ADA Glycemic Control Targets

- **A1C** < 7%
- Preprandial plasma glucose: 70-130 mg/dl
- Postprandial plasma glucose (PPG): <180 mg/dl

A1c goal must be customized for the individual patient, with consideration of numerous factors such as comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications.

### DCC Results

**HbA1c and Relative Risk of Diabetic Complications**

- **6.5%**
- **Average US HbA1c Range: 7.5-8.5%**
- **AACE recommendation is 6.5%**

**Relative Risk of Complications**

- **Eye disease**
- **Kidney disease**
- **Nerve damage**

**Most Patients on Diabetes Therapies not Reaching A1C < 7%**

<table>
<thead>
<tr>
<th>% of Subjects</th>
<th>Oral</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>27%</td>
<td>32%</td>
</tr>
<tr>
<td>80</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>60</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>40</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>20</td>
<td>15%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*NHANES III = Third National Health and Nutrition Examination Survey

**What are some of the obstacles?**

- Delayed diagnosis of diabetes
- Delay in starting insulin in patients failing oral agents
- Weight gain with intensification of glycemic control
- Hypoglycemia with intensification of glycemic control
- Patient and provider resistance to starting insulin as well as clinical inertia
- Inappropriate managed care practices

**Most patients with T2DM will eventually require insulin therapy**


Adapted from DCC Research Group. NEJM, 1993;329:977-986

Normal Insulin Secretion

In Normal Insulin Secretion, levels are highest after breakfast and逐渐下降 during the day.

Natural History of Type 2 Diabetes

- **Impaired Glucose Tolerance**
- **Frank Diabetes**

**Serum insulin** levels:
- **70** at 12:00 PM
- **1030** at 3:00 AM
- **50** at 6:00 AM
- **0** at 9:00 AM

**Serum glucose levels**:
- **12:00 AM**
- **3:00 AM**
- **6:00 AM**
- **9:00 AM**

Indications for Insulin in T2DM

- **Symptomatic Hyperglycemia**
  - BG > 250 mg/dL
- **Inadequate glycemic control**
  - Patient specific (HbA1c > 7%)
- **Oral agents cannot be tolerated/contraindicated**
- **Longstanding Type 2 Diabetes**
  - Not responding to oral meds
- **Transient poor control**
  - Intercurrent illness
  - Glucocorticoid therapy

Goals of Insulin Therapy

- **HbA1c < 7%** (patient specific)
  - Fasting and pre-prandial: 70 - 130 mg/dL
  - 2 hr after start of meal: < 180 mg/dL
- **Avoid frequent or severe hypoglycemia** with physiologic insulin replacement therapies
- **Minimize weight gain**

Symptoms of Hypoglycemia

- **Neurogenic (autonomic)**
  - Caused by falling glucose and marked sympathetic overstimulation
  - Symptoms typically identified by the patient as indicative of an episode:
    - Trembling
    - Palpitations
    - Sweating
    - Anxiety/arousal
    - Hunger
    - Tingling
    - Dry mouth
    - Pupil dilation
  - Glycemic threshold for symptoms is ~50-55 mg/dL
- **Neuroglycopenic**
  - Caused by glucose deprivation in the CNS
  - Symptoms:
    - Cognitive impairments
    - Difficulty concentrating/thinking
    - Confusion
    - Behavior changes
    - Difficulty speaking
    - Weakness/fatigue
    - Shakiness
    - Sensations of warmness
    - Loss of consciousness

References:
Framework for Setting the Glycemic Target Range

<table>
<thead>
<tr>
<th>Most Intensive Level, Approximately 6.0%</th>
<th>Factors</th>
<th>Least Intensive Level, Approximately 8.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly motivated, adherent, knowledgeable, strong self-care capability</td>
<td>Psychosocial considerations</td>
<td>Less motivated, nonadherent, less knowledgeable, weak self-care capability</td>
</tr>
<tr>
<td>Adequate Resources or support systems</td>
<td>Inadequate</td>
<td></td>
</tr>
<tr>
<td>Low Risk of hypoglycemia</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Short Duration of type 2 diabetes</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Long Life expectancy</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Microvascular disease, Advanced</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Cardiovascular disease, Established</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Coexisting conditions, Multiple, severe, or both</td>
<td></td>
</tr>
</tbody>
</table>

Mimicking Nature With Insulin Therapy

**Basal/Bolus Concept**

- Suppresses glucose production between meals and overnight
- Nearly constant levels
- 50% of daily needs

**Physiologic Insulin Secretion**

- Basal glucose
- 50% of daily needs
- Between meals and overnight
- Nearly constant levels
- 24-hr profile
- Basal insulin

**Types of Insulin and How They Work**

**Basal Insulin**

- Intermediate Acting
  - NPH
- Long-Acting Analogs
  - Glargine (Lantus)
  - Detemir (Levemir)

**Pharmacokinetic Profiles of Human Insulin and Insulin Analogs**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>10-15 mins</td>
<td>60-90 mins</td>
<td>4-5 hr</td>
</tr>
<tr>
<td>Regular</td>
<td>30-60 mins</td>
<td>2-4 hours</td>
<td>5-8 hr</td>
</tr>
<tr>
<td>NPH</td>
<td>1-5 hr</td>
<td>8-12 hours</td>
<td>12-18 hr</td>
</tr>
<tr>
<td>Detemir</td>
<td>90 mins</td>
<td>Relatively constant</td>
<td>12-24 hr</td>
</tr>
<tr>
<td>Glargine</td>
<td>180 mins</td>
<td>Peakless</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

**NPH Insulin**

- Human Insulin Isophane Suspension
- Pharmacokinetics
  - Onset: 2 - 4 hour
  - Peak: 4 - 10 hours
  - Duration: 10 - 16 hours
  - 40% variance!!
  - Can be mixed with Regular and Rapid Acting insulin
Insulin Glargine (Lantus)
- Recombinant human insulin analog
- Pharmacokinetics
  - Onset: 2 - 4 hour
  - Peak: Peakless
  - Duration: 24 hours
- Administration:
  - Once Daily at anytime of day
  - When converting from once daily NPH, same dose used.
  - When converting from twice daily NPH, start with 20% less

Insulin Detemir (Levemir)
- Recombinant human insulin analog
- Pharmacokinetics
  - Onset: 2 - 4 hour
  - Peak: Peakless
  - Duration: 12 hours
- Administration:
  - Once or Twice Daily
  - Same dose as once daily NPH
  - 20% less than twice daily NPH
  - May actually require more detemir than glargine
- Shown to be associated with weight loss/less weight gain than other insulin

Insulin glargine (Lantus)
Insulin detemir (Levemir)
- Similar rates of absorption from abdominal, thigh and deltoid region
- Cannot be mixed with any other form of insulin or IV solution
- Incidence of nocturnal and severe hypoglycemia were less frequent compared to once-daily NPH insulin
- CLEAR solution
- Available in Pen Device

Basal Insulin Replacement Therapy

Average Glucose Concentration Can Be Estimated from A1C

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Average Glucose Concentration (mg/dL) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>97 (76-120)</td>
</tr>
<tr>
<td>6</td>
<td>126 (100-152)</td>
</tr>
<tr>
<td>7</td>
<td>154 (123-185)</td>
</tr>
<tr>
<td>8</td>
<td>183 (147-217)</td>
</tr>
<tr>
<td>9</td>
<td>212 (170-259)</td>
</tr>
<tr>
<td>10</td>
<td>240 (193-282)</td>
</tr>
<tr>
<td>11</td>
<td>269 (227-314)</td>
</tr>
<tr>
<td>12</td>
<td>298 (240-347)</td>
</tr>
</tbody>
</table>

PPG Contributes to 50% or More of Overall A1C When A1C Is 8.4 or Below

Average Glucose Concentration Can Be Estimated from A1C


Average Glucose Concentration Can Be Estimated from A1C

**BOLUS INSULIN**

- **Short Acting**
  - Regular
  - Rapid-Acting Analogs
    - Aspart (NovoLog)
    - Lispro (Humalog)
    - Glulisine (Apidra)

**Regular Insulin**

- **Human Insulin (soluble)**

  - **Pharmacokinetics**
    - Onset: 0.5 - 1 hour
    - Peak: 2 - 3 hours
    - Duration: 3 - 6 hours (as long as 8 hours)

  - **Administration:**
    - 30 - 45 minutes BEFORE meals
    - Can be mixed with NPH insulin
    - Only insulin that can be given IV

**Rapid-Acting Insulin Analogs**

- **Equipotent to Regular Insulin**

  - **Products**
    - Lispro (Humalog)
    - Aspart (NovoLog)
    - Glulisine (Apidra)

- **Goal:** to mimic physiological prandial response

**Why is Mealtime Control Important?**

- 99% of patients with A1Cs $\geq 7\%$ have 2-hour postprandial glucose (PPG) levels $\geq 200\, \text{mg/dL}$

Relationship Between 2-Hour Plasma Glucose and All-Cause Mortality

The Relationship Between 2-hour Plasma Glucose and All-Cause Mortality in Subjects Not Known as Diabetic:

According to DECODE:
- High 2-hour plasma glucose is associated with an increased risk of death independent of fasting blood glucose.
- Mortality associated with fasting glucose depended on the 2-hour glucose in all categories of fasting glucose.

Adjusted for age, center, sex, mean duration of follow-up 7 years. Total of 140,000 person-years of accumulated follow-up.

Basal-Bolus Insulin Therapy: Insulin Glargine at HS and Mealtime Lispro or Aspart

Premixed Insulin

**HUMAN**

- 70/30
  - 70% NPH
  - 30% REG
- 50/50
  - 50% NPH
  - 50% REG
- Dual Peak
- Administration:
  - Must be injected 30-45 min. before a meal
  - Once or twice daily dosing

Advantages:
- Convenience
- Accuracy
- Visually impaired
- Manual dexterity challenges

Disadvantages:
- Inability to adjust only one component
- Nocturnal Hypoglycemia
- MUST eat CONSISTENTLY timed meals

**ANALOG**

- 70/30 MIX (Novolog)
  - 70% Aspart protamine
  - 30% Aspart
- 75/25 (Humalog)
  - 75% Lispro protamine
  - 25% Lispro
- One Peak followed by "long Tail" (No NPH)
- Administration:
  - Must be injected within 15 minutes before a meal
  - Once, twice or three times daily dosing

Advantages:
- Convenience
- Accuracy
- Visually impaired
- Manual dexterity challenges
- Flexibility with meals
- Less Nocturnal Hypoglycemia

Disadvantages:
- Inability to adjust only one component
Mixed Insulin Replacement Therapy

- Normal Insulin Secretion at Meal Time
- Analog Mix
- PreMix 70/30 (NPH/REG)

Change in Serum Insulin

Time (hours) 75/25 Lispro Mix
70/30 Aspart Mix

Now What?

FIRST Correct FASTING

- Then, Tackle Postprandial if A1C still >7%!

Possible Approaches for Adding Insulin

- Using a basal insulin with continued oral agents
- Using pre-mixed insulin with continued oral agents
- Stopping oral agents and initiating insulin using various regimens:
  - Pre-mixed insulin
  - Prandial insulin with largest meal - with a basal insulin once (or twice) daily
  - Prandial insulin with each meal - with a basal insulin once (or twice) daily

Start a Basal Insulin “Treat to Target”

- Continue oral agent(s) at same dosage
  - Do NOT stop insulin secreting agent
- Add single, evening insulin dose (0.1 - 0.2 U/kg)
  - 10 - 20 units
  - Glargine, Detemir or NPH (bedtime)
- Increase insulin dose every 3-4 days as needed
  - Increase 3 - 5 U if FBG >150 mg/dL
  - Increase 1 - 2 U if FBG = >110, <150 mg/dL
- Treat to target FBG (usually <120 mg/dL)

Basal Insulin May Not Cover Postprandial Excursions and May Increase Risk for Hypoglycemia
"Overbasalization" May Lead to Inadequate Glycemic Control

- Continued titration of basal insulin may not achieve A1C goals and may require a change in treatment strategy.
- Overbasalization can be described as continued titration of basal insulin without any appreciable improvement in glucose control.

Traditional "Sliding Scale"

- An arbitrary insulin dosing algorithm based only on pre-meal blood glucose values.

<table>
<thead>
<tr>
<th>Pre-Meal BG (mg/dl)</th>
<th>Insulin Dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 151</td>
<td>0</td>
</tr>
<tr>
<td>151-200</td>
<td>2</td>
</tr>
<tr>
<td>201-250</td>
<td>4</td>
</tr>
<tr>
<td>251-300</td>
<td>6</td>
</tr>
<tr>
<td>301-350</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 351</td>
<td>10</td>
</tr>
</tbody>
</table>

Adding a meal time bolus:

- Stop insulin secreting agent.
- Add Bolus insulin before meals (REG or analog).
- Isocaloric meals:
  - Add 10 units and redistribute total dose 50/50.
    - Pt taking 30 units Lantus already.
    - Add 10 units to a new total dose of 40 units.
    - 50% will be basal (20 units).
    - 50% in divided doses will be the meal time bolus (i.e. 7/6/7).
- Carb counting and correction factors.
- BG checks a must! "blind leading the blind".
- SAFETY.

Total Daily Insulin

- Total daily insulin requirement is calculated by body weight.
  - T2: need about 1.2 units/kg (range 1 - 1.4).
  - BGs at goal without hypoglycemia.
  - 40-50% basal (background).
  - 50-60% bolus (meal doses).

Calculating "Basal–Bolus" Insulin

- Calculate TDD:
  - T2: need about 1.2 units/kg (range 1 - 1.4).
  - Basal dose: 40 - 50% of TDD.
  - Bolus dose: 50-60% of TDD:
    - Divide equally for three meals And/O or
    - Sensitivity Factor = 1700/TDD.
    - 1 unit will drop BG by XX points.
    - Carbohydrate Ratio = 500/TDD.
    - 1 unit for every XX gm carbs.
    - Blood Glucose (Target before meals).
- (Pt BG – target) / (SF) = CORRECTION.
- Now add carb ratio for meal.
For Example: Above Target at Lunch

- Pre meal target: 100
- Pt BG before lunch: 160
- Will be eating a meal of 65 gm CHO
- 160 - 100 = 60 points too HIGH before eating
- Sensitivity Factor = 12
  - 60/12 = 5 (will need 5 units to correct to target)
- Carb ratio = 1 : 3
  - 65 gm CHO / 3 = 21 (will need 21 units for the meal)
5 units + 21 units = 26 units before lunch

For Another Example: Below Target at Lunch

- Pre meal target: 100
- Pt BG before lunch: 80
- Will be eating a meal of 65 gm CHO
- 80 - 100 = -20 points too LOW before eating
- Sensitivity Factor = 12
  - -20/12 = -1.6 >> -2 (will need -2 units to correct to target)
- Carb ratio = 1 : 3
  - 65 gm CHO / 3 = 21 (will need 21 units for the meal)
21 units - 2 units = 19 units before lunch

Sliding scale: Correction

- **Correction Scales:**
  - Helpful for sick days/NPO
  - Still need to calculate the TDD and the insulin sensitivity
  - Example: TDD = 137; SF 1:12
  - WILL NOT COVER FOR CARBS, ONLY TO CORRECT
    - <100-125, no insulin,
    - 126-150, 2 units
    - 151-175, 4 units
    - 176-200, 6 units
    - 201-225, 8 units
    - 226-250, 10 units, etc

Sliding scale: Correction + Carbs

- **Incorporates BOTH the correction and the meal requirements**
  - Just need to calculate the TDD, sensitivity factor, and carbohydrate ratio
  - Works best for consistent carb intake (may have different scale for each meal)
  - Example: TDD = 137 units
    - SF = 1:12
    - CR = 1:3
    - Eats approx 65 gm carbs at each meal
    - <70, no insulin or reduced dose given at end of meal
      - 71-75, 21 units
      - 76-80, 23 units
      - 81-85, 25 units
      - 86-90, 27 units
      - 91-95, 29 units
      - 96-100, 31 units

What’s the dose range?

- **Type 2:** 0.3 to 1.2 units/kg
  - “Thin type 2’s” are more insulin deficient
  - “Heavy type 2’s” are more insulin resistant
  - Most pts with T2DM need insulin doses of 1 to 1.2 units/kg to achieve an A1c <7%
    (basal dose of 0.5 to 0.6 units/kg per day)

What Does The Future Hold?

- New long acting Insulin
- New Pens
**Injection Problems**

- **Lipoatrophy (immune response)**
  - Breakdown (pitting) of fat tissue
  - Indentation in the skin
- **Lipohypertrophy**
  - Thickening (lumps) of SQ fat
  - Causes: repeated injections same site, needle reuse
  - Delays insulin absorption
- **Bruising at Site: ✔ technique**

**Insulin Delivery Systems**

- **Insulin syringes**
  - Know Needle Gauges (29-32), Lengths
  - Short Needle: 8mm, Longer: 12.7mm
  - Syringe size: 1/4ml, 3/10ml, 1/2ml, 1ml
- **Insulin pens**: Nano ® (4mm), mini (5mm), short (8mm), long (12.7mm) needles
- **Continuous insulin infusion pump**
  - Uses bolus insulin only