Insulin Therapy

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Agenda

- Indications
- Different insulin preparations
- Insulin initiation
- Insulin intensification
Indications for insulin therapy

- Type 1 diabetes
- Women with diabetes who become pregnant or are breastfeeding
- Transiently in type 2 diabetes in special situations
- In type 2 diabetes, inadequately controlled on glucose-lowering medicines (secondary failure)
Progressive beta cell damage

- Type 2 diabetes is a progressive disease

- At the time of diagnosis, patients with type 2 diabetes have an estimated loss of about 50% of their insulin-producing
FIGURE 3. Progressive decline of beta-cell function in patients on conventional therapy (primarily diet) in the UKPDS, beginning with the year of diagnosis (green line). Extrapolating back from the data (dotted line) shows beta-cell loss begins almost a decade before diagnosis.
**Type 2 diabetes: A progressive disease**

![Graph showing median hemoglobin A1c (%) over years after randomization for conventional and intensive treatments.]

**FIGURE 1.** Progressive increase in hemoglobin A1c in patients with type 2 diabetes, regardless of treatment, in the United Kingdom Prospective Diabetes Study (UKPDS).

Need for Insulin

- Insulin therapy is thus *frequently required* during the course of the disease to maintain glycemic control and prevent diabetes complications.

- In the UK Prospective Diabetes Study, 9 years after diagnosis almost *80%* of patients on oral agents required insulin supplementation.
Insulin

- A hormone secreted by the beta cells
- Secreted in response to glucose or other stimuli, such as amino acids
- Normal response characterized by low basal levels of insulin, with surges of insulin triggered by a rise in blood glucose
Insulin action

1. Increases glucose uptake, particularly in muscle, liver and adipose tissue
2. Suppresses glucose output from the liver
3. Increases formation of fat
4. Inhibits breakdown of fats
5. Promotes amino-acid uptake and prevents protein breakdown
Insulin remains the most potent antihyperglycemic agent available for uncontrolled T2DM patients

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected ↓ in HbA$_{1c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5%</td>
</tr>
<tr>
<td>Glinides</td>
<td>1 to 1.5%$^a$</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5 to 1.4%</td>
</tr>
<tr>
<td>$\alpha$-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>~0.8%</td>
</tr>
</tbody>
</table>

$^a$ Repaglinide is more effective than nateglinide

# Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Class</th>
<th>Preparation</th>
<th>Onset of Effect</th>
<th>Peak Effect (hr)</th>
<th>Duration of Action (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>Lispro, aspart, or glulisine</td>
<td>10–15 min</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular (R)</td>
<td>30 min</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>NPH (N) or Lente</td>
<td>2–4 hours</td>
<td>6–12</td>
<td>16–24</td>
</tr>
<tr>
<td>Long acting</td>
<td>Ultralente (U)</td>
<td>4–6 hours</td>
<td>8–16</td>
<td>~24</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>2–4 hours</td>
<td>No peak</td>
<td>&gt;30</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>1 hour</td>
<td>No peak</td>
<td>Up to 24</td>
</tr>
</tbody>
</table>
# Summary of available insulin preparations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type / Administration</th>
<th>Glucose lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Intermediate-acting human</td>
<td>Basal ✓</td>
</tr>
<tr>
<td></td>
<td>Once or twice daily at bedtime ± breakfast</td>
<td>Post-meal ✓</td>
</tr>
<tr>
<td>Detemir</td>
<td>Long-acting analogue</td>
<td>Basal ✓</td>
</tr>
<tr>
<td></td>
<td>Once or twice daily at bedtime ± breakfast</td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>Long-acting analogue</td>
<td>Basal ✓</td>
</tr>
<tr>
<td></td>
<td>Once daily at bedtime or before breakfast</td>
<td></td>
</tr>
<tr>
<td>Premixed</td>
<td>Human or analogue mix</td>
<td>Basal ✓</td>
</tr>
<tr>
<td></td>
<td>Twice daily before breakfast and dinner</td>
<td>Post-meal ✓</td>
</tr>
<tr>
<td>Regular</td>
<td>Fast-acting human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before meals</td>
<td>Basal ✓</td>
</tr>
<tr>
<td>Aspart, glulisine, lispro</td>
<td>Rapid-acting analogue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before meals</td>
<td>Basal ✓</td>
</tr>
</tbody>
</table>
MIMICKING NATURE WITH INSULIN THERAPY

The Basal/Bolus Insulin Concept

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

- **Bolus Insulin (Mealtime or Prandial)**
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of total daily insulin requirement at each meal
The Ideal Basal Insulin

- 1 injection daily covers 24 hours
- No peaks
- Low incidence of hypoglycemia
- Good glycemic control
- Less weight gain
- Safe
- Predictable
INSULIN TACTICS:
Insulin Glargine
A New Long-acting Insulin Analogue

- Modifications to human insulin chain
  - Substitution of glycine at position A21
  - Addition of two arginines at position B30
  - Gradual release pattern from injection site
INSULIN DETEMIR

☑ 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
INSULIN TACTICS:
Glargine Vs. NPH Insulin in Type 1 DM
Action Profiles by Glucose Clamp

Glycerol Utilization Rate (mg/kg/h)

Time (h) after S.C. Injection

End of observation period

Glargine insulin
NPH insulin
NPH

Relative Insulin Level

Time (hours after injection)
Basal Insulin

**Long acting (e.g. glargine)**
- Provides optimal basal insulin coverage with a once daily dosing
- Lower risk of hypoglycemia
- Flat release profile

**Intermediate acting (e.g. NPH)**
- Less optimal as a basal insulin, because it doesn’t have a flat insulin release profile
- More hypoglycemic episodes
NPH vs Glargine

- Three large RCT have compared once-daily, bedtime NPH or Glargine added to oral agents in pts with type 2 DM
- Less nocturnal hypoglycemia
- Less weight gain
- HbA1c, No difference

Diabetes care, 2001, 24:631-636
Diabetes care, 2000, 23:1130-1136
Diabetes care, 2003, 26(11):3080-3086
Activity Profile of Insulin Lispro

Based on a study of 6 patients with type 1 diabetes and some residual β-cell function and 6 control subjects without diabetes

Adapted from Pampanelli S et al. *Diabetes Care* 1995;18:1452-1459
Lispro/Aspart

Relative Insulin Level

Time (hours after injection)
Regular

**Graph:**
- **Y-axis:** Relative Insulin Level
- **X-axis:** Time (hours after injection)

- **Peak at 2 hours:** 100%
- **50% at 12 hours**

**Legend:**
- Regular Insulin
Pharmacokinetic Profiles of Human Insulin and Insulin Analogs

- Aspart, lispro (4–6 hr)
- Regular (6–10 hr)
- NPH (12–20 hr)
- Extended zinc insulin (18–24 hr)
- Glargine (20–24 hr)

Relative Plasma Insulin Level vs. Hours
ADA Standards of Medical Care in Diabetes-2017
Updates to standards of medical care in diabetes 2016

Diabetes Care 2017;40(Suppl. 1):S1–S138
Treatment: stepwise approach

1. Diet & exercise
2. One oral medicine
3. Combination of oral medicines
4. Oral plus insulin
5. Insulin
Start with monotherapy unless:

- A1c is greater than or equal to 9%, **consider dual therapy**
- A1c is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL or patient is markedly symptomatic, consider **combination injectable therapy**

### Monotherapy: Metformin

| **Efficacy** | high |
| **Hypo Risk** | low risk |
| **Weight** | neutral/loss |
| **Side Effects** | GI/lactic acidosis |
| **Costs** | low |

If A1c is not achieved approximately after 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference- choice dependent on variety of patient- & disease-specific factors)

### Dual Therapy: Metformin +

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (Basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>hypoglycemia</td>
<td>Edema, HF, fxs</td>
<td>rare</td>
<td>GU, dehydration, fxs</td>
<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1c is not achieved approximately after 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference-choice dependent on variety of patient- & disease-specific factors)
**Triple Therapy**

- Sulfonylurea + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist + Insulin (Basal) +

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylurea +</td>
</tr>
<tr>
<td>TZD</td>
</tr>
<tr>
<td>DPP-4-i</td>
</tr>
<tr>
<td>SGLT2-i</td>
</tr>
<tr>
<td>GLP-1-RA</td>
</tr>
<tr>
<td>Insulin $</td>
</tr>
</tbody>
</table>

If A1c is not achieved approximately after 3 months of triple therapy, and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin or (3) on optimally titrated basal insulin, addaGLP-1 RA or meal time insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessary complex or costly regimens. (i.e. adding fourth antihyperglycemic agent).

**Dual Therapy**

- Sulfonylurea + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + Insulin (Basal) +

<table>
<thead>
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<td>DPP-4-i</td>
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<td>SGLT2-i</td>
</tr>
<tr>
<td>GLP-1-RA</td>
</tr>
<tr>
<td>Insulin $</td>
</tr>
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</table>

**Combination Injectable Therapy**

Fig 8.1: Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chart is determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. $ Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al 2015


Diabetes Care 2017;40(Suppl. 1):S1–S138
Insulin Therapy Indications in Type 2 DM

1) HbA$_{1c}$ $\geq$ 10% or BS $<$ 300 mg/dl

2) Symptomatic (e.g., sudden persistent weight loss, ketosis)

3) When multiple non-insulin therapies fail to achieve targets
AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2017

Initiate 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 units once or twice weekly to reach FBG target
- For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

If A1C not controlled, consider combination injectable therapy
Consider different proportions in Mixed Insulin (75/25, 50/50)

Add 1 rapid-acting insulin injection before largest meal

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- If A1C not controlled, **advance to basal-bolus**

Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Add GLP-1 RA

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen

- If goals not met, **consider changing to alternative insulin regimen**

Change to premixed insulin twice daily (before breakfast and supper)

- **Start:** Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
- **Adjust:** ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- If A1C not controlled, **advance to 3rd injection**

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

- **Start:** Add additional injection before lunch
- **Adjust:** ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
Initiation of Basal Insulin

- Add single insulin dose in the evening (10 U or 0.1 U/kg)
- NPH
- Insulin glargine
- Insulin detemir
• Adjust dose on the basis of FBG
• Increase insulin every 3-5 days as needed (provided no hypoglycemia occurs)
• Increase by 2 U if FBG > 120 mg/dL
• Increase by 4 U if FBG > 140 mg/dL
• Increase by 6 U if FBG > 160 mg/dL
When to add the first prandial insulin

FBS at Target

AND

HbA1c > Target
Patients should be instructed to monitor FBG and 2-hpp.

Rapid-acting insulin analogs can be added before the meal(s) associated with the highest post prandial.

This prandial insulin should be adjusted to achieve 2-hpp target glucose.
stepwise pattern

- For example, a patient may be started on 3-4 U of rapid-acting insulin before the biggest meal, and the dose can be adjusted by 1-2 U as needed according to 2-hpp.
stepwise pattern

- Once target levels are achieved at one meal, additional prandial boluses of rapid-acting insulin can be added at other meal times and adjusted in a similar pattern.
stepwise pattern

- Oral insulin secretagogues should be stopped at this point, but insulin sensitizers can be continued.

- With this stepwise pattern, the patient is gradually transitioned to a basal-bolus regimen similar to that used in type 1 diabetes.
Premix insulins

- Biphasic Human insulin (NPH + Regular)
- Insulin analogues (Insulin Aspart 70/30, Lispro 75/25 and 50/50,)
Formulation of premixes

Premixed suspension of:

- Soluble insulin aspart (30%)
- Protamine-crystallised insulin aspart
- NPH
- Premixed human insulin

NovoMix® 30
Premixed regimen

• This strategy may be appropriate for certain patients who eat regularly and may be in need of a simplified approach beyond basal insulin

• Disadvantages: inability to titrate the shorter- from the longer-acting component
Premix insulin

• No need for self mixing
• Minimizing dosing error
• Less injections (attractive alternative to basal bolus)
• Fixed ratio (Less flexibility)
NovoMix® 30: A consensus statement
Simple algorithms for intensification

Basal insulin OD or BID

HbA1c 7-8%  
FPG > 6 mmol/L  
(FPG > 110 mg/dL)  
Titrate basal to achieve  
FPG < 6 mmol/L  
(110 mg/dL)

HbA1c > 8.0%  
FPG: 4-6 mmol/L  
(FPG > 73-110 mg/dL)

Switch TO BIAsp 30 BID

*If recurrent hypoglycaemia limits up-titration of the basal dose, or the daily dose reaches 0.5 U/kg (insulin units per kg body weight), switching to BIAsp 30 twice daily can be considered
<table>
<thead>
<tr>
<th>FBS</th>
<th>Change in Dose of Predinner Insulin</th>
<th>Predinner Blood Glucose Level</th>
<th>Change in Dose of Prebreakfast Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>-4U</td>
<td>&lt;60</td>
<td>-4U</td>
</tr>
<tr>
<td>60-80</td>
<td>-2U</td>
<td>60-80</td>
<td>-2U</td>
</tr>
<tr>
<td>81-110</td>
<td>NO CHANGE</td>
<td>81-110</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>111-140</td>
<td>+2U</td>
<td>111-140</td>
<td>+2U</td>
</tr>
<tr>
<td>141-180</td>
<td>+4U</td>
<td>141-180</td>
<td>+4U</td>
</tr>
<tr>
<td>&gt;180</td>
<td>+6U</td>
<td>&gt;180</td>
<td>+6U</td>
</tr>
</tbody>
</table>
Staying on NovoMix® 30

Intensification from NovoMix® 30 twice daily to three times daily:

Add 2-6 units or 10% of total daily dose of NovoMix® 30 before lunch
Criteria for successful insulin therapy

- Efficacy: HbA$_{1c}$ < 7.0%
- Low rates of hypoglycaemia
- Minimal weight gain
- Flexibility
- Treatment satisfaction
# How to Switch Between Insulin Products

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPH to Long-acting</strong></td>
<td></td>
</tr>
<tr>
<td>NPH to insulin detemir (<em>Levemir</em>)</td>
<td>• Convert unit-per-unit.¹</td>
</tr>
<tr>
<td></td>
<td>• Some patients on basal-bolus insulin may require more <em>Levemir</em> than NPH.¹</td>
</tr>
<tr>
<td></td>
<td>• Give <em>Levemir</em> once daily, or divided twice daily if necessary for control.¹</td>
</tr>
<tr>
<td></td>
<td>• Do not mix <em>Levemir</em> with other insulins.¹</td>
</tr>
<tr>
<td>NPH to insulin glargine (<em>Lantus</em>)</td>
<td>• NPH once daily: convert unit-per-unit and give once daily.²</td>
</tr>
<tr>
<td></td>
<td>• NPH twice daily: reduce daily dose by 20% and give once daily.²</td>
</tr>
<tr>
<td></td>
<td>• Do not mix <em>Lantus</em> with other insulins.²</td>
</tr>
<tr>
<td><strong>Long-acting to NPH</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir (<em>Levemir</em>) to NPH</td>
<td>• Convert unit-per-unit.³</td>
</tr>
<tr>
<td></td>
<td>• Give NPH at bedtime or split twice daily (e.g., 50:50 or 2/3 in AM and 1/3 before dinner or at bedtime).³④⑤</td>
</tr>
<tr>
<td>Insulin glargine (<em>Lantus</em>) to NPH</td>
<td>• Convert unit-per-unit.³</td>
</tr>
<tr>
<td></td>
<td>• Give NPH at bedtime or split twice daily (e.g., 50:50 or 2/3 in AM and 1/3 before dinner or at bedtime).³④⑤</td>
</tr>
</tbody>
</table>
Goal achievement?

- Attainment of glycemic targets using insulin remains difficult

- In a recent review of 48 randomized clinical trials using insulin in T2DM patients with a mean baseline HbA1c of 8.7%, only 40–54% achieved an HbA1c of less than 7%
Thank You!