Before and After

One of the first patients to ever receive insulin therapy
Key Messages: Insulin

- Insulin is highly effective but can be perceived as being a challenge for both patients and physicians
- Basal-bolus insulin regimens require more injections but provide better insulin coverage and better glycemic control
- Insulin regimens and insulin dosing must be adjusted for each individual patient

Key Messages: Monitoring

- The use of glycemic monitoring patterns is key to making insulin dose adjustments
- Monitoring schedules should be individualized for each patient to gather the specific information you need to manage that person’s treatment program
Some Common Terms

- **Basal insulin**: The background insulin present at all times throughout the day and night. Exogenously administered long-acting insulin is used to replicate this pattern.
- **Prandial insulin**: Insulin that acts during and after a meal or snack to prevent or minimize a postmeal rise in blood glucose.
- **Bolus insulin**: Short-acting insulin that is used to provide an increased level of insulin for a short period, usually used as prandial coverage.

Some Common Terms

- **Correction insulin**: Bolus insulin administered to lower a high blood glucose level.
- **Split-mix insulin**: Combination of short- and intermediate-acting insulin used to cover both fasting and prandial insulin needs.
- **Fixed-mixture insulin**: Insulin that is prepared by the manufacturer, premixed in a vial or pen, at a fixed ratio of rapid-acting or regular insulin to intermediate insulin.

Physiologic Insulin Secretion: 24-hour Profile

- **Insulin** (µU/mL)
  - **Basal insulin**
- **Glucose** (mg/dL)
  - **Basal glucose**
Possible Evolution Pathways of an Insulin Treatment Program for Type 1 DM

Diagnosis of type 1 diabetes

Full-day "conventional" coverage
- BID premixed insulin
- Custom-designed "split mix" variant

Full physiologic insulin coverage
- Bedtime long-acting analog plus
- Premeal rapid-acting insulin

Possible Evolution Pathways of an Insulin Treatment Program for Type 2 DM

PM insulin treatment for basal coverage

Full-day "conventional" coverage
- BID premixed insulin
- Custom-designed "split mix" variant

Full physiologic insulin coverage:
- Bedtime long-acting analog plus
- Premeal rapid-acting insulin

Aggressive Control of Diabetes: Goals of Treatment

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>70–130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>2-hour postprandial glucose (mg/dL)</td>
<td>&lt;180</td>
<td>&lt;140</td>
</tr>
</tbody>
</table>

A1C is “gold standard” measure of diabetes control over previous 2–3 months

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Suggested Sequence for Assessment of Glycemic Patterns

- Fasting value
- General premeal and bedtime values and trends throughout the day
- Postprandial values – absolute levels
- Relative change, pre- to postprandial glycemic levels
  ➔ Also, continually monitor nocturnal glycemia

Relative Contribution of FPG and PPG to Overall Hyperglycemia Depending on A1C Quintiles


Defining Ideal Insulin Therapy

- Insulin therapy should provide:
  - Predictable kinetics
  - Reproducible kinetics
  - Precise dosing (narrow therapeutic window)
  - Constancy of absorption from site to site
  - Painless administration
  - Potential for both basal and bolus kinetics

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Current Limitations of Insulin Delivery

- Lack of "closed" feedback loop to control dosing
- Requirement for parenteral administration, or...
- Discontinued Inhaled insulin had min. adjustments of 2–3 units
- Lack of portal administration
- Poor reproducibility, site-to-site and day-to-day
- Limitations in true basal or true bolus kinetics
- Empiric therapy adjusted for each patient
- Need for multiple injections/doses or continuous infusion for very good to excellent glycemic control

Variability in Daily Glucose Values for People Using Insulin Therapy

- Food quantity
- Food types (glycemic index)
- Activity
- Stress – psychological and physical
- Hypoglycemia and rebound
- GI absorption rate
- Insulin absorption rate

Action Profiles of Injectable Insulins

- Aspart, glulisine, lispro 4–6 hours
- Regular 6–8 hours
- NPH 12–20 hours
- Basal insulin glargine, detemir
Sequential Insulin Strategies in T2DM


Desired Characteristics of Replacement Basal Insulin

- Mimics natural pancreatic basal insulin secretory pattern
- No distinct peak effect
- Continued effect over 24 hours
- Minimizes risk of nocturnal hypoglycemia
- Administered once daily for optimal patient adherence
- Reliable absorption pattern
Basal Insulins (Glargine & Detemir): Long-Acting Insulin Analogues

- Compared to NPH:
  - Smooth continuous injection site release, flat action profile
  - Longer duration of action, up to 24 hours
  - Lowers FPG with less nocturnal hypoglycemia than NPH
- Equal absorption: arm, leg, or abdominal sites
- Various and conflicting studies have suggested there may or may not be some differences in action between the two, but ultimately clinical need of individual patients will dictate actual usage
  - Once vs. twice daily
  - Dose differences when switching basal insulins??
  - PM vs. AM use

ORIGIN Trial:

- 6-year RCT
- Insulin glargine vs. standard care
- Eligibility:
  - pre-diabetes or early type 2 diabetes
  - high CV risk
- 12,500 participants worldwide
- 6,264 randomized to glargine, titrated to achieve fasting normoglycemia.
- Composite Endpoints:
  - 1st CV death, non-fatal MI, or non-fatal stroke
  - 2nd Composite of CV death, non-fatal MI, non-fatal stroke, revascularization procedure, or hospitalization for heart failure.

The ORIGIN Trial Investigators, Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. NEJM; nejm.org 10.1056/nejmoa1203858

ORIGIN Trial: Key Messages

- No increased or decreased risk of CVD with early use of glargine (basal) insulin
- No increased risk of cancer with use of glargine
- Insulin can slightly increase the risk of hypoglycemia and weight gain
- Early use of insulin may have a beneficial impact on short-term loss of β-cell function. Long term impact is unknown; further study is needed

Adapted from: The ORIGIN Trial Investigators, Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. NEJM; nejm.org 10.1056/nejmoa1203858
At least 70% of subjects in each group achieved A1C ≤ 7%.


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NPH = neutral protamine Hagedorn.


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NPH = neutral protamine Hagedorn.


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Hypoglycemia Rates with Detemir vs NPH

Overall

Hypoglycemic Events/
Patient/Year

Major

0.001

0.001

Detemir + OAD

NPH + OAD

Adapted from Hermansen K et al. Diabetes Care. 2006;29:1269-1274.

Detemir and Glargine Cause Less Hypoglycemia Than NPH (Meta-Analysis)

Clinical Features of Rapid-Acting Analogues: Aspart, Glulisine, and Lispro

- Administration immediately prior to meals
- Faster onset of action matches timing of carbohydrate absorption
- Limits postprandial hyperglycemic peaks
- Shorter duration of activity
  - Reduced risk of late postprandial hypoglycemia
  - Frequently can have late postprandial hyperglycemia
- Glulisine can be given after meals if needed *

* Garg S et al. American Diabetes Association 64th Scientific Sessions; June 4-8, 2004; Orlando, FL; Abstract 530-P.
Adding Bolus Insulin

- Consider adding prandial (mealtime) insulin in about 3-6 months if:
  - A1C is elevated
  - Significant postprandial glucose excursions occur (>180 mg/dl)
  - There are significant drops in glucose between meals or overnight as the basal insulin dose is increased.
  - Likely needed if the total daily insulin dose exceeds 0.5 units/kg/day.


Adding Bolus Insulin

- Add prandial insulin before meal with largest glucose excursion (>180 mg/dl), which is typically the meal with the largest CHO content.
- Other meals can be covered subsequently.
- Alternatively start with coverage of all three meals at once.
- TDD: 0.3 – 0.5 U/kg; 50/50 basal/prandial
- Antihyperglycemic medications:
  - Generally, stop insulin secretagogues (SU, DPP-4 inhibitors, glinides)
  - Reduce or stop TZD’s

Exenatide plus Glargine: Change in Glucose Levels over 30 weeks


* p < 0.001 for between-group diff.
† p < 0.010 for between-group diff.

Liraglutide plus Metformin, with and without Detemir: Self-Monitoring Glucose Profiles


P = 0.0141

Role for Premixed Insulin

- **Advantages**
  - Easy (no mixing, single product, pens avail.)
  - Covers insulin requirements through most of day
- **Disadvantages**
  - Not physiologic
  - Less Flexible: requires consistent meal/exercise pattern, and cannot titrate individual insulins unless custom mixed insulin is used
  - ↑ Nocturnal hypoglycemia (presupper NPH)
  - ↑ Fasting hyperglycemia (presupper NPH wears off)
  - Higher A1C (realistic goal of ≤8%)

Premixed vs Basal-Bolus Insulin Regimen

Cumulative percentage of patients achieving specific target A1C values after 24 weeks of treatment with PPT or BBT. *P < 0.05.

Rate of Hypoglycemic Event Occurrence

<table>
<thead>
<tr>
<th>Description of Event (Adjusted Rate)</th>
<th>Insulin Glargine/Insulin Glulisine-3 (Events/Patient-Year) (SE) (n=194)</th>
<th>Insulin Glargine/Insulin Glulisine-1 (Events/Patient-Year) (SE) (n=194)</th>
<th>Premixed Insulin Aspart 70/30 (Events/Patient-Year) (SE) (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMBG &lt;70 mg/dL (with symptoms)</td>
<td>7.31 (0.99)*</td>
<td>7.11 (0.99)*</td>
<td>12.33 (1.46)</td>
</tr>
<tr>
<td>SMBG &lt;50 mg/dL (with symptoms)</td>
<td>0.80 (0.15)*</td>
<td>0.80 (0.15)*</td>
<td>1.81 (0.34)</td>
</tr>
<tr>
<td>SMBG &lt;36 mg/dL</td>
<td>0.15 (0.03)</td>
<td>0.10 (0.03)*</td>
<td>0.32 (0.08)</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0.17 (0.05)</td>
<td>0.10 (0.03)*</td>
<td>0.31 (0.08)</td>
</tr>
</tbody>
</table>

Inulin glargine/insulin glulisine-3 and insulin glargine/insulin glulisine-1 groups had lower hypoglycemic event rates than premixed insulin aspart 70/30 group.


Multihormone Regulation of Glucose: Amylin and Insulin

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Insulin and Amylin Co-secreted

Koda et al, Diabetes. 1995; 44 (s1): 238A.

Amylin is Deficient in Diabetes

Fineman et al, Diabetologia. 1996; 39 (s1): A147.
Insulin data on file.

Pramlintide + Insulin: Effect on Postprandial Glucose Concentration

Kotternier et al, Diabetologia. 1996.
Basal-Bolus Insulin Treatment with Injectable Insulin Analogues

B=breakfast; L=lunch; D=dinner

Examples of “Pen” Insulin Delivery Devices
**Sample Insulin Adjustment Algorithm: Pre-Meal Prandial and Bedtime Basal Insulin**

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Supper</th>
<th>Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>51 - 100</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>101 - 150</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>151 - 200</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>201 - 250</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>251 - 300</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>301 - 400</td>
<td>12</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>OVER 400</td>
<td>14</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

* Treat with food first, retest, then use algorithmic dose.

**EXAMPLE: Converting from Intermediate Insulin to Basal Insulin**

- **Currently using:**
  - Prebreakfast: 8 Regular + 22 NPH
  - Presupper: 8 Regular
  - Bedtime: 12 NPH

- **Total Daily Dose of 50 units**

- **Total daily dose for basal & rapid acting insulin program with 20% reduction = 40 units**
  - Give about \( \frac{1}{3} - \frac{1}{2} \) as basal insulin (glargine or detemir)
  - Give the remainder as rapid-acting insulin:
    - 40% of that at breakfast, 30% at lunch, and 30% at supper

- **The starting base dose (pre-adjustments) would be:**

  **Ultimately, these doses may be adapted to a carbohydrate counting program**

**Carbohydrate Counting**

- Carbohydrate is the food component that most affects blood glucose
- This system tracks the grams of carbohydrate consumed for the purposes of adjusting insulin doses
- The more carbohydrate consumed, the more insulin taken
- Particularly useful for people treated with variable pre-meal doses of rapid-acting insulin
- Requires pre- and postprandial glucose checks
Glucose Monitoring

- No one should perform a single glucose test unless he or she knows what to do with the result!
- There is a difference between glucose checking (testing) and glucose monitoring
- Record-keeping is of crucial importance to the monitoring process

Insulin Pumps

External Insulin Pump Using Rapid Acting Insulin

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**Patch Pumps for Type 2 Diabetes**

**CGM Devices**

**Continuous Glucose Monitoring Provides a More Comprehensive Picture of the Patterns**

Fingerstick blood glucoses (Type 1)
Factors Influencing Therapeutic Choices

- Medical needs and treatment goals
  - A1C level and distance from target
  - Postprandial glycemia
- Safety
- Need for flexibility in treatment program
- Patient issues with respect to insulin use
  - Intellect and judgment
  - Psychosocial and cultural considerations
  - Physical capabilities and limitations
  - Other medical conditions and issues relating to use of other non-insulin medications

A Stepwise Perspective on Insulin Treatment

- Ability to identify people for whom insulin is indicated and discuss this need with them
- Capability or identified referral resources to oversee insulin treatment initiation and support
- Ability to teach insulin use:
  - Techniques
  - Knowledge and Skills for self-management
  - Spectrum of programs, from basal to pumps
- Ability to identify people for whom the current program is inadequate and advancement of therapy is indicated
- Troubleshooting
- Referral management

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Take-Away Messages

- Insulin is highly effective but can pose a challenge for both patients and physicians
- Basal-bolus insulin regimens require more injections but provide better insulin coverage and better glycemic control
- Insulin regimens and insulin dosing must be adjusted for each individual patient
- Monitoring of glycemic patterns is a key tool to be used to guide therapeutic decisions

“Insulin is a remedy for the wise and not the foolish, be they patients or doctors. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more brains.”

Elliott P. Joslin, MD, ScD
Diabetic Manual, 1959

Case Vignette # 1
History
- 55-year-old white man
- Type 2 diabetes for 15 years
- Initially treated with lifestyle changes, then multiple antidiabetes medications (Su, Met, TZD)
- Insulin started 5 years ago
  - Basal insulin, once daily at bedtime, titrated upward
  - Sulfonylurea stopped, Rx metformin, TZD
- Currently: Symptoms of hypoglycemia pre-lunch, yet A1C was 8.2%

Medications & Other Data
- BMI: 33
- Basal insulin: 50 units daily at bedtime
- Metformin extended release 2000 mg daily
- Pioglitazone 30 mg daily
- Recent A1C 8.2%

Self-Monitoring Data

<table>
<thead>
<tr>
<th>Mon</th>
<th>127</th>
<th>255</th>
<th>89</th>
<th>93</th>
<th>301</th>
<th>261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tues</td>
<td>95</td>
<td>143</td>
<td>272</td>
<td>226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wed</td>
<td>141</td>
<td>274</td>
<td>137</td>
<td>72</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>Thur</td>
<td>82</td>
<td>130</td>
<td>69</td>
<td>165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fri</td>
<td>103</td>
<td>274</td>
<td>133</td>
<td>69</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Sat</td>
<td>143</td>
<td>152</td>
<td>134</td>
<td>276</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Sun</td>
<td>135</td>
<td>72</td>
<td>84</td>
<td>179</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Basal: 50 units, Metformin, Pioglitazone  A1C 8.2%
Case Vignette # 2

History
- 41-year-old white man, accompanied by wife
- Type 1 diabetes since age 25
- A1C range: 7% to 8.3%
- Weight stable
- Three severe hypoglycemic events in those years
- Married since age 23, two teenaged children
- Works in construction/renovation
  - Does demolition, framing, finish carpentry

History (cont.)
- Often has to reschedule appts. due to work
- Last appt. 1 year ago, wife was not present
- Last appointment instructions:
  - Increase basal 22 → 24 units
  - Further increases based on FBS
  - Could reduce premeal doses as needed
  - Mail results to CDE for review
- He actually only increased the basal to 24 units. No other actions due to fear of hypoglycemia.
- Current A1C: 7.5%
Insulin Doses

- **Long-acting**
  - 24 units of basal insulin daily at bedtime

- **Rapid-acting insulin: carbohydrate ratios**
  - Breakfast: 1:10 (for him, about 6 units)
  - Lunch: 1:10 (for him, about 8 units)
  - Supper: 1:10 (for him, about 14 units)

- **Sensitivity (correction) factor**
  - 25 points per unit, targeting 140 mg/dL

Self-Monitoring Data

<table>
<thead>
<tr>
<th>Mon</th>
<th>70</th>
<th>143</th>
<th>133</th>
<th>468</th>
<th>4-9-14-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tues</td>
<td>267</td>
<td>261</td>
<td>376</td>
<td>42</td>
<td>11-13-26-24</td>
</tr>
<tr>
<td>Wed</td>
<td>412</td>
<td>221</td>
<td>172</td>
<td>342</td>
<td>11-11-17-24</td>
</tr>
<tr>
<td>Thur</td>
<td>433</td>
<td>332</td>
<td>73</td>
<td>196</td>
<td>17-15-25-24</td>
</tr>
<tr>
<td>Fri</td>
<td>81</td>
<td>253</td>
<td>417</td>
<td>278</td>
<td>5-14-25-24</td>
</tr>
<tr>
<td>Sat</td>
<td>179</td>
<td>188</td>
<td>208</td>
<td>419</td>
<td>8-10-16-24</td>
</tr>
<tr>
<td>Sun</td>
<td>312</td>
<td>204</td>
<td>311</td>
<td>376</td>
<td>13-11-21-24</td>
</tr>
</tbody>
</table>

Basal: 24 units; B 1:10; L 1:10; S 1:10; Correction 25-9140

Additional Events

- **Patient’s wife spoke up and expressed her concern, adding a few points:**
  - Patient occasionally forgets to take his injections before meals, and instead takes them afterward.
  - He goes to parties/sports bars and nibbles for hours, not sure how to adjust insulin.
  - Unsure how to adjust for sports
  - More frequent moderate night reactions

- **Patient recreated notes on the last week’s data sheet**
Self-Monitoring Data:

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Post-breakfast</th>
<th>Pre-Lunch</th>
<th>Post-Lunch</th>
<th>Pre-supper</th>
<th>Post-supper</th>
<th>Bed-time</th>
<th>Comment and actual insulin doses taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>70</td>
<td>143</td>
<td>133</td>
<td>468</td>
<td></td>
<td></td>
<td></td>
<td>Took supper insulin 1 hr after</td>
</tr>
<tr>
<td>Tues</td>
<td>267</td>
<td>261</td>
<td>376</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td>Eats Basketball, med, nite low</td>
</tr>
<tr>
<td>Wed</td>
<td>402</td>
<td>221</td>
<td>172</td>
<td>342</td>
<td></td>
<td></td>
<td></td>
<td>Evening sports bar with friends</td>
</tr>
<tr>
<td>Thur</td>
<td>421</td>
<td>312</td>
<td>73</td>
<td>386</td>
<td>54</td>
<td></td>
<td></td>
<td>Forgot presupper insulin, took after supper</td>
</tr>
<tr>
<td>Fri</td>
<td>81</td>
<td>203</td>
<td>417</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
<td>Evening, went to bed early</td>
</tr>
<tr>
<td>Sat</td>
<td>179</td>
<td>186</td>
<td>258</td>
<td>419</td>
<td></td>
<td></td>
<td></td>
<td>Evening party, ate more</td>
</tr>
<tr>
<td>Sun</td>
<td>312</td>
<td>204</td>
<td>313</td>
<td>376</td>
<td></td>
<td></td>
<td></td>
<td>TV sports all afternoon</td>
</tr>
</tbody>
</table>

Basal: 24 units; B 1:10; L 1:10; S 1:10; Correction 25-p-140

Key Patterns and Events:
- Forgetting premeal insulin; taking it after the meal
- Evening basketball
- Evening sports bar
- Evening party with prolonged nibbling before main dinner
- Sedentary day

Additional Scenarios

You can find a series of additional Rapid Pattern Review exercises IN THE Insulin Therapy Clinical Center on JPEC

www.jpec.joslin.org

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