

A Practical Case-Based Approach to Insulin Therapy in Type 2 Diabetes

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Disclosures

Nothing to disclose

Learning Objectives

- Describe a practical approach to the use of insulin in patients with type 2 diabetes.
- Review the addition of basal insulin in patients with type 2 diabetes not well controlled on non-insulin therapies.
- Manage patients who cannot get good glycemic control with basal insulin alone.
- Describe an approach to managing the severely insulin resistant patient.

Active Learning Questions

1. Which of the following is true about insulin therapy in the management of type 2 diabetes:
 1. Associated with significant risk of hypoglycemia
 2. There is no maximum dose
 3. Insulin makes you hungry and therefore causes weight gain
 4. Meal time insulin is almost never needed in type 2 diabetes
2. The indications for using insulin in type 2 diabetes include all of the below except:
 1. Pregnancy
 2. Poor control on non-insulin agents
 3. Severe hyperglycemia
 4. Chronic kidney disease

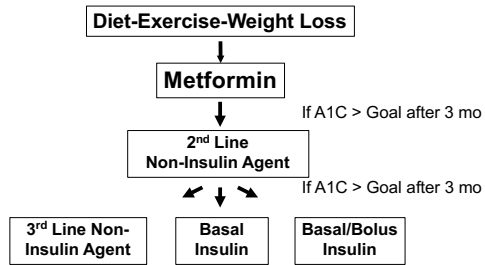
Case 1:

- 48 y/o woman presents for follow up of Type 2 Diabetes which she has had for some time. She reports some polyuria and polydypsia. She has peripheral neuropathy and mild retinopathy. Her BG's have crept up and continue to run in the 200's. Her diet and weight have remained stable. She denies chest pain.
- She currently takes metformin, sitagliptin, empagliflozin, lisinopril, HCTZ, sertraline, levothyroxine, ASA
- Physical Exam: BMI 30, BP 141/86
↓sensation in her feet.
- Labs: HbA1c – 10.2% FBG - 210 mg/dl

Case 1: Assessment/Plan

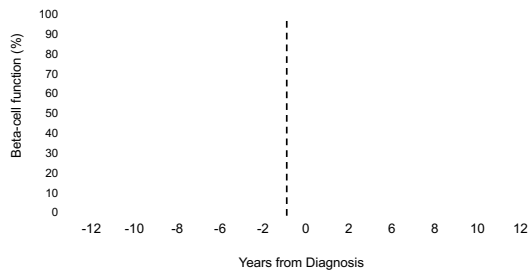
1. Type 2 Diabetes: poor control on triple oral therapy
 - Reinforce Lifestyle Modification and weight loss
 - Education
 - Step therapy
 - Add a GLP-1 analog or switch instead of the DPP4 inhibitor?
 - Add or switch to insulin?
2. Don't forget other problems:
 - HTN, Hyperlipidemia, Cardiac Risks?

Type 2 Diabetes: Individualized Therapy



adapted from Inzucchi S, Diabetes Care 2012; 35:1364-79

Decline in β -Cell Function: UKPDS



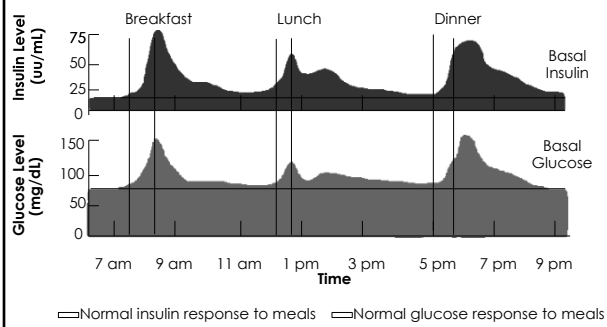
Indications for Insulin Therapy in Type 2 Diabetes

- Poor control on non-insulin agents
- Cannot take/tolerate oral agents
- Severe hyperglycemia
- Hyperosmolar State and/or Ketoacidosis
- Pregnancy

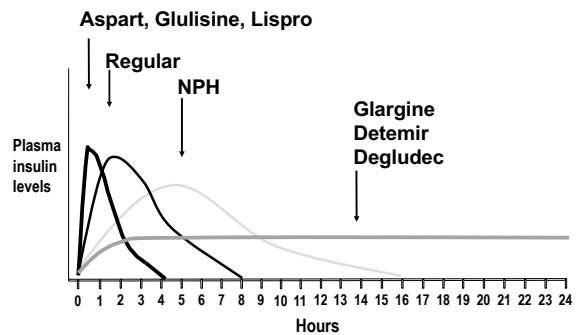
- Consider whether this could in fact be Type 1 Diabetes?

How Should We Add Insulin?

Normal Physiology of Insulin and Glucose Response to Meals



Profiles of Insulin Preparations



Human Insulin and Analogs Typical Times of Action

Insulin Preparations	Onset of Action	Peak	Duration of Action
Aspart (<i>Fiasp</i>)	~2.5 min	60 min	
Aspart (<i>Novolog</i>) Glulisine (<i>Apidra</i>) Lispro (<i>Humalog</i>)	~15 min	60-90 min	2-4 hours
Human Regular	30-60 min	2-4 hours	4-6 hours
Human NPH	1-4 hours	6-10 hours	12-20 hours
Detemir (<i>Levemir</i>)	1-2 hours	Relatively Flat	18-24 hours
Glargine (<i>Lantus</i> , <i>Toujeo</i> , <i>Basaglar</i>)	1-2 hours	Flat	~24 hours
Degludec (<i>Tresiba</i>)	1-2 hours	Flat	~42 hours

“Other” Insulin Preparations

- Pre-Mixed Insulins
 - NPH/Regular 70/30
 - NPH/Aspart (*Novolog*) 70/30
 - NPH/Lispro (*Humlog*) 70/25 and 50/50
 - Degludec/Aspart 70/30 (*Ryzodeg*)
- Concentrated Insulins
 - Regular U-500
 - Lispro U-200 (*Humalog U-200*)
 - Glargine U-300 (*Toujeo*)
 - Degludec U-200 (*Tresiba U-200*)
- Inhaled Technosphere Insulin (*Afrezza*)
- Basal Insulin + GLP-1 receptor analogs
 - Glargine/Lixisenatide 100/33 (*Soliqua*)
 - Degludec/Liraglutide 100/3.6 (*Xultophy*)

Adding/Starting Basal Insulin in T2DM

- Theory and Practical:
 - Provide some insulin and allow the pancreas to continue to make the rest
 - Especially good for persistent fasting hyperglycemia
 - Allows the prandial insulin to come from a more naturally regulated source
 - Can often be done with a single shot a day
 - Usually add to current regimen
 - If dosed properly, risk of hypoglycemia is VERY low even if people skip meals, change mealtimes...

Adding/Starting Basal Insulin in T2DM

- Delivery Options:
 - Detemir, Glargine, or Degludec
 - NPH (bedtime/BID)
- Start with 10-15 units daily (bedtime?)
 - Likely "under-dosing" but want to avoid hypoglycemia
- Ask patient to monitor fasting and occasional bedtime blood glucose
- "Self" titration vs at provider visits:
 - Ex: ↑ insulin by 2-5 units every 3 days until reach desired FBG (ex 90-130)
 - Watch overdosing with basal insulin!!!
 - Aim for FBG = HS

Case 1: Management

- Type 2 Diabetes: poor control on double oral therapy
 - Reinforce Lifestyle Modification and weight loss
 - Education
 - Step therapy
 - Continued oral therapies
 - Started glargine 10 units at bedtime
 - Self-titrated every 3 days by 2 units
 - f/u by phone at 2 weeks – doing well
 - 3-month clinic f/u: up to 30 units of glargine daily with FBG 120's on average, A1c now 7.0% and no hypoglycemia

Case 1: Follow-Up

- Patient did well for some time. she was seen by another provider who up-titrated her basal insulin to 50 units daily for worsening fasting hyperglycemia.
- FBG are <140 but her A1c is back up to 8.1%
- More frequent monitoring reveals:

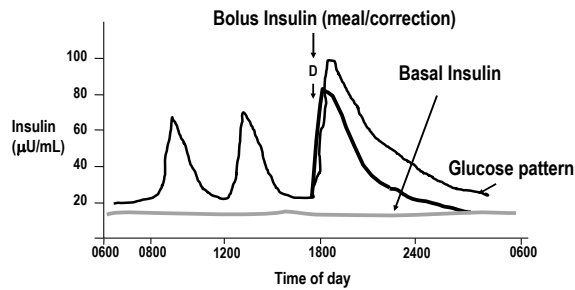
AM	noon	dinner	HS
135	180	240	300
128	175	286	325
- Has occasional BG <70 in morning

So what's going on here?

Adding Mealtime/Prandial or Bolus Insulin

- Ultimately may need true basal-bolus therapy
- Consider adding a fixed dose of a fast acting insulin before the largest meal of the day
 - Start with a dose that is 10-30% of the basal dose.
 - Usually use a rapid-acting analog insulins
 - Regular can also be used when cost is an issue OR in patients with gastroparesis
 - Consider inhaled insulin
- Can also consider split/mixed regimens or “premixed” insulin preparations
- Can also consider premixed basal + GLP-1 preparations

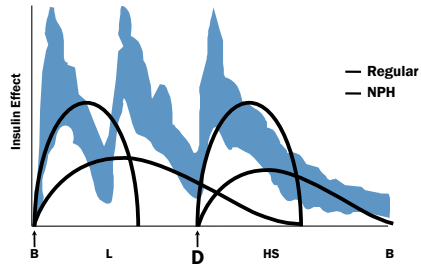
Basal + Bolus with Biggest Meal



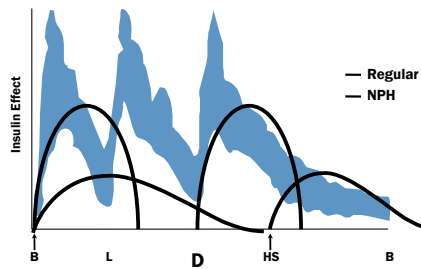
Split-Mixed Therapy

- NPH + Regular or Rapid-Acting Analog
 - given before breakfast and dinner
 - mixed or premixed (70/30, 75/25, 50/50)
- Pros:
 - Fewer injections
 - Less expensive?
- Cons:
 - Not physiologic
 - Prone to hypoglycemia
 - Snacks often needed to prevent lows → weight gain?
 - Regular must be taken 30-60 min before meals!

Twice-daily Split-Mixed Therapy



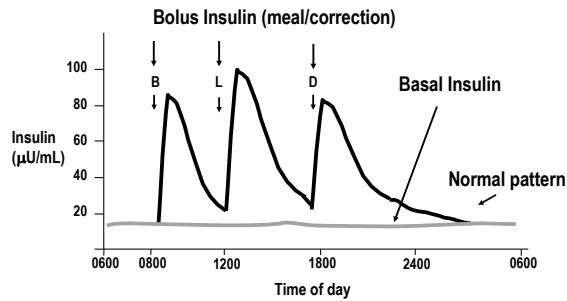
3-Injection Split-Mixed Therapy



Adding Mealtime/Prandial or Bolus Insulin

- Check some pre and post (2-hr) prandial BG
- If still not well controlled:
 - Increase dose at the single meal
 - Add similar dose to a second meal
 - Add a correction factor (CF)
- Continue to increase/add doses until patient is on “full” basal-bolus insulin
- Consider discontinuing insulin secreting medications once on basal-bolus therapy

Basal-Bolus Insulin Treatment



Basal-Bolus Insulin Therapy

- Pros:
 - More physiologic
 - More flexibility
 - Less hypoglycemia
 - Better glycemic control
- Cons:
 - More monitoring
 - More injections
 - More expensive

Basal-Bolus Therapy - Summary

- Basal Insulin (whether eating or not)
 - Glargine, Degludec or Detemir (once or twice daily)
 - NPH twice daily (preferably AM + HS)
 - ~50% of daily needs
- Bolus Insulin (only if eating)
 - Rapid-Acting Analog with, during or after meals
 - Regular 30-45 min before meals
 - 10% to 20% of daily needs at each meal
- Supplemental or Correction Insulin
 - Rapid-Acting or Regular insulin in addition to prandial insulin and/or at bedtime
- Insulin Pump Therapy?

Blood Glucose Monitoring

- More is better
- “qAC and qHS”
 - OK, but don’t necessarily know if pre-meal numbers reflect basal or bolus needs
- 6-point profile: before and 2-hr after each meal
 - Good for making adjustments to basal/bolus therapy
- 2-3 AM BG
 - Good for evaluating for Somogyi Effect
- When sick or symptoms of hypoglycemia
- Consider Libre Flash™ or Continuous Glucose Monitoring

Bolus Therapy: Carb Counting

- We don’t always eat the same amount of carbohydrate from meal to meal and day to day, so fixed dosing doesn’t make much sense
- Teach patient to estimate carbohydrate intake
- Determine a ratio of units of insulin to grams of carb, ex: 1 unit : 15 g
- May depend on the meal
- May depend on other macronutrients
- Monitor pre- and post-meal BG’s to adjust

Correction Factor (CF)

- Goal is to lower an elevated BG down to a desired goal such as 100 or 150 mg/dl
- CF is given in addition to mealtime insulin
- Use “1650” rule: every unit of rapid-acting insulin will reduce BG by $\sim 1650/\text{TDD}$
 - Ex: if TDD is 50 units, then CF will be 1 unit of insulin will reduce BG by ~ 33 mg/dl
- Patient can make calculations or you can create a “sliding scale”
- If use CF at bedtime use $\frac{1}{2}$ dose

Correction Factor (CF)

- Goal is to lower an elevated BG down to a desired

Blood Glucose (mg/dl)	Insulin Dose (units)
0-150	0
151-200	1
201-250	2
251-300	3
301-350	4
>350	5

- If use CF at bedtime use ½ dose

Case 2:

- The patient is a 46 yo man with Type 2 Diabetes who presents for follow up. He reports erratic BG numbers ranging from 32 to 380 but doesn't check as frequently as he used to. He reports hypoglycemia 2-4 times a week with frequent occurrences during the night. He is sometimes unaware of his low BGs. He is struggling with personal stressors and substance abuse. He admits to frequently missing insulin doses.
- Meds: metformin 1,000 mg BID, Levemir 55 units qHS, Lispro insulin 10-15 units with meals
- Labs: HbA1c 11.7% FBG 70-290

Case 2: Assessment & Goals

- Type 2 Diabetes
 - Poor control!
 - Frequent hypoglycemia with unawareness!!
 - Neuropathy? Gastroparesis? Psychosocial issues
 - Is this "Brittle Diabetes"?
 - Can almost always find an explanation for erratic BGs
 - Most important issues are usually psycho-social in nature
- Goals:
 - Reduce hypoglycemic events!!!
 - Reverse hypoglycemia unawareness!!!
 - Then start working on long-term glycemc goals
 - Work on psycho-social issues

Hypoglycemia

- Normal fasting blood glucose is 70 to 100 mg/dl
- Symptoms of hypoglycemia usually begin when the plasma blood glucose falls to <50-60 mg/dl
 - varies from patient to patient
 - may lessen with duration of diabetes
 - Symptoms may occur with big changes in BG, ie if the patient usually “lives” at 200 he may “feel” low with a BG of 100
- Type 1 diabetes >> type 2 diabetes
- Hypoglycemia is about 2-3 time more common with intensive insulin regimens

Symptoms of Hypoglycemia

Adrenergic

- Sweating
- Tremor
- Tachycardia
- Anxiety
- Hunger

Neuroglycopenic

- Dizziness
- Headache
- Decreased mental activity
- Clouding of vision
- Confusion
- Convulsions
- Loss of consciousness

Hypoglycemic Unawareness: Hypoglycemia begets hypoglycemia

- Loss of adrenergic warning signs
- Altered mental status with no warning
- More common in patients who have frequent hypoglycemia
 - alterations in delivery of glucose to the brain
- One episode of hypoglycemia can lead to hours of unawareness
- Chronic hypoglycemia can lead to cognitive dysfunction
- Treatment: *avoidance of hypoglycemia* for 3 or more weeks

Management of Hypoglycemia

- If symptomatic patient should check BG level
- If BG < 70 treat with 15 grams of carbohydrate
 - Glucose tablets or gel
 - Dextrose based candy (Smarties®, SweetTarts®, etc)
- Retest BG in 15 min and retreat until BG > 70
- When BG > 70
 - eat meal/snack if appropriate time
 - If >30 min before next meal/snack eat 15 g of “slower” acting carbohydrate + protein, such as 1/2 sandwich, cheese & crackers, 1 cup low-fat milk or yogurt
- Glucagon
 - If unable to take po
 - Teach family member how to inject

Case 2: Management

- Evaluate his “Stage of Change”
- Consider using strategies like “Motivational Interviewing”
- Consider referral for and treatment of psycho-social issues
- Education!
 - Emphasize compliance especially with basal insulin
- Good candidate for switching to “true” once daily basal insulin versus changing his Levemir to BID
- Consider changing him to 70/30 insulin twice daily if you think that will help with compliance
- Reinforce frequent BG monitoring especially while making adjustments

Case 3:

- 52 y/o woman presents for follow up of Type 2 Diabetes which she has had for some time. She has been requiring more and more insulin yet can't seem to get a handle on her blood sugars. Her most recent A1c was 9.2%. Her AM BGs range in the 190-220's, in the evening her BGs are in the mid to higher 200's.
- She currently takes glargine 100 units 2x daily, aspart insulin 30-50 units with meals
- Physical Exam: BMI 43, BP 148/86
acanthosis nigricans, 1+ pedal edema
- Labs: A1c 9.1%

What About the Severely Insulin Resistant Patient?

Consider U-500 insulin

- What is it?
 - 5 x concentrated Human Regular Insulin
 - Onset within 30 min, peak 2-4 hrs, lasts 6-10 hrs
 - Similar profile to NPH
- Who's a good candidate?
 - > 200 units/day or > 2 units/kg/day
- How to use?
 - Stop all other forms of insulin
 - If A1c <8 ↓ dose 10-20%; If A1c >10 ↑ dose 10-20%
 - If TDD is 100-300 use BID - 60% BF, 40% D
 - If TDD is 300-600 use TID - 40% BF, 30% L, 30% D

Case 1: Assessment/Plan

- Type 2 Diabetes: poor control on high dose insulin therapy and severe insulin resistance
 - Reinforce Lifestyle Modification and weight loss
 - Education
 - Consider changing her to U500?
 - TDD = ~300 units
 - Change her to 180 units qAM and 120 units qPM?
 - Add an insulin sensitizer?
 - Metformin - why isn't she on this?
 - TZD
 - Consider bariatric surgery?

Reality and Practical Tips With Insulin Therapy

- Efficacy is very high
 - Improves "glucose toxicity"
 - Indirectly improves insulin sensitivity and β -cell function
 - No maximum dose!
- Hypoglycemia
 - Don't use basal insulin to cover meal-related needs!
 - Less hypoglycemia with insulin analogs
- Weight Gain
 - Insulin is an "anabolic" hormone so can lead to wt gain
- Bolus Insulin
 - Consider starting bolus insulin with biggest meal
 - Don't take it if you don't eat!

Questions?
