Insulin Replacement Therapy: Individualizing the Design and Management

Before and After
One of the first patients to ever receive insulin therapy

Key Messages – Insulin Therapy
- Insulin is a highly effective diabetes treatment
- Individualize treatment goals and regimens
  - Consider pathophysiology, self-care, and safety
- Use pattern assessment to adjust dosing
- Consider basal-bolus insulin therapy when conventional insulin programs are ineffective
- Recognize and address patient, provider, and practice-level barriers to insulin therapy
- Some treatment services should be provided in the practice, others obtained by consultation
Aggressive Control of Diabetes: Goals of Treatment

<table>
<thead>
<tr>
<th></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</td>
<td>70–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-hour postprandial</td>
<td>&lt; 180</td>
<td>&lt; 140</td>
</tr>
<tr>
<td>glucose (mg/dL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


ACCORD & Advance

- ACCORD: more unexpected deaths in the intensive glycemic treatment group, unrelated hypoglycemia, specific drugs Rx
- Advance: intensive glucose control significantly reduces risk of DM vascular complications; VADT: similar findings
- Implications: no change in guidelines (early aggressive control likely still a benefit)
- However, individualize treatment goals, and avoid “tight” control where it might be dangerous (CAD, elderly)


Insulin Therapy in Type 1 Diabetes

- ADA
  - Intensive therapy (3+ injections/day or pump) is a “key part of…better outcomes”
  - Base prandial insulin on food intake, blood glucose, planned activity
  - Consider rapid- and long-acting insulin analogs
- AACE
  - No formal RCT of physiologic vs nonphysiologic insulin regimens
  - Insulin analogs reduce hypoglycemia, do not affect A1C when compared to regular insulin

Endocrine Practice. 2011;17(Suppl 2):1-53. (AACE Guideline)
When to Start Insulin for Type 2 Diabetes

- High glucose levels despite maximal antidiabetes medication therapy
- Unintentional weight loss
- Low C-peptide
- Very high blood glucose levels at diagnosis (glucose toxicity)
- At start of pregnancy
- In hospitalized patients with diabetes
- Consider starting early:
  - To overcome glucose toxicity in severe hyperglycemia
  - To achieve and maintain glycemic control


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


HEART2D

**HEART2D**

Percentage of HEART2D patients aged >65.7 years not experiencing a first CV event (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome) vs days in the trial by insulin strategy.


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**Meal-Induced Increases in Inflammatory Markers Are Attenuated by Prandial vs Basal Insulin vs Prandial Alone in People With Type 2 Diabetes**

Black bars with dotted line trend:
- Insulin lispro mix (50/50) before meals + metformin
- Prandial + Basal

White bars with solid line trend:
- Insulin glargine at bedtime + metformin
- Basal only


---

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**ORIGIN Trial**

- 6-year RCT
- Insulin glargine vs standard care
- Eligibility:
  - Prediabetes or early type 2 diabetes
  - High CV risk
- 12,500 participants worldwide
- 6,264 randomized to glargine, titrated to achieve fasting normoglycemia
- Composite endpoints:
  1. CV death, nonfatal MI, or nonfatal stroke
  2. Composite of CV death, nonfatal MI, nonfatal stroke, revascularization procedure, or hospitalization for heart failure


**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.


**Insulin Use: Clinical Perspectives**

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Clinical Inertia: "Failure to advance therapy when required"

Percentage of Subjects Advancing When A1C > 8%

- Diet: 66.6%
- Sulfonylurea: 35.3%
- Metformin: 44.6%
- Combination: 18.6%

At insulin initiation, the average patient had:
- 5 years with A1C > 8%
- 10 years with A1C > 7%


Key Parameters Reflecting Glycemic Control

- A1C
- Preprandial glucose levels
- Postprandial glucose levels

Glucose Monitoring for Regimen Adjustment

- Monitoring is important in adjusting insulin
- Individualize monitoring programs: patients must use results to act or call for help!!
- Glucose checking ≠ glucose monitoring
- Record-keeping is crucial:
  - Date and time
  - Glucose values
  - Insulin dose
  - Food and/or carbohydrate intake
  - Activity and other factors impacting glycemic patterns

Physiologic Insulin Secretion

Daytime Meals

Breakfast | Lunch | Supper | Snack

Insulin Replacement Therapy: Individualizing the Design and Management

Action Profiles of Injectable Insulins

Plasma insulin Levels

Hours

Rapid (Aspart, Glulisine, Lispro)

Short (Regular)

Intermediate (NPH)

Basal (Detemir)

Basal (Glargine)

Insulin Titration Strategies in T2DM

Approach to the Initiation of Basal Insulin

- Initiate basal insulin at a relatively low dose:
  - Bedtime or AM basal insulin analog (glargine or detemir)
  - Use of NPH is an alternative
  - 0.1–0.2 Units/kg/day or 10 units total initially (0.2–0.3 U/kg if initial A1C is > 8%)

- Recommended basal insulin titration every 2–3 days
  - ↑ 1 Unit if fasting glucose is 110–139 mg/dL
  - ↑ 2 Units if fasting glucose is 140–180 mg/dL
  - ↑ 4 Units if fasting glucose > 180 mg/dL
  - If hypoglycemia or FPG < 70 mg/dL
    - Reduce basal ins. by 4 Units or 10–20%, whichever is greater
    - FPG < 40 mg/dL: reduce dose by 20–40%


Addition of Basal Insulin or NPH to Oral Therapy: Treat-to-Target Trial
756 Patients With Type 2 Diabetes on 1 or 2 Oral Agents

PG = plasma glucose

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

Favors Detemir/Glargine Favors NPH
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 TZDs


Fewer Nocturnal Hypoglycemic Events in Patients Treated With Aspart vs Regular Human Insulin

Data on file, Novo Nordisk Inc.

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Exenatide Plus Glargine: Change in Glucose Levels Over 30 Weeks

- Glargine + Exenatide, baseline
- Glargine + Placebo, baseline
- Glargine + Exenatide, 30 wk
- Glargine + Placebo, 30 wk


Liraglutide Plus Metformin, With and Without Detemir: Self-Monitoring Glucose Profiles

- Liraglutide + Detemir, baseline
- Liraglutide Alone, baseline
- Liraglutide + Detemir, 26 wk
- Liraglutide Alone, 26 wk


Role for Premixed Insulin

- **Advantages**
  - Easy (no mixing, single product, pens available)
  - Covers insulin requirements through most of day
- **Disadvantages**
  - Not physiologic
  - Less flexible: requires consistent meal and 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**

**Overall Reduction in A1C**

<table>
<thead>
<tr>
<th>Change in A1C (%)</th>
<th>BBT</th>
<th>PPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.09%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**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.

**Reduction in A1C by Key Intervals**

<table>
<thead>
<tr>
<th>Description of Event</th>
<th>(Adjusted Rate)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SMBG &lt; 70 mg/dL (with symptoms)</td>
<td>7.23 (0.50)b</td>
<td>7.11 (0.50)b</td>
</tr>
<tr>
<td>SMBG &lt; 50 mg/dL (with symptoms)</td>
<td>0.89 (0.15)b</td>
<td>0.83 (0.15)b</td>
</tr>
<tr>
<td>SMBG &lt; 36 mg/dL</td>
<td>0.15 (0.03)</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0.17 (0.05)</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>Serious hypoglycemia</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

a P < 0.01 vs premixed insulin aspart 70/30

b P ≤ 0.001 vs premixed insulin aspart 70/30

c Hypoglycemic events requiring assistance and either BG <36 mg/dL or prompt response to countermeasures

d Hypoglycemia with coma/loss of consciousness or seizure/convulsion.

N/A = not applicable; SMBG = self-monitored blood glucose.

Riddle et al. ADA Scientific Sessions 2011.
**Insulin Therapy: Indications for “Basal-Bolus” Treatment**

- Significant insulinopenia
- Instability of glucose patterns (usually the result of significant insulinopenia)
- Difficulty with hypoglycemia
- Lifestyle needs
- Achieving therapeutic goals
- Weight loss

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**Sample Insulin Adjustment Algorithm: Premeal Rapid-Acting and Bedtime Basal Insulin**

An option for determining premeal insulin doses if carbohydrate counting is not possible

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Supper</th>
<th>Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 70*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>71 – 100</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>101 – 150</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>151 – 200</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>201 – 250</td>
<td>6</td>
<td>9</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>251 – 300</td>
<td>7</td>
<td>10</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>301 – 400</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>OVER 400</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td>—</td>
</tr>
</tbody>
</table>

Basal Insulin: 20

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

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**Carbohydrate Counting: Summarized**

- Carbohydrate is the food component that most affects blood glucose
- Tracks grams of carbohydrate consumed to adjust insulin doses
- The more carbohydrate consumed, the more insulin taken
- Particularly useful for people treated with variable premeal doses of rapid-acting insulin
- Requires pre- and postprandial glucose checks
- For more information, see: [https://www.joslin.org/info/Carbohydrate_Counting_101.html](https://www.joslin.org/info/Carbohydrate_Counting_101.html)
Examples of “Pen” Insulin Delivery Devices

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

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Joslin Diabetes Center
Joslin Diabetes Forum 2013: The Impact of Comorbidities on Glucose Control
Insulin Replacement Therapy: Individualizing the Design and Management

Continuous Glucose Monitoring in Older People

<table>
<thead>
<tr>
<th>CGM</th>
<th>A1C 8-9% n = 14</th>
<th>A1C &gt;9% n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Sex (female) (%)</td>
<td>64.29</td>
<td>61.54</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>19.7</td>
<td>18.9</td>
</tr>
<tr>
<td>At least 1 hypo episode/3 days (%)</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>Type 2 (%)</td>
<td>62</td>
<td>85</td>
</tr>
<tr>
<td>On insulin (%)</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>Cognitive dysfunction (%)</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Falls</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>Fear of falls (%)</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Lives alone (%)</td>
<td>21</td>
<td>8</td>
</tr>
</tbody>
</table>


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Continuous Glucose Monitoring in Older People

<table>
<thead>
<tr>
<th>All Patients with Hypoglycemia</th>
<th>A1C 8–9%</th>
<th>A1C &gt;9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 15</td>
<td>n = 9</td>
<td>n = 6</td>
</tr>
<tr>
<td>Average hypo episodes/pt</td>
<td>5.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean duration (hours)</td>
<td>4.7</td>
<td>2.3</td>
</tr>
<tr>
<td>No. pts with nocturnal episodes</td>
<td>100 %</td>
<td>50 %</td>
</tr>
<tr>
<td>Mean duration of nocturnal episodes (hours)</td>
<td>2.39</td>
<td>3.03</td>
</tr>
<tr>
<td>Number of episodes not recognized by fingerstick or symptoms/pt</td>
<td>5.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Cognitive dysfunction (%)</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>No. of pts with falls in past 6 months (%)</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>No. of pts with fear of falls (%)</td>
<td>38</td>
<td>83</td>
</tr>
<tr>
<td>No. of pts on insulin (%)</td>
<td>88.9</td>
<td>100</td>
</tr>
</tbody>
</table>


A Stepwise Perspective on Insulin Treatment: Office Practice Capabilities

- 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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- Troubleshooting
- Referral management
Take-Away Messages

- Treatment goals, program design, and monitoring recommendations must be individualized
- Monitoring of glycemic patterns is a key tool to guide therapeutic decisions
- Basal-bolus regimens require more injections but provide better insulin coverage and glycemic control
- Patient, provider, and practice systems barriers to insulin therapy must be recognized and addressed
- Self-assess office capabilities in the context of insulin treatment support

“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