Intensifying Insulin In Type 2 Diabetes

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Disclosures

• Off label and investigative use of some medications will be discussed
• Speaker’s Bureau, Novo Nordisk
Objectives

• Review use of current guideline based diabetes medication management
• Assess patients with type 2 diabetes requiring more intensive glycemic management
• Describe the use of intensive insulin management in appropriate patients in a clinical setting
ADA/EASD Type 2 Medication Guideline April 2012

Healthy eating, weight control, increased physical activity

Metformin
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea
  - high
  - moderate risk
  - gain
  - hypoglycemia

- Metformin + Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, fx's

- Metformin + DPP-4 Inhibitor
  - intermediate
  - low risk
  - neutral

- Metformin + GLP-1 receptor agonist
  - high
  - low risk
  - loss
  - GI

- Metformin + Insulin (usually basal)
  - highest
  - high risk
  - gain
  - hypoglycemia

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + GLP-1-RA
- Metformin + DPP-4 Inhibitor + GLP-1-RA
- Metformin + GLP-1 receptor agonist + Insulin
- Metformin + Insulin (usually basal) + DPP-4-i

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

- Insulin (multiple daily doses)
Intensifying Insulin Management in Type 2 Diabetes
Role of Basal Insulin in Type 2 Diabetes

Beta-cell function declines as Type 2 diabetes progresses

Beta-cell function (%)

Years from diagnosis

Long-Acting Insulin

- Detemir (Levemir)
- Glargine (Lantus)
- (Human NPH (N) )
- Taken 1 or 2 times daily
- “Basal” insulin
Rapid Acting Insulin

- Aspart (Novolog)
- Lispro (Humalog)
- Glulisine (Apidra)
- (Human Regular)

- Taken with meals and snacks
- “Bolus” insulin
Basal Insulin in Type 2 Diabetes

- Glargine (Lantus), Detemir (Levemir)
- (NPH)
- Good, potent add-on for improved A1C
- Second line agent for some patients
- A1C >9, diabetes longer than 5 to 7 years
What do we do when basal insulin + other meds aren’t enough?

Practical Clinical Approaches
Recall Insulin Types

- Basal (long acting) insulin often given once daily (sometimes twice daily)

- Bolus (rapid acting) insulin often given with meals and maybe snacks
Adding Bolus Insulin for Meals in Type 2 Diabetes

- Lispro (Humalog)
- Aspart (Novolog)
- Glulisine (Apidra)

- Why might bolus insulin be important in some Type 2 patients?
Fasting and Postprandial Glycemic Excursions as a Function of A1C


A1C (%) Quintiles

<table>
<thead>
<tr>
<th>Quintile</th>
<th>A1C (%)</th>
<th>Postprandial Hyperglycemia</th>
<th>Fasting Hyperglycemia</th>
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<tr>
<td>1</td>
<td>(&lt;7.3)</td>
<td>70 ± 5</td>
<td>30 ± 5</td>
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<tr>
<td>2</td>
<td>(7.3–8.4)</td>
<td>60 ± 5</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>(8.5–9.2)</td>
<td>50 ± 5</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>4</td>
<td>(9.3–10.2)</td>
<td>40 ± 5</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>5</td>
<td>(&gt;10.2)</td>
<td>30 ± 5</td>
<td>70 ± 5</td>
</tr>
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</table>
3 Ways to Intensify Insulin In Type 2 Diabetes

• **Simple:** 90/10: 2 injection program
  1 basal, 1 bolus (w/biggest meal)

• **Advanced:** Non-Carb Counting
  1 basal, 3 boluses
  estimated dosing based on meal “size”

• **Sophisticated:** Carb-counting
  1 basal, 3 boluses (+ maybe snack boluses)
  calculated on carb intake
Moving Toward Multiple Daily Injections (MDI)

- As type 2 patients take larger doses of basal insulin, temptation is to split basal dose and give BID.
- If going to 2 injection program, better to keep basal once daily and add a rapid acting insulin injection with largest meal (90/10 rule).
Basal/Bolus Injection

2 injection program

Rapid (Lispro, Glulisine, Aspart)

Long (Detemir, Glargine)

adapted from R. Bergenstal, IDC
Initiate 2 Injection Program

- 90/10 rule (90% basal, 10% bolus) for 2 injection regimen
- Start with largest meal of the day
- Often stop TZD, always stop SU, need to consider dosing of other meds
90/10 Rule For Initiating MDI

- For example:

- Patient on 50 units of basal (long acting) (Glargine or Detemir)

- Want to add bolus (rapid acting) (aspart, lispro, glulisine)

with largest meal of the day
90/10 Rule

• Reduce basal insulin by 10% to 45 units
• Add that  5 units of bolus insulin to largest meal

• 45 units basal (glargine or detemir)
• 5 units bolus(aspart, lispro, glulisine)
Basal/Bolus Insulin
Multiple Daily Injections (MDI)

• Many patients will accept a 2 injections program as first step in advancing to MDI (90/10 rule)
• Many patients will resist going from a 1 injection daily regimen to a 4 injections daily regimen (Basal + mealtime insulin)
• Eventually some will need 4 injections daily
Basal/Bolus Insulin Multiple Daily Injections (MDI)

- Basal (long acting) insulin daily + bolus (rapid acting) insulin with each meal
- 2 strategies:
  1) Non-carb counting
     Simple
  2) Carb counting
     Calculated dose based on carb intake

*Diabetes Care* July 2008 31:1305-1310
Basal/Bolus Injection

- Insulin Effect
- Hours

Rapid (Lispro, Glulisine, Aspart)

Long (Detemir, Glargine)

adapted from R. Bergenstal, IDC
Basal/Bolus Insulin in Type 2 Diabetes:
Non-Carb Counting
Non-Carb Counting

• Fixed dose of basal (long acting) insulin
• Mealtime bolus (rapid acting) insulin is split evenly per meals or estimated roughly on meal size
Basal/Bolus Non-Carb Counting

Of total daily dose,

~50% basal (long acting) insulin

~50% bolus (rapid acting) insulin
Basal/Bolus Non-carb Counting

Adding Bolus (rapid acting) Insulin:
First, consider reducing basal (long acting) (glargine or detemir)
by 50% at initiation of bolus insulin
Basal/Bolus Insulin

Add mealtime rapid acting insulin (bolus) (aspart, lispro, glulisine)

which will be the other 50% of total daily dose

So, 50% of total daily dose will be basal, and 50% of total daily dose will be bolus
Basal/Bolus Insulin

Example:
Patient currently on 50 units of glargine or detemir once daily
- cut glargine or detemir by 50%
  So, down to 25 units daily

Then, calculate bolus insulin.....
Basal/Bolus Insulin

- Add mealtime bolus (rapid acting) insulin
  - 25 total units daily
  (bolus- 50% of total daily insulin dose)

- Can split up into 3 equal doses with meals
  - 8 units/meal

Or....
Basal/Bolus Insulin

Split up bolus (rapid acting) insulin based roughly on meal size:

- ~50% with largest meal  
  13 units
- ~33% with next largest meal  
  8 units
- ~17% with smallest meal  
  4 units
Basal/Bolus Insulin Non-carb counting

So, our patient finishes this consult with:

- **Basal (long acting)** (~50% of daily total) 25 units once daily
- **Bolus (rapid acting)** 8 units with each meal (~50% of daily total)

Or split up by approx meal size: 13 units large meal
8 units medium meal
4 units small meal
Basal/Bolus Insulin in Type 2 Diabetes:

Carb Counting
Basal/Bolus Insulin Carb-Counting

- Reduce basal (long acting) 30-40% when starting bolus (rapid acting) insulin

- Bolus (rapid acting) ~2u/15 gram carb
- Correction (sensitivity factor)
  ~1 u to drop blood sugar 30 points
- Need to know pre-meal blood sugar
Calculating Bolus (rapid acting) with Carb Counting and Correction

Example:

• Blood sugar pre-meal was 200, target 110
• 60gram carb meal = 2u/15gram = 8 units
• Correction insulin 1u/30pts = 3 units (90pts)
• Meal (carb) 8 units + correction 3 units = 11 units for this meal
Case Study
Case Study

• 54 y/o white male

• Diagnosed with type 2 diabetes after 2 fasting blood sugars of 154 and 142 and A1C of 6.8%

• Also has high blood pressure and cholesterol disease (common in type 2)
Case Study

• Metformin 500 mg prescribed twice daily, titrated to 1000mg BID
• ASA 81 mg daily
• Lisinopril 10 mg daily
• Simvistatin 40 mg daily
• Fish Oil 1000mg BID
Case Study

• Referred to Diabetes Educator and Dietician
• Recommend developing graduated exercise plan (exercise prescription)
• Six months after diagnosis, A1C = 6.8% (target <7%)
Case Study

• Three years later, patient’s A1C has risen to 8.4% (target <7%)

• Blood pressure and cholesterol effectively treated

• Now what?
Case Study

• Choices include
  – Adding a basal insulin once daily
  – Adding any other oral agent
  – Adding exenatide twice daily (or weekly) or liraglutide once daily

• Any of these are good choices

• Choice may be made on individual factors
Case Study

- Patient chose additional oral agent (sitagliptin), but others would be OK
- A1C:
  - 6 months later = 7.4% (target <7%)
  - 3 years later = 8.1% (target <7%)

Now what?
Case Study

• Sitagliptin, metformin continued
• Basal insulin started with titration
• Eventually added bolus insulin with largest meal (90/10 rule)
• Likely will add bolus with other meals over time—non-carb counting strategy or carb counting strategy
3 Ways to Intensify Insulin In Type 2 Diabetes

• **Simple:** 90/10: 2 injection program
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• **Advanced:** Non-Carb Counting
  1 basal, 3 boluses equal split or estimate based on meal “size”

• **Sophisticated:** Carb-counting
  1 basal, 3 boluses (+ maybe snack boluses)
  calculated on carb intake+ glucose value
Other Insulins

Premix

• 70/30, 75/25, 50/50
• Combine R or rapid acting with NPH or an “NPH-like” component
• Certain applications may be appropriate
• 1, 2, or 3 times daily
• Limitation: change 2 insulins at once

U-500

• Sometimes in severe insulin resistance
Severely Insulin Resistant

- 200-300+ units total daily dose
- Obesity
- Lipodystrophies
- Genetic Syndromes

Garg NEJM 2004
Semple et al Clin Endocrinol. 2010
Severely Insulin Resistant

• Consider occult infections (UTI, abcess, sinus, etc)
• Consider other inflammatory conditions (periodontal disease, etc)
Severely Insulin Resistant

Options:
- U-500
- Add Symlin
- Add GLP-1
- Change/add “insulin sensitizing” agents
- Bariatric Surgery
- Sometimes pump- better absorption, maybe lower daily dose
- Some new insulins may be U-200
Pumps and Sensors:
Considerations in Type 2 Diabetes for Intensification of Insulin Management
Pumps and Sensors

• **Pump:** Continuous Subcutaneous Insulin Infusion (CSII)

• **Sensor:** Continuous Glucose Monitoring System (CGMS)
Pumps - Basic Components
Animas

Current Glucose Level updates every 5 minutes

Trend Arrows tell you where you're headed and how fast you're moving

Trend Screen Views with options of 1, 3, 6, 12, and 24 hours of continuous glucose information

Glucose Trend-Wave shows you where you've been

Customizable Low Glucose Alert notifies you when you are going low

Customizable High Glucose Alert notifies you when you are going high
Omnipod pump with remote

Not shown- “patch pumps”
Investigational

Navigator CGMS
Ultra-sleek design requires very little skin “real estate.”

The MiniLink REAL-Time Transmitter kit includes the transmitter and charger.

Medtronic Minimed
Pumps and Sensors

- Interfaced devices developed last 3 to 4 years
- Still not “closed loop”
- Patient gets info, has to act on it
- High/low alarms, trends alarm (more rapid rise or decline)
Logbook Data
Basal/Bolus Insulin

With injections:
• 2 different insulins
• Long-acting insulin \textit{basal}
• Rapid-acting insulin \textit{bolus}

With pump:
• Only use rapid acting insulin
• Some delivered continuously \textit{basal}
• Some delivered as \textit{bolus}
Basal/Bolus Injection

Insulin Effect

Hours

Rapid (Lispro, Glulisine, Aspart)

Long (Detemir, Glargine)

adapted from R. Bergenstal, IDC
Basal / Bolus Therapy

Insulin Pump

- Variable basals (not fixed)
- Bolus-Immediate, Square, Dual Wave

Time of Day

Insulin Needs

Basal Insulin

Bolus Insulin
Advanced Features

• Dual wave/square wave insulin delivery
• Variable basal/temporary basal rates

• Neither of these can be replicated with injections
• To get full benefit, should be using these features
Pump/Sensors in Type 2 Diabetes

- Younger patients typically
- Technologically savvy
- Like type 1, those requiring more intensive management, not meeting goals on MDI
Wrap It Up Dr. J.....

Home of the Chicago Cubs
Typical Type 2 Timeline

- Metformin at diagnosis or soon after
- Add something else
- Consider insulin if:
  - Duration >5-7 years
  - A1C>9
- Multiple daily injections (or pump?) for appropriate type 2 patients
Review

• For many patients, a simple basal insulin or basal insulin + 1 bolus is a good fit

• For some select patients, basal insulin + multiple daily bolus or a pump may be a good fit

• Choice depends on individual factors and resources
Summary

• Diabetes is common
• Consider individual factors and goals
• Lots of choices, but nearly all will need insulin eventually, many will be good with basal + other meds, maybe MDI or pump
Acknowledgements

• Silvio Inzucchi, M.D.  Yale University School of Medicine
• American Diabetes Association Primary Care Committee
• M. Sue Kirkman, M.D.  American Diabetes Association
• James Brosseau, M.D., M.P.H. Altru Diabetes Center
• William Zaks, M.D., Ph.D., Altru Diabetes Center
• Altru Diabetes Center Team
• Melissa Gardner, Department of Family and Community Medicine, UNDSMHS