduction only limited by risk of hypoglycemia.
- Patients with type 2 diabetes are at lower risk for hypoglycemia than type 1 patients.
- Significant increase in types & varieties of insulin products over the past 10-15 years.

Insulin Overview

<table>
<thead>
<tr>
<th>Insulin Types</th>
<th>MOA</th>
<th>Actions</th>
<th>↓A1c</th>
<th>Benefits</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human NPH</td>
<td>Activates insulin receptors</td>
<td>Peripher al glucose disposal</td>
<td>Unlimited</td>
<td>Microvascular risk</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Human Regular</td>
<td></td>
<td>Hepatic glucose production</td>
<td></td>
<td>Universally effective</td>
<td>Weight gain</td>
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<tr>
<td>Human premix</td>
<td></td>
<td>Proteolysis</td>
<td></td>
<td></td>
<td>Mitogenic effects (?)</td>
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<tr>
<td>Glargine</td>
<td></td>
<td>Protein synthesis</td>
<td></td>
<td></td>
<td>Injectable</td>
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<tr>
<td>Glargine U-300</td>
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<td>Lipolysis</td>
<td></td>
<td></td>
<td>Training requirements</td>
</tr>
<tr>
<td>Detemir</td>
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<td>TG synthesis</td>
<td></td>
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<td>“Stigma”</td>
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<tr>
<td>Degludec*</td>
<td></td>
<td>Ketogenesis</td>
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<tr>
<td>Lispro</td>
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<td>Aspart</td>
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<tr>
<td>Glulisine</td>
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<tr>
<td>Analog premix</td>
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<td></td>
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<tr>
<td>Inhaled insulin</td>
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</table>

* not in US
The time course of action of any insulin may vary in different individuals, or at different times or different injection locations in the same individual. Due to such variation, the time periods described above should be used as general guidelines only.
Breakfast Lunch Dinner SLEEP

Insulin Level

“Basal Only” Insulin Therapy

Basal Insulin

Insulin Therapy

164 patients with baseline HbA1c ≥ 7.5% on diet, oral agents, or insulin; mealtime hyperglycemia persists after 3 months of treatment intensification.

Glucose (mg/dL)

Postprandial Hyperglycemia Persists After Basal Therapy

164 patients with baseline HbA1c ≥ 7.5% on diet, oral agents, or insulin; mealtime hyperglycemia persists after 3 months of treatment intensification.

A1C > 7% (n = 44)

A1C ≤ 7% (n = 120)


“Basal Only” Insulin Therapy

Insulin Level

Hypo risk

Long-Acting Basal Insulin

0 2 4 6 8 10 12 14 16 18 20 22 24
**Basal - Bolus** Insulin Therapy

- **Basal** Insulin
  - Suppresses HGP between meals and overnight
  - Nearly constant levels throughout the day and night
  - ~ 50% of daily needs
  - Start at 0.2-0.3 U/kg/day (or 15-20 U)
  - Adjust based on FPG

- **Bolus** Insulin (mealtime or prandial)
  - Limits post-prandial hyperglycemia
  - Immediate rise and sharp peak at ~ 1 hour
  - ~ 10-20% of total daily insulin requirement at each meal
  - Start at 0.05 U/kg/meal (or 3-6 U AC)
  - Adjust based on 2hr-PG.

### Advanced Bolus Therapy

1. Dose adjusted by carbohydrate intake ('carb-counting'): e.g., 1 unit ∞ 15 g)

1. Adjust for pre-meal hyperglycemia (similar to a ‘sliding scale’): e.g., add 1-2 units for every 50mg/dl starting @150mg/dl.

1. Adjust by anticipated activity level after the meal (e.g., subtract 2-4 units for exercise or reduce dose by 25-50%).

**Premixed ('Biphasic') Insulin BID**

- Premixed insulin may be appropriate...
  - When basal/bolus cannot be used
  - For those with regular lifestyles, who eat similar amounts at similar times each day
  - Those who wish only 2 injections/day
Summary of Comparative T2DM Insulin Trials

1. Any insulin will lower glucose and HbA1c; the more injections and the higher the dose, generally the better the control.

2. All insulins result in some degree of weight gain and increase the risk of hypoglycemia.

3. In most studies, basal insulin analogues reduces the incidence of hypoglycemia vs. human insulins - but generally do not result in better overall glycemic control.

4. In most studies, rapid insulin analogues improve post-prandial glucose and are more convenient to use vs. regular insulin – but do not result in better overall glycemic control.

5. Adding prandial dosing (i.e., basal-bolus; premixed) will typically reduce HbA1c to a greater extent than basal-only, but at the expense of more weight gain and hypoglycemia.
**U-500 Insulin**

- Used when insulin needs >200-300 U/day
- 1 volumetric ‘unit’ (i.e. 0.01 ml) = 5 actual units
- Given BID-TID
- PK profile in-between Regular U-100 & NPH
- Lower dose by 20% when initiating
- Instructions must be very clear – dosed in tenths of mls instead of conventional ‘units’

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**Insulin Pens**

- Available for most insulin types
- Disposable
- 300 units (0.3 ml) per pen
- Sold in boxes of 5 pens
- More convenient
- More accurate
- Hurts less (31-32 gauge, 6-8 mm)
- Typically do not require refrigeration (<30 days)
- But more expensive (2X!)
Barriers to the Use of Insulin in T2DM

**Patient**
- Fear of needles
- Need of more intensive monitoring
- Need for greater regimentation of lifestyle
- Fear of hypoglycemia
- Fear of weight gain
- "My disease is getting worse"

**Physician**
- "Therapeutic Inertia"
- Patient training
- Risk of hypoglycemia
- Risk of weight gain
- ? Atherogenic
- ? Mitogenic

Strategies to Overcoming Barriers

- Frame the message positively
- Don’t ‘blame’ the patient.
- Avoid using insulin as a threat.
- Begin discussions about insulin early on in disease course
- Address cultural taboos, erroneous beliefs, social hang-ups.
- Begin with simplest regimen possible
- Use insulin strategies that minimize hypo risk.
- Use tools to facilitate patient adherence.
- Collaborate with CDEs, pharmacists, etc.

Safe and Effective Insulin Use (in Type 1 Diabetes)

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**Unique Aspects of T1DM (vs. T2DM)**

- Absolute insulin deficiency (after 1-2 years)
- Except for non-adherent patients, the only credible treatment involves either...
  - Basal-bolus insulin therapy OR
  - Continuous subcutaneous insulin infusion (CSII, insulin pump)
- Usually lean, but can be overweight or even obese
- Tend to be insulin sensitive (total daily dose of insulin is typically 0.5-0.7 U/kg/day (in T2DM, typically 0.5-1.0+ U/kg/day)
- Glycemic control tends to be more labile than in T2DM
- Ketosis-prone
- Other autoimmune disease frequently coexist (thyroid, etc.)

**Insulin Delivery Method in T1DM**

- **Injections/Pens**
  - <6: 67%
  - 6-<13: 53%
  - 13-<18: 50%
  - 18-<26: 48%
  - 26-<50: 39%
  - ≥50: 39%

- **Pump**
  - <6: 33%
  - 6-<13: 47%
  - 13-<18: 50%
  - 18-<26: 52%
  - 26-<50: 61%
  - ≥50: 59%
**Insulin Pumps**

- Mainly used in Type 1 DMs
- SubQ catheter changed q 2-3 days
- Variable basal rates pre-programmed
- Boluses triggered by patient (can enter carb grams into pump)
- One type of insulin (rapid analogue)
- $6000-7000 + $10-15/day supply costs
- Modestly better control than with multiple daily injections (MDI) in some - but not all - studies
- Rarely used in Type 2 DMs
Continuous Glucose Monitor Use in T1DM

<table>
<thead>
<tr>
<th>Age</th>
<th>Use (%)</th>
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<tbody>
<tr>
<td>&lt;6</td>
<td>3%</td>
</tr>
<tr>
<td>6–13</td>
<td>3%</td>
</tr>
<tr>
<td>13–18</td>
<td>2%</td>
</tr>
<tr>
<td>18–26</td>
<td>3%</td>
</tr>
<tr>
<td>26–50</td>
<td>14%</td>
</tr>
<tr>
<td>≥50</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Reads interstitial glucose continuously
- Reports values q 5 min.
- Graphic display for trends
- Download capacities
- Alarm features
- Sensor changed q 3 to 7 days

Initial CGM Tracing in a Man with T1DM
Follow-up CGM Tracing 1 Week Later

Sensor Data (mg/dL)

RT-CGM
Control

8 - 14 yrs 15 - 24 yrs > 25 yrs

p=0.29  p=0.52  p<0.001


CGM Improved Glycemic Control Mainly in Adults
CGM Use

- 0% CGM Use
- 20% CGM Use
- 40% CGM Use
- 60% CGM Use
- 80% CGM Use

Age
≥ 25 Age 15-24 Age 8-14

Percentage of subjects
<4.0 days/week
4.0-<6.0 days/week
≥ 6.0 days/week

Change in glycated hemoglobin


STAR 3 Sensor-Augmented Pump Trial

- The SAP group achieved a greater A1C reduction vs. MDI at 3 months and sustained it over 12 months

A1C Reduction for SAP and MDI Groups

<table>
<thead>
<tr>
<th>Months</th>
<th>A1C Reduction for SAP</th>
<th>A1C Reduction for MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.5%</td>
<td>8.0%</td>
</tr>
<tr>
<td>3</td>
<td>8.0%</td>
<td>7.5%</td>
</tr>
<tr>
<td>6</td>
<td>8.0%</td>
<td>7.5%</td>
</tr>
<tr>
<td>9</td>
<td>8.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>12</td>
<td>8.1%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Values are means ± SE. Comparisons between SAP group and MDI group are significant for each time period (P<0.001).


A1C Correlates with Increased Sensor Use

- The majority of patients used sensors ≥61% of the time
- Patients who used sensors ≥81% of the time reduced their mean A1C by 1.2% at 1 year vs. baseline

Values are the difference between the means ± SE. p=0.003 for association between sensor use and A1C reduction at 1 year. Only 7 participants had sensor use of 20% or less, with a change in A1C of -0.43 at 1 year vs. baseline.

1. Many patients with T2DM will require insulin therapy as their endogenous beta-cell function fails and they no longer respond to oral or other injectable agents.

2. There are many insulin types available, the most popular being genetically engineered analogues that mimic normal insulin dynamics (basal, meal-time).

3. Most T2DM patients will do fine for years, however, on basal insulin alone.

4. When more advanced therapies are needed, ‘basal-plus’, ‘basal-bolus’, and pre-mixed insulins are reasonable strategies, but require additional effort from the patient.

5. In contrast, T1DM patients are severely insulin deficient from diagnosis, and eventually produce no insulin. They are optimally treated with basal-bolus or an insulin pump.

6. Generally, the more complex the regimen, the better the control. In selecting the optimal strategy, consider the patient’s capacities for testing, dose calculations, & administration.

7. Importantly, determining the best A1c target for your patient will strongly inform your decision about which strategy to employ.

8. CGM is an important new tool to help guide patients on intensive insulin therapy.
Emerging Insulin Formulations & Delivery Systems

- "Bio-similars" (i.e., lower cost generics)
- Inhaled insulins
- Ultra-Long Acting Insulins (Degludec, LY2605541 [PEGylated Lispro])
- Ultra-concentrated insulins (U-200 Degludec, U-300 Glargine)
- Ultra-Fast Acting Insulins (other monomeric recombinants, hyaluronidase accelerated, EDTA-potentiated)
- Liver-selective Insulins
- “Smart Insulins”
- Patch-pumps, microneedles, heated patches
- Implantable pumps
- ‘Artificial pancreas’ (fully integrated pump-sensor)