Insulin therapy in type 2 diabetes – When and how?

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Disclosures

- None relevant to today’s talk

Learning Objectives

Upon completion of this session, participants should be able to:

- Recognize clinical scenarios requiring or prompting consideration for insulin therapy in type 2 diabetes
- List pharmacokinetics of currently-available insulin therapies
- Develop at least 2 strategies for initiating insulin therapy in type 2 diabetes
- Understand basic paradigms for adjusting insulin therapy
- Outline factors that may increase or decrease insulin dose requirements
Cases

- 38 y.o. woman with type 2 diabetes (T2D) x 8 years, on dapagliflozin 10 mg and albiglutide 50 mg SQ Qwk with A1c 8.6%, 189 lb, BMI 31, eGFR >60 mL/min
- 53 y.o. woman with T2D x 17 years, CKD stage 3a, neuropathy, COPD. On metformin 1 g BID, glipizide XR 20 mg QD, wt 73 kg, BMI 29, A1c 7.3%. Now eGFR 39 mL/min.
- 59 y.o. man with HTN, obesity, depression, no DM. Polyuria, polydipsia, blurry vision. Wt 97 kg, BMI 34, Glucose 276, creatinine 0.8, A1c 11.8%. Takes metoprolol, HCTZ, sertraline, simvastatin, ASA.

The pancreas secretes 30 units of insulin per day

Insulin is secreted in response to food: “glucose*-stimulated insulin secretion”

*and incretin-stimulated
But insulin is also secreted to maintain a basal level at all times

Who needs insulin?
When do patients with T2D need it?

- ALL patients with type 1 diabetes
- Some patients with type 2 diabetes
  - If lifestyle modifications and non-insulin combinations don’t achieve blood glucose targets
  - Contraindications to non-insulin agents
    - Renal or hepatic dysfunction, congestive heart failure, pancreatitis history, medullary carcinoma - thyroid
  - May be initiated earlier when selecting glucose-lowering therapies

Insulin treatment for type 2 diabetes - ALWAYS, if:

- Signs of insulin deficiency on presentation
- Weight loss
- Fasting blood glucose >250 mg/dL
- Random blood glucose >300 mg/dL
- Hemoglobin A1c >10%
- Hospital admission for diabetic emergency
- Hyperglycemic hyperosmolar state
- Diabetic ketoacidosis

Watch for clues that insulin can be tapered or stopped
Over 30% of adults with DM in the U.S. are on insulin therapy

http://www.cdc.gov/diabetes/statistics/meduse/fig2.htm

Where does insulin fit in the progression of glucose-lowering treatment?


Starting insulin in type 2 diabetes

NHANES: difference in insulin regimens in older vs younger (age <70)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Difference in the number of insulin regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (≥70 years)</td>
</tr>
<tr>
<td>One injection (%)</td>
<td>10 (3.0)</td>
</tr>
<tr>
<td>Two injection (%)</td>
<td>30 (44)</td>
</tr>
<tr>
<td>Three injection (%)</td>
<td>21 (26.5)</td>
</tr>
<tr>
<td>Four injection (%)</td>
<td>10 (13.0)</td>
</tr>
<tr>
<td>Five injection (%)</td>
<td>2 (2.7)</td>
</tr>
</tbody>
</table>

Fig. 1: What insulin regimens. Group A: patients aged >70 years, Group B: patients aged <70 years. NS: not significant.

Barriers to insulin therapy

- **Patient**
  - Fear of injections
  - Fear of hypoglycemia
  - Fear of gaining weight
  - Belief that being on insulin means diabetes is really bad
  - Belief that insulin causes blindness and other problems
  - Inconvenience

- **Provider**
  - Uncertainty about whether insulin is really necessary
  - Difficulty initiating and adjusting therapy
  - Time
  - Experience
  - Staffing
  - Fear of hypoglycemia
  - Fear of inducing weight gain

adapted from Endocrine Practice 2006;12(Supp. 1):98-304

What regimen to use?

- **Patient’s age**
- **Duration of diabetes**
- **Complication(s)**
  - Hypoglycemia unawareness?
  - Retinopathy?
- **Patient’s motivation**
- **Patient’s self-management skills**
- **Daily schedule – skipped meals?**
- **Activity?**
Most insulins are available as U-100 (100 units/mL) in 10 mL vials
- 0.3, 0.5 and 1.0 mL syringes
OR
- Insulin pens
- U-500 (20 mL)
- U-200 - Lispro
- New: degludec U-200, U-100
- Newer: glargine U-300
- Newer: inhaled insulin

### Insulin preparations

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled</td>
<td>5-15</td>
<td>1</td>
<td>2.5-3</td>
</tr>
<tr>
<td>Rapid acting*</td>
<td>5-15</td>
<td>1-1.5</td>
<td>3-5</td>
</tr>
<tr>
<td>Regular</td>
<td>30-60</td>
<td>2</td>
<td>6-8</td>
</tr>
<tr>
<td>U-500</td>
<td>30-60</td>
<td>6-8</td>
<td>12-16</td>
</tr>
<tr>
<td>NPH - cloudy</td>
<td>1-3</td>
<td>6-8</td>
<td>12-16</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1</td>
<td>-</td>
<td>12-20</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>1.5</td>
<td>-</td>
<td>~24</td>
</tr>
<tr>
<td>Degludec (Tresiba)</td>
<td>1</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Varies</td>
<td>Varies</td>
<td>Up to 16 hr</td>
</tr>
</tbody>
</table>

*lispro (Humalog), aspart (Novolog), glulisine (Apidra)

### New insulin: degludec (Tresiba)

- Ultra-long-acting
- U-100 and U-200
- QD dosing
- Ryzodeg 70/30 (insulin degludec/insulin aspart)
Newer insulin formulation: U-300 Glargine (Toujeo)
- 3-fold more concentrated
- Only available in a pen (order pen needles)
- No dose conversion needed

Biosimilar insulin: Basaglar
- Approved Dec 2015
- Will be available Dec 2016
- Kwikpen device

U-500
- 20 mL vials
- Concentration: 500 units/mL
- Onset: like regular insulin
- Peak: like NPH
- Duration: like NPH

Now in pen form – do not convert dose
- 5 units on pen = 5 units of U-100. 5 unit increments

Newer insulin: Afrezza (inhaled)
- Rapid-acting but peak at 1 hr, duration 2.5 hr
- 4-unit and 8-unit cartridges (max 3 per dose)
- DO NOT use in asthma or COPD
- Can cause acute bronchospasm
- Measure FEV1 prior to starting
  (Baseline, 6 mo, qyr)
- Stop if FEV1 ↓20%
**Insulin pharmacokinetics**

- Lispro / Aspart / Glulisine / inhaled
- Regular
- NPH
- Detemir
- Glargine
- Degludec

**Basal insulin**

- Insulin taken to suppress hepatic glucose production and to maintain normal fasting blood glucose levels

**Basal insulin - methods**

- Glargine QD
- Detemir QD or BID
- Degludec (U-100 or U-200) QD
- Glargine U-300 QD
- NPH QHS or BID
- U-500 BID-TID
Bolus (prandial, meal) insulin

- Insulin taken to cover the rise in glucose from a meal: fixed dose OR according to carbohydrate content of meal

- Lispro QAC
- Aspart QAC
- Glulisine QAC
- Regular insulin QAC

Correctional insulin

- Insulin taken to correct pre-meal hyperglycemia
  - Often added to meal/prandial dose
  - Can be taken alone (in between meals)
  - Caution: avoid “stacking” corrections to prevent hypoglycemia

Summary of ADA/EASD consensus algorithm and update

- NPH QHS or glargine/detemir QD: 10 units or 0.1-0.2 u/kg
  - Check fasting BG (FBG) every morning (QAM)
  - Increase by 10-15% or 2-4 units 1-2 x/wk until FBG target reached OR
  - Increase dose by 2 units q3 days until <130 mg/dL
    - If fasting BG >180, increase by 4 units q3 days

Inuzzi SE, et al. Diab Care 2015;38:140-149.
Nathan et al. Diabetes Care 2009;32:193
Treating to target:
Self-titration of basal insulin

- **3-0-3**: Take average of 3 days of fasting BG
  - If <80, lower by 3 units
  - If 80-110, no change
  - If >110, increase by 3 units
- **2-0-2**: Take average of 3 days of fasting BG
  - If <80, lower by 2 units
  - If 80-110, no change
  - If >110, increase by 2 units
- Re-assess when dose is up to 0.5 units/kg/day!

Key point

Is the basal insulin actually treating prandial needs?
- Hypoglycemia with skipped meals
- Very large dose of basal insulin
- If suspected, ask your patient to check at least 3 bedtime BG’s and fasting BG’s the next morning
  - If BG drops by more than 20-30 mg/dL, then cut basal and add bolus insulin

Potential causes for fasting hyperglycemia

- Inadequate dose of basal insulin
- Inadequate duration of action of basal insulin
- Poor absorption (too high a dose?)
- Nocturnal hypoglycemic episode
- Dawn phenomenon

- Other possible causes for hyperglycemia:
  - Injection sites, injection technique, insulin ok?
What non-insulin medications should be stopped? When?

- ALWAYS continue metformin if possible
- STOP:
  - Sulfonylureas, meglitinides – when adding bolus insulin
  - Fluid retention/weight gain
    - Thiazolidinediones (pioglitazone, rosiglitazone)
- Ok to continue:
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - SGLT2 inhibitors
  - All others

In what order should glucose-lowering medications be down-titrated?
Reduce insulin dose first

Summary of ADA/EASD update (2)

- Check HbA1c q3 months; if at goal, continue regimen
- If hypoglycemia occurs, determine/address cause, reduce dose by at least 4 units or 10-20%
- If HbA1c is above goal but FBG is at goal or dose >0.5 units/kg/day, treat PPG (postprandial glucose)
  - Add rapid-acting insulin before largest meal, 4 units or 0.1 unit/kg or 10% basal to start
  - If A1c <8%, consider ↓basal by same amount
  - Increase by 0.2 or 2-4% 1-2x/wk until target reached
- OR
  - Switch to pre-mixed insulin (2/3, 1/3, or half and half)

Caveat: “Good” A1c Good control
Hypoglycemic symptoms without hypoglycemia

- Persistent hyperglycemia can lead to symptoms of hypoglycemia at higher BG’s
- Educate patient
  - Rapidly falling BG can also cause hypoglycemic symptoms
    - If this is soon after injection and still concerned, check again in 30-60 minutes
  - DO NOT treat unless BG <80 mg/dL
  - Always check BG if symptoms of hypoglycemia
- This will disappear after a period of good control (weeks to a few months)

Multiple daily injections
“Basal-bolus”, “intensive insulin therapy”

- glargine / detemir
- lispro / aspart / glulisine / afrezza

AM meal Noon meal PM meal HS
Basal amount ~50% Bolus amount ~50%

Key points about basal bolus insulin therapy

- Requires a lot of education
- This type of regimen allows for:
  - Flexible meal pattern – #, timing, content
  - Unrestricted activity pattern – timing, intensity
  - Adjust regimens based on glucometer download and CGM data, meals, activity
- The most intensive regimen may not be appropriate for all patients (other factors)
Overall paradigm for adjusting insulin

- Eliminate the lows
  - When is it happening? Why?
  - Focused questioning, discern BG patterns
  - Reduce total daily dose of insulin by at least 10-20% in a targeted way

- Eliminate the highs
  - Missed doses? Is the basal insulin treating meals?
  - When are they happening? Why?
  - Focused questioning, discern BG patterns
  - Increase total daily dose of insulin by 10-20% in a targeted way

Caveat: the actual pharmacokinetics of injected insulin may vary

- Volume
- Concentration
- Body site (thigh vs. abdomen vs. upper arm)
- Presence of lipodystrophy
- Intradermal vs. subcutaneous vs. intramuscular
  - If site is warm, rubbed or exercised

Factors leading to hyper- and hypoglycemia

- Hyperglycemia
  - Calories – carbs, fat, protein
  - Infection
  - Illness
  - Glucocorticoids, meds
  - Menstruation
  - Less activity
  - Hyperthyroidism
  - Peritoneal dialysate
- Hypoglycemia
  - Skipping a meal
  - Smaller meal
  - Overestimating carb content
  - Renal disease
  - Adrenal insufficiency
  - Hypothyroidism
  - Increased activity
  - Liver disease
Cases

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Active areas of research in insulin therapy

- Super-fast acting insulins
- “Smart” insulins
- Insulin depots
- Bioengineering an artificial pancreas