“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*

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**Before and After**

One of the first patients to ever receive insulin therapy

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Insulin is a highly effective treatment for diabetes, but can pose design and treatment challenges for patients, physicians, and diabetes educators. Treatment goals, and the resulting insulin regimens and insulin dosing, must be individualized. Basal-bolus insulin regimens require more injections, but provide better glycemic control in the context of lifestyle freedom and flexibility while minimizing risks of hypoglycemia.

Insulin (μU/mL)

- Basal insulin
- Breakfast
- Lunch
- Diner
- Basal glucose

Glucose (mg/dL)

- Preprandial plasma glucose (mg/dL)
- Peak postprandial plasma glucose (mg/dL)

**American Diabetes Association**

- A1C (%) < 6 < 7
- Preprandial plasma glucose (mg/dL) < 100 70–130
- Peak postprandial plasma glucose (mg/dL) < 140 < 180

**American Association of Clinical Endocrinologists (AACE)**

- A1C (%) < 6 ≤ 6.5
- Preprandial plasma glucose (mg/dL) < 100 < 110
- 2-hour postprandial glucose < 140 < 140

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

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Schematic Course of DCCT/EDIC Intensive and Conventional Groups

Value of Insulin Therapy in Type 2 DM

- Controlling fasting glucose and thus improving day-long glycemic control
- Overcoming glucose toxicity
- Later in the natural history of the disease, addressing basal and prandial insulin needs
- Individualizing regimens to attain and maintain safety

The Kumamoto Trial: Effects of Conventional vs Intensive Insulin Therapy

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


DECODE Trial: Relative Risk of Death, Shown by Blood Glucose Level


When to Start Insulin? Autoimmune DM

Conventional T1DM
Latent Autoimmune Diabetes of Adulthood (LADA)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide, GAD-65 antibodies, IA-2 antibodies, Insulin autoantibodies</td>
<td>Depends upon residual C-peptide level and glycemic control</td>
</tr>
<tr>
<td>Full basal-bolus therapy will ultimately be needed, with interim control provided by antidiabetes agents and/or basal insulin</td>
<td></td>
</tr>
</tbody>
</table>

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When to Start Insulin? Type 2 DM

- High BG on optimized antidiabetes therapy
- Unintentional weight loss
- Low C-peptide
- Very high BG at diagnosis (glucose toxicity)
- During pregnancy, pending achievement of glycemic goals with diet and exercise
- In hospitalized patients with DM not at glycemic goals or for whom other therapy is contraindicated (metformin, TZD)

Clinical Inertia: “Failure to Advance Therapy When Required”

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

Percentage of Subjects Advancing when A1C > 8%

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% of Subjects Advancing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>66.6%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>35.3%</td>
</tr>
<tr>
<td>Metformin</td>
<td>44.6%</td>
</tr>
<tr>
<td>Combination</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

Plasma Insulin Levels

- Regular 6–8 Hours
- NPH 12–20 Hours
- Basal Insulin Glargine, Detemir

Aspart, Glulisine, Lispro 4–6 Hours

- 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 (nursing home, unpredictable PO intake)*

*Garg S et al. ADA 64th Scientific Sessions; June 4-8, 2004; Orlando, FL; Abstract 500-P.

Better Mean PPG Levels after Meals with Aspart vs Regular Human Insulin

*P<0.05
BB=before breakfast; BL90=min after breakfast; BL=before lunch; L90=90 min after lunch; BD=before dinner; D90=90 min after dinner; BL=bedtime

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

Data on file, Novo Nordisk Inc.

Sequelae of Recurrent Hypoglycemia

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

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**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

---

**24-h Glucose Profiles for Glargine and Detemir**

![Graph showing glucose profiles for glargine and detemir](image)


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**Hypoglycemia Rates with Detemir vs NPH**

![Graph showing hypoglycemia rates](image)

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

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Risk of Malignancies in Patients with Diabetes Treated with Human Insulin or Analogs

- Population study (N=127,031) showed a dose-dependent cancer risk increase with glargine Rx compared with human insulin Rx ($P<0.0001$), but no increased risk was found for aspart ($P=0.30$) or lispro ($P=0.96$)
  - Scottish national diabetes database showed a cancer rate in all glargine users the same as for those not using glargine, but...
  - The subset using glargine alone had higher cancer incidence, particularly breast, than those using it in combination with other insulins
  - However, it was suggested that this was an allocation bias
- Analysis of a database of glargine RCTs showed no increased cancer incidence, including breast, compared with comparator group
- Comparison of cancer risk in people with type 2 diabetes from a database of another study showed no difference, glargine vs NPH

Home PD, Lagarenne P. Diabetology. 2009 Published online: 15 September 2009.

Starting Basal Insulin in Type 2 DM

- Continue antidiabetes medications at same dose
- Add single insulin dose (10 U or 0.1–0.2 U/kg) at bedtime
  - Insulin glargine/insulin detemir
  - NPH only if cost issues
- Adjust dose according to fasting glucose
- Increase insulin dose every 2 to 5 days as needed (amount pending response to starting insulin dose)
  - Increase by 1–2 units if FBG >120 mg/dL
  - Increase 2–3 units if FBG >140 mg/dL
  - Increase 3–4 units if FBG >160 mg/dL

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Monitor patterns: FBG, 2-hour postprandial, and premeal/bedtime glucose levels during the day. Advance basal based on premeal values, but watch potential for hypoglycemia at key times during the day/night.

Options if postmeal elevations (BG >160 mg/dL) suggest the need for premeal coverage
- Add premeal rapid-acting insulin to basal insulin program
- Consider change to a premixed insulin program in patients with a fixed, consistent carbohydrate intake

Once patient has advanced to >1 daily insulin injection
- Consider stopping insulin secretagogue, particularly if using rapid-acting (premeal) insulin
- Continue insulin sensitizer(s)

Advantages
- Relatively easy to use
- Covers insulin requirements through most of day

Disadvantages
- Not an accurate replication of physiological patterns
- Greater likelihood of nocturnal hypoglycemia from peak of presupper NPH*
- Greater chance of fasting hyperglycemia as presupper NPH wears off*
- More hypoglycemia and weight gain if seeking strict glycemic goals

*Possible solution for these problems is to split the second dose, giving rapid-acting insulin at suppertime and NPH at bedtime.

Provide rapid- and intermediate-acting insulin in one injection without the need to mix insulins

Ability to intensify from a starting regimen of 1 injection of premixed insulin to 2 or 3 injections with same insulin

Require a relatively consistent meal and exercise pattern, as the ratio of rapid to intermediate insulin is fixed
Insulin Therapy: Indications for "Basal-Bolus" Treatment

- Severity of hyperglycemia / low C-peptide
- Lability of glucose levels
- Frequent hypoglycemia
- Lifestyle needs
- Failure to achieve therapeutic goals
- Progressive unintentional weight loss

Carbohydrate Counting

- Carbohydrate is the food component that most affects blood glucose
- This system tracks the grams of carbohydrate consumed for the purpose of adjusting insulin doses
- The more carbohydrate consumed, the more insulin taken
- Particularly useful for people treated with variable premeal doses of rapid-acting insulin
- Pre- and postprandial glucose checks are required to optimize the insulin-to-carbohydrate ratio

<table>
<thead>
<tr>
<th>RAA Insulin</th>
<th>RAA Insulin for Carbs and / BG</th>
<th>RAA for / BG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breakfast</td>
<td>Lunch</td>
</tr>
<tr>
<td>71–100</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>101–150</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>151–200</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>201–250</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>251–300</td>
<td>11</td>
<td>9</td>
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<tr>
<td>301–350</td>
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<td>10</td>
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<td>351–400</td>
<td>13</td>
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<td>401–450</td>
<td>14</td>
<td>12</td>
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<td>451–500</td>
<td>15</td>
<td>13</td>
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<td>501–550</td>
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<td>14</td>
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<td>551–600</td>
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<td>15</td>
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<td>601–650</td>
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<td>16</td>
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<tr>
<td>651–700</td>
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<td>17</td>
</tr>
<tr>
<td>701–750</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Over 750</td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

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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 of glucose values, time, insulin dosage, carbohydrate intake, and activity are all crucially important to regimen optimization.

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, judgment, and life expectancy
  - Psychosocial and cultural considerations
  - Physical capabilities and limitations
  - Comorbid conditions and non-DM medications (psychotropics, glucocorticoids, etc)
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![Multihormone Regulation of Glucose: Amylin and Insulin](image1)

**Insulin and Amylin Co-secreted**

![Insulin and Amylin Co-secreted](image2)

**Amylin Is Deficient in Diabetes**

![Amylin Is Deficient in Diabetes](image3)

Data on file. (Fineman)

Insulin data on file.

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Pramlintide + Insulin: Effect on Postprandial Glucose Concentration


Insulin Pumps

External Insulin Pump Using Rapid-Acting Insulin
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**Continuous Glucose Monitoring Provides a More Comprehensive Picture of the Patterns**

<table>
<thead>
<tr>
<th>Glucose measurement</th>
<th>Glucose measurement</th>
<th>Glucose measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin bolus</td>
<td>Insulin bolus</td>
<td>Insulin bolus</td>
</tr>
<tr>
<td>No bolus</td>
<td>No bolus</td>
<td>No bolus</td>
</tr>
</tbody>
</table>

**Cameron**

**MiniMed REAL-Time Paradigm**

- FreeStyle Navigator
- DexCom Seven Plus
- MiniMed REAL-Time Guardian

**Changes in A1C in Type 1 DM > 25 Years of Age**

- RT-CGM
- Control

- Difference -0.53%
- \( P < 0.001 \)

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**Secondary A1C Outcomes in Type 1 DM >25 Years of Age**

![Chart showing secondary A1C outcomes in Type 1 DM >25 years of age.](chart)

**Percent Values <50 mg/dL in Type 1 DM Age >25 Years**

![Chart showing percent values <50 mg/dL in Type 1 DM age >25 years.](chart)

"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

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