مواطين

(ربمثيل)
Insulin Therapy

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Primary Objectives of Effective Management

Diagnosis

- A1C %
- SBP mm Hg
- LDL mg/dL

Reduction of both micro- and macrovascular event rates ...by 75%!
Relative Risk of Progression of Diabetes Complications (DCCT)

Control your Diabetes well

Life is better under Seven

HbA1c < 7
Approach to hyperglycemia management:
Several factors should be considered

- Patient attitude; expected treatment efforts
- Resources; support system
- Risks associated with hypoglycemia
- Established vascular complications
- Disease duration
- Important comorbidities
- Life expectancy

HbA1c goal
Percentage of Patients Achieving Glycemic Targets in Various Settings

Europe (CODE-2)$^a$
- $\text{HbA}_{1c} < 6.5\%$
  - Achieved glycemic target: 31\%
  - Failed to achieve glycemic target: 69\%

Canada (DICE)$^b$
- $\text{HbA}_{1c} < 7\%$
  - Achieved glycemic target: 49\%
  - Failed to achieve glycemic target: 51\%

US (NHANES)$^c$
- $\text{HbA}_{1c} < 7\%$
  - Achieved glycemic target: 43\%
  - Failed to achieve glycemic target: 57\%

---

## Expected HbA$_{1c}$ reduction according to intervention

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected ↓ in HbA$_{1c}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle interventions</td>
<td>1 to 2%</td>
</tr>
<tr>
<td>Metformin</td>
<td>1 to 2%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1 to 2%</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>No</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5 to 1.4%</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5 to 0.8%</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>0.5 to 1.0%</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5 to 1.0%</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>0.5 to 0.8%</td>
</tr>
</tbody>
</table>

The most powerful agent we have to control glucose

Banting & Best  1921
A 3-year-old boy before and after 3 months of insulin therapy (1922).

The first successful clinical test of insulin on a human diabetic on January 23, 1922,

The miracle of Insulin
Types of Insulin

- More than 20 types of insulin
- Different time of onset and duration of action.
- Among the criteria considered in choosing insulin are:
  - How soon it starts working (onset)
  - When it works the hardest (peak time)
  - How long it lasts in the body (duration)
## Available insulin injections

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>Novolog</td>
<td>10-30 min.</td>
<td>0.5-3 h.</td>
<td>3-5 h.</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
<td>10-30 min.</td>
<td>0.5-3 h.</td>
<td>3-5 h.</td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
<td>10-30 min.</td>
<td>0.5-3 h.</td>
<td>3-5 h.</td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>0.5-1 h.</td>
<td>2-5 h.</td>
<td>Up to 12 h.</td>
</tr>
<tr>
<td></td>
<td>Novolin R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH insulin</td>
<td>Humulin N</td>
<td>1.5-4 h.</td>
<td>4-12 h.</td>
<td>Up to 24 h.</td>
</tr>
<tr>
<td></td>
<td>Novolin N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
<td>0.75-4 h.</td>
<td>Minimal peak</td>
<td>Up to 24 h.</td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus</td>
<td>0.75-4 h.</td>
<td>Minimal peak</td>
<td>Up to 24 h.</td>
</tr>
</tbody>
</table>

Available insulin injections include different types: **Rapid-Acting**, **Short-Acting**, **Intermediate-Acting**, and **Long-Acting**. Each type has specific products with their onset, peak, and duration times.
Insulin Analogues: 2000

Lispro  Aspart  Glulisine  Glargine  Detemir

June 29, 2010, ADA 70th Scientific Session:

- Ultrarapid = Technosfer (Inhaled Insulin)
- Ultralong = Degludec
Inhaled insulin

Exubera

Pfizer, taken off the market in October 2007

Technosphere (Afresa)

2004 - 2007

2010
Conventional Insulins

- **REGULAR**: Traditional Bolus insulin since 1921
- **NPH**: Traditional Basal insulin replacement since 1950

Several well known limitations:

* Absorption Variation: unfavorable plasma profiles
* Duration of action
* Peak effect
* Fasting hyperglycemia
* Nocturnal hypoglycemia
Regular Human Insulin Peak Time: 2-4 Hours

- Exist in solution in hexameric form
- Onset of action: 0.5 – 1 hour after SC
- It peaks 2 – 4 hours after SC
- The duration of action range 8 – 10 h.
- It peaks much later than the blood glucose rise
- Risk of hyperglycemia in the first 30 minutes and hypoglycemia many hours after meals
- Protamine molecule + human regular
- Slower absorption and longer duration of action
- Onset of action = 1 - 2 hours after SC
- It peaks 4 – 8 hours after SC
- The duration of action range 10 – 20 h.

**NPH Insulin**
Rapid Analogs

- Exist in solution in monomeric form
- Onset of action: up to 0.5 hour after SC
- Peaks 1–2 hours after SC
- The duration of action up to 4 hours
- Peak when the blood glucose rise
- No risk of hyper- or hypoglycemia
- Dose given immediately pre-meal

○ Lispro
○ Aspart
○ Glulysine
Time Action Profile of Rapid-Acting Analogues: Aspart, Glulisine, and Lispro

Earlier onset & peak of biologic activity = lower postprandial glucose

Dose 15-20 min before meals

Long acting analogous

Glargine & Detemir

- Were designed to provide a reliable, constant basal insulin concentration to control basal metabolism.

- They are more predictable than conventional insulins and allow simplified insulin-replacement strategies.
Insulin Glargine

A- chain has an Asparagine to Glycine substitution at position A21.
Two positively charged Arginine are added at the C terminus of the B chain.
Mechanism of Action

Injection of an acidic solution (PH 4.0)

Precipitation of insulin glargine in subcutaneous tissue (PH 7.4)

Slow dissolution of free insulin glargin hexamers from micro precipitates (stabilized aggregates)

Protracted action
Pharmacokinetics:

Slow dissolution of the Glargine hexamers at the injection site results in a relatively constant release with no pronounced peak over a period of up to 24 hours.

Onset of action = 2 hours

Peak = flat

Duration = 24 hours
Presentation of Glargine (Lantus)

- Clear solution
- Once-daily dosing
- Not suitable for mixing with other insulins
- Pen delivery system
A soluble derivative of human insulin

Threonine has been removed at position B30

A 14-carbon fatty acid side-chain has been attached to position B29
Pharmacokinetics:

The fatty acid enables Detemir to bind albumin in subcutaneous tissue and circulation.

98% of Detemir in the bloodstream is albumin bound.

Detemir distributes more slowly to peripheral target tissues.

It does not precipitate during administration or absorption.

Protracted absorption may contribute to reduced variability in Detemir action.

Onset of action = 2 hours
Peak = flat
Duration = 14 – 16 hours
(dose dependent: 0.4 IU/Kg, average 20 hours)
Glargine or NPH Added to Regimen Have Similar Efficacy

NS = not specified.
Riddle MC, et al. Republished with permission.
Less Hypoglycemia With Basal Analogues vs NPH

*P < .05.

Ultralong Acting Insulin = Degludec

- **Insulin degludec** is an ultralong-acting basal insulin analogue being developed by Novo Nordisk under the brand name Tresiba

- Unlike insulin glargine, is active at a physiologic pH. and forms of multi-hexamers in subcutaneous tissues. This allows for the formation of a subcutaneous depot that results in slow insulin release into the systemic circulation

- **Insulin degludec** might only need to be administered three times a week
Once-daily Degludec provides similar A1C control compared to insulin Glargine.

Both administered as basal-oral therapy or in combination with insulin aspart.

Benefit: lower rates of hypoglycemia, particularly nocturnal hypoglycemia.

Insulin Degludec has also been shown to offer dosing flexibility, with administration at any time of the day without compromising glycemic control or safety.
Ultralong Acting Insulin = Degludec

- Insulin **Degludec** has an onset of action of 30-90 minutes (similar to insulin Glargine and insulin Detemir).
- There is no peak in activity, due to the slow release into systemic circulation.
- The duration of action of insulin Degludec is reported as being longer than 24 hours.
Lower Nocturnal Confirmed Hypoglycemia With Insulin Degludec*

*The FDA has not approved this medication for use.
Zinman B, et al.[34]
Insulin treatment regimens
Pulsatile insulin secretion

Insulin is normally secreted in coordinated secretory bursts. In humans, pulses occur about every 10 minutes.

After oral ingestion of glucose (arrow), which produces a glucose stimulus and an incretin effect, an increase in the amplitude of the bursts is seen, as well as an increase in frequency, with intervals decreasing from about 7 to 5 minutes.
Insulin Secretion After A Meal In Normal Individual

- First Phase (acute) release
- Second Phase
- Basal
Insulin secretion in Type 1 and 2 DM

- Normal
- Type 1
- Type 2

Bolus

Basal level of insulin

Breakfast  Lunch  Supper
Healthy eating, weight control, increased physical activity, and diabetes education

### Metformin

<table>
<thead>
<tr>
<th>Efficacy*</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low</td>
<td>neutral / loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Monotherapy +</th>
<th>Dual therapy +</th>
<th>Triple therapy +</th>
<th>Combination injectable therapy +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Sulfonylurea</td>
<td>Metformin +</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>Metformin +</td>
<td>highest</td>
</tr>
<tr>
<td></td>
<td>moderate risk</td>
<td>Thiazolidinedione</td>
<td>high</td>
</tr>
<tr>
<td></td>
<td>low risk</td>
<td>DPP-4 Inhibitor</td>
<td>high</td>
</tr>
<tr>
<td></td>
<td>gain</td>
<td>SGLT2 Inhibitor</td>
<td>intermediate</td>
</tr>
<tr>
<td></td>
<td>gain</td>
<td>GLP-1 receptor agonist</td>
<td>high</td>
</tr>
<tr>
<td></td>
<td>hypoglycemia</td>
<td></td>
<td>high</td>
</tr>
<tr>
<td></td>
<td>low</td>
<td></td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>DPP-4 Inhibitor</td>
<td>SGLT2 Inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
<td></td>
</tr>
<tr>
<td>or DPP-4-I</td>
<td>or SGLT2-I</td>
<td>or GLP-1-RA</td>
<td>or Insulin$^b$</td>
<td>or DPP-4-I</td>
<td></td>
</tr>
<tr>
<td>or SGLT2-I</td>
<td>or GLP-1-RA</td>
<td>or Insulin$^b$</td>
<td>or DPP-4-I</td>
<td>or SGLT2-I</td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-I:

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Basal insulin +</th>
<th>Mealtime insulin</th>
<th>GLP-1-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>or</td>
<td></td>
</tr>
</tbody>
</table>
How is insulin normally secreted?

- **Basal (50%)**
  
  Serves to balance the rate of hepatic glucose production and peripheral uptake during overnight and prolonged periods between meals.

- **Bolus (50%)**

  Serves to control postprandial hyperglycemia in response to food intake.
Insulin Time Action Curves

Relative Insulin Effect

- Rapid (Lispro, Aspart, Glulysine)
- Short (Regular)
- Intermediate (NPH)
- Long (Glargine)

Time (Hours)

0 2 4 6 8 10 12 14 16 18 20
Insulin treatment regimens

Conventional

Advanced insulin regimen
Insulin treatment regimens

Conventional
Single insulin dose

- Is rarely able to achieve normoglycemia,
  Least effective regimen and rarely suitable
  - Occasionally in newly diagnosed T1DM
  - Diabetic patients with ESRD on dialysis
For people with type 2 diabetes, in whom basal insulin replacement is not as critical, once or twice daily regimens can still work satisfactorily with reasonable glycemic control achieved.

- NPH, Glargine, or Detemir are most often given at bedtime.

- For patients who eat large amounts of carbohydrates at dinner, an insulin mixture, regular and NPH or a premixed insulin, can be given prior to dinner.
NPH = 0.5-1.0 U/kg (20-30 IU) in the morning

**Normal pattern**

**Insulin concentration (µU/mL)**

**Time of day (h)**

**AM**

**PM**

**AM**
Twice daily insulin dose

- The most frequently used regimen
- **NPH+ Regular insulin**
- **Starting dose**: 0.5 – 1 U/Kg (TDD)
  - 2/3 of TDD in the morning
  - 1/3 of TDD in the evening
- **Frequent late afternoon and midnight hypoglycemia**
<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin to be changed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>Bedtime or supper intermediate- or long-acting</td>
</tr>
<tr>
<td>Post-breakfast</td>
<td>Morning short- or rapid-acting insulin</td>
</tr>
<tr>
<td>Pre-lunch</td>
<td>Morning intermediate-acting insulin</td>
</tr>
<tr>
<td>Post-lunch</td>
<td>Morning intermediate-acting insulin or lunchtime short- or rapid-acting insulin</td>
</tr>
<tr>
<td>Pre-supper (dinner)</td>
<td>Morning intermediate-acting insulin</td>
</tr>
<tr>
<td>Post-supper (dinner)</td>
<td>Supper-time short- or rapid-acting insulin</td>
</tr>
<tr>
<td>During the night</td>
<td>Supper-time or bedtime intermediate-acting</td>
</tr>
</tbody>
</table>
Twice daily insulin dose

![Insulin concentration graph showing normal pattern for regular (NPH) insulin.](https://example.com/insulin-graph.png)
Twice-daily injection

In many patients with type 1 diabetes, especially those with a long duration of diabetes, it may not be possible to achieve optimal glycemnic control with two injections.
Conventional regimens

Problems

- Lack of flexibility
- Inadequate coverage of post-lunch glycemia
- Fasting hyperglycemia
- Nocturnal hypoglycemia
Insulin treatment regimens

Advanced insulin regimen

Multidose, Flexible, Functional,

Physiologic, Basal-bolus
Basal-Bolus insulin injection

- 3 or more daily injections of insulin.
- Combined regular or rapid acting with intermediate- or long-acting.
- Adjusted to needs of individual patient.
- The new analogues are more predictable than conventional Insulins and allow simplified insulin replacement strategies.
Basal-Bolus insulin injection

More compatible with physiologic insulin secretion

Lispro, glulisine, or aspart or regular

µU/mL

Time of day

Glargine

Normal pattern

Detemir
Determining initial insulin for Basal-Bolus

- **TDD**: 0.5 – 1 IU X Kg weight
- **Bedtime Insulin**: 35 – 50 % TDD
- **Meal Boluses Insulin** (% of TDD):
  - Breakfast = 20 – 25 %
  - Lunch = 10 – 15 %
  - Dinner = 20 – 25 %
Determining initial insulin for Basal-Bolus

Total Daily Dose = 60 IU

- Bedtime NPH or Long acting: \(60 \times 0.50 = 30\) IU

- Meal Boluses Regular or Rapid acting
  - Breakfast = \(60 \times 0.20 = 12\) IU
  - Lunch = \(60 \times 0.10 = 6\) IU
  - Dinner = \(60 \times 0.20 = 12\) IU
Titrate basal insulin as long as FPG > target

INITIATE
- Bedtime or morning long-acting insulin
- Daily dose: 10 units or 0.2 units/kg

Check FPG daily

TITRATE
- Increase dose by 2 units every 3 days until FPG is (70–130 mg/dL)
- If FPG is >180 mg/dL, increase dose by 4 units every 3 days

In the event of hypoglycemia or FPG level < 70 mg/dL
- Reduce bedtime insulin dose by ≥4 units, or by 10% if >60 units

MONITOR
Continue regimen and check HbA1c every 3 months
Making adjustment in bolus insulin dosage

- Calculates how much blood glucose decreases for each unite of bolus insulin
- **ISF** (For human insulin) = $\frac{1500}{\text{TDD}}$
- **ISF** (For analogue insulin) = $\frac{1800}{\text{TDD}}$
- **Example:** TDD = 50 :
  - Human Insulin: $\text{ISF} = \frac{1500}{50} = 30$
  - Analogue Insulin: $\text{ISF} = \frac{1800}{50} = 36$

  It means that each unit of bolus Regular decreases blood glucose by 30 mg/dl and Analogue by 36 mg/dl.

- For every 30 or 36 mg/dl above the premeal glucose target (150 mg/dl), add 1 unit of insulin Regular or Rapid acting, respectively.
Supplemental Insulin for Correction of Hyperglycemia

• In general, 1 units of Regular or Rapid acting insulin will lower the blood glucose by 30-50 mg/dl.

• For example, If pre-meal glucose is 240 mg/dl:

  240 - 150 = 90

2 to 3 units of insulin should be added to the usual dose of pre-meal insulin.
Exercise improves insulin sensitivity:

- For morning exercise:
  Reduce pre-breakfast insulin (~25%)

- For early-afternoon exercise:
  Reduce the pre-lunch insulin

- For evening exercise:
  Reduce pre-dinner insulin
Place of premixed insulins

- Premixed insulins are not recommended:
  - For initiation or during adjustment

- If the proportion of rapid- and intermediate-acting insulin is similar to the fixed proportions available.

- Can be used before breakfast and dinner

- Easy for some patients
Approach To Starting and Adjusting Insulin in Type 2 Diabetes

**Basal insulin**
(usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine and address cause; ↓ dose by 4 U or 10-20%.

If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin (Consider initial GLP-1-RA trial.)

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**Add 1 rapid insulin injection before largest meal**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; corresponding dose by 2-4 U or 10-20%.

**Change to premixed insulin twice daily**

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; corresponding dose by 2-4 U or 10-20%.

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**Add ≥2 rapid insulin injections before meals (“basal-bolus”)**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; corresponding dose by 2-4 U or 10-20%.

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