Initiation, Titration And Maintenance Of Basal Insulin In Type 1 Versus Type 2 Diabetes: An Important Foundation To Successful Insulin Management

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Comparing and Contrasting Type 1 and Type 2 Diabetes...
Sometimes It’s Like Comparing Apples to Oranges

....and Sometimes It’s Like Comparing Apples to Apples

Type 1 and Type 2 Diabetes Are Very Different
› Misperceptions and Physical Appearance
› Incidence and Prevalence
› Hereditary Influence
› Etiology and “Natural History”
› Characteristics and Associated Conditions
› Treatment Strategies
› Approaches to basal insulin management strategies
Incidence and Prevalence of Type 1 vs Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in the US</td>
<td>1,250,000</td>
<td>31,000,000</td>
</tr>
<tr>
<td>Diagnosed Every Day in the US</td>
<td>110</td>
<td>6,000</td>
</tr>
</tbody>
</table>

Type 1 Race/Ethnicity
- White Non-Hispanic: 81%
- Black Non-Hispanic: 1%
- Hispanic or Latino: 1%
- Native Hawaiian/Other Pacific Islander: 1%
- Asian: 1%
- American Indian/Alaskan Native: 1%
- More than One Race: 3%

81% White

Trends Among Adults With Type 2 Diabetes in the U.S. 1990

No Data  Less than 4%  4% - 6%  Above 6%

Trends Among Adults With Type 2 Diabetes in the U.S. 2018
Over 300 billion dollars a year!

Estimate in 2050: ~33%!!!!!!

Risk of Developing Type 1 vs Type 2

General Population
0.3% 8-11%

If you have a sibling with T1D
4% ~30%

If your mother has T1D
2 - 3% ~30%

If your father has T1D
6 - 8% ~30%

If you have an identical twin with T1D
~50% 100%

Natural History of Type 2 Diabetes
Natural History and Cause of Type 1 Diabetes

Autoimmune condition

- Genetic predisposition
- Damage to the cells of the pancreas
- Pre-diabetes: Time = months to a few years
- Diabetes

Putative Trigger

Immune System Dysfunction

Circulating Auto Antibodies (ICA, GAD)

Symptoms

- 100% Insulin making cells of the pancreas

Potential Trigger

Immune System Dysfunction

Circulating Auto Antibodies (ICA, GAD)

Autoimmune condition

- High rate of hypothyroidism and celiac disease
- 5–10% of all PWD

Type 1
Jeremy Pettus
Diagnosed Age 15

- Usually average weight
- Dx usually before age 25
- Beta cell destruction
- Autoimmune condition
- High rate of hypothyroidism and celiac disease
- 5–10% of all PWD

• Mary Tyler Moore
• Chris Dudley
• Charlie Kimball
• Jay Cutler
• Nick Jonas
• Sharon Stone
• Gary Hall Jr.
• Phil Southerland

Age at Diagnosis of T1D

You can get type 1 diabetes at any age!
Latent Autoimmune Diabetes in Adults (LADA)

- The most missed diagnosis in diabetes
- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Typically does not have features of the Metabolic Syndrome
- Blood test positive for type 1 diabetes (GAD auto antibodies)

Generic and Trade Names: Insulin

<table>
<thead>
<tr>
<th>Category</th>
<th>Insulin Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-Acting Insulin</td>
<td>Regular U-500</td>
<td>Humulin R U-500</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td>Fiasp</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>NPH</td>
<td>Humulin N Novolin NPH</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td>Glargine U-100</td>
<td>Lantus</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic</td>
<td>Glargine*</td>
</tr>
<tr>
<td>Long-Acting</td>
<td>Glargine U-200</td>
<td>Toujeo*</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic</td>
<td>Tresiba*</td>
</tr>
</tbody>
</table>

Shortcomings of Basal Insulins Include:

- Hypoglycemia resulting in:
  - Insulin under-dosing
  - Insufficient glycemic control
- Weight gain
- Inconsistent insulin action...leading to inconsistent blood glucose levels
- Not enough flexibility with timing of injections
- Insufficient duration of action...therefore, requiring a minimum of 1 and, sometimes, 2 injections/day
- Large volume injections required for some patients
Two New Basal Insulins Recently Added to Our List of Options
Both approved by the FDA and now available for patients
1. U-300 glargine a long-acting basal insulin
2. U-100 and U-200 degludec a long-acting basal insulin

U-300 Glargine
A more concentrated (300 units/ml) form of traditional glargine insulin (100 units/ml)
Compared to U-100 glargine, U-300 glargine has less intra-subject variability, less hypoglycemia and less weight gain.
Flat, stable and prolonged action up to 30 hours (needs 5 days to equilibrate...tell your patients!)
In the clinical trials patients on U-300 glargine with type 1 and type 2 diabetes may require a dose 12 to 18% higher than previous U-100 glargine (still with less hypo and less weight gain).
Pen holds 450 units
New Pen holds 900 units and can give 150U at one time

PK/PD Profile with Glar U-300 vs Glar U-100
May need 13 to 17% more than previous dose of glargine
Glucose Infusion Rate In Subjects With Type 1 Diabetes Insulin Glargine U-300

50 T1D subjects underwent two euglycemic clamp studies after 6 days of receiving Insulin glargine U-300


U-100 and U-200 Insulin Degludec

Available as either 100 units/ml (~detemir) or 200 units/ml
Long duration of action up to 42 hours (needs 5 days to equilibrate...tell your patients!)
Peakless
Low intra-subject variability
Less hypoglycemia and variability compared to U-100 glargine
Disposable pens hold a maximum of 300 (U-100) and 600 (U-200) units
160 units can be given at one time.

Press release: http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=a1b5d012-c7cb-4b56-9525-b9c779d01dde

Pharmacodynamics of Insulin Degludec® U-100 and U-200 in Patients with T2DM: Same time course of action

4. Press release: http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=a1b5d012-c7cb-4b56-9525-b9c779d01dde
First Goal in Starting Basal Insulin in Type 2 Diabetes: Correct Fasting Hyperglycemia

Second Goal: Control Postprandial Hyperglycemia if A1c Still >7% (or above individual goal)

Combination Therapy: Adding Basal Insulin to Oral Agents an Effective Strategy to Initiate Insulin Therapy in T2D
- Only 1 injection per day is typically required
- No need for mixing different types of insulin
- Convenience (usually given at night or first thing in the morning)
- Slow, safe, and simple titration
- Low dosage needed compared to a full insulin regimen
- Limited weight gain – especially compared to insulin only regimens
- Effective improvement in glyemic control by suppressing hepatic glucose production


Second Pitfall in Initiating and Titrating Basal Insulin
(First one is too slow titration after starting)

Not Paying Attention To The Bedtime Glucose Value

1. Ask the patient to do paired testing (test at bedtime and again the next morning).
2. If the bedtime BG is high, then that needs to be addressed by either lifestyle modification including reduced caloric consumption and/or post dinner exercise.
3. Other options include prandial insulin or a GLP-1 RA

Simple Daily Self-Titration Option*
(much easier to follow by the patient than the once or twice a week method)

Increase by 1 to 2 Units every 1 day until FPG ≤ 120 mg/dL

EXAMPLE
Less than 100: decrease by 2 units
Between 100 and 150: no change
Over 150: increase by 2 units

The goal can be individualized

*Adapted from consensus algorithm in patients need

Appropriate Self-Titration is Critical to the Success of Insulin Therapy

An ADA/EASD consensus algorithm for the initiation and adjustment of basal insulin:

Start with a long-acting basal insulin
Initiate at 10 units/day or 0.2 units/kg/day
Check fasting glucose daily and increase dose by:
Increase 10 to 15% or 2 to 4 units once or twice a week until fasting glucose is in target range

Example
Less than 100: decrease by 2 units
Between 100 and 150: no change
Over 150: increase by 2 units

The goal can be individualized

ADI, American Diabetes Association; EASD, European Association for the Study of Diabetes.
Nathan et al. Diabetes Care. 2018

Increase by 1 to 2 Units every 1 day until FPG ≤ 120 mg/dL
Start your basal insulin once a day in the morning.

2. Starting dose: 20 units.

3. Every _day(s), adjust your dose based on your fasting blood sugar that morning before eating or drinking:
   - If fasting blood sugar is over 140, increase your dose by _.
   - If fasting blood sugar is under 90, decrease your dose by _.
   - If fasting blood sugar is between 90 and 140, keep the same amount.

Baseline dose:

***Case: 61 Year Old Overweight Male With Type 2 Diabetes For 8 years***

- Initial A1c was 9.5%
- Eventually started on metformin, sequentially followed by a sulfonylurea, a DPP-4 inhibitor and a SGLT-2 inhibitor over a 4 year period.
- PMH: HTN, CHF, dyslipidemia, arthritis and ED
- Exercises irregularly and "tries to follow a diet"

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>140 - 220 mg/dL</td>
<td>&gt;147 mg/dL</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>111 - 182 mg/dL</td>
<td>&gt;147 mg/dL</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>91 - 155 mg/dL</td>
<td>&gt;159 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>140 - 231 mg/dL</td>
<td>&gt;184 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia.
Which of the following would you suggest if he was your patient?

A. Start a pre-mixed insulin at dinner time
B. Initiate basal insulin
C. Start a GLP-1 RA
D. Start pioglitazone

Case continued
- U-300 Glargine was added at night (20 units)
- and titrated up to 120 units over the next 10 weeks
- I asked him to test 2x/day (bedtime and the next morning)
- It is important to make sure the patient is not going to bed high

<table>
<thead>
<tr>
<th></th>
<th>Pre-Breakfast</th>
<th>Pre-Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>82 – 155 mg/dL</td>
<td>128 – 183 mg/dL</td>
<td>128 – 183 mg/dL</td>
</tr>
</tbody>
</table>

- A1c dropped to 7.1%, no hypoglycemia. Gained 2 lbs in 3 months
- Oral agents can be continued unless hypoglycemia occurs during the day, in which case the sulfonylurea should be reduced or withdrawn.

Domino Effect
If you control the blood glucose at a particular time of the day, the subsequent number will also improve. Make one change at a time!
Case 62 year old female with type 2 diabetes for 12 years
Currently on maximum doses of 3 oral agents: metformin, SFU and a DPP-4 inhibitor.
A1c > 8.5% for the past 2 years
She was started on basal insulin and the HCP titrated her dose based on her morning glucose value. Her current dose is 78 units
Current SMBG (mg/dl) below:

<table>
<thead>
<tr>
<th>Day</th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>243</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>221</td>
<td></td>
<td></td>
<td>154</td>
</tr>
<tr>
<td>Wednesday</td>
<td>54</td>
<td></td>
<td></td>
<td>239</td>
</tr>
<tr>
<td>Thursday</td>
<td>267</td>
<td></td>
<td></td>
<td>287</td>
</tr>
</tbody>
</table>

Which of the following is the single most likely explanation for her low glucose value of 54 mg/dl?

A. She did an unusual amount of exercise that morning
B. She had a much lighter dinner than usual
C. She took twice the amount of basal insulin by accident
D. The value from her glucose meter was not correct

Case continued
She was asked to do some paired testing (bedtime and the next morning for several days in a row

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<tr>
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</thead>
<tbody>
<tr>
<td>Friday</td>
<td>201</td>
<td></td>
<td></td>
<td>234</td>
</tr>
<tr>
<td>Saturday</td>
<td>192</td>
<td></td>
<td></td>
<td>154</td>
</tr>
<tr>
<td>Sunday</td>
<td>82</td>
<td></td>
<td></td>
<td>239</td>
</tr>
<tr>
<td>Monday</td>
<td>212</td>
<td></td>
<td></td>
<td>287</td>
</tr>
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Her basal dose has been titrated up too high and the main issue is that she is going to bed too high.
Clinical Pearls: Combination Therapy with Basal Insulin

1. Start with 10 to 20 units (also consider FBS, weight)
2. The key to success is frequent follow-up after initiation to avoid failure (most patients will need 40 to 70 units/day)
3. Have the patient follow a self-titration regimen and return to clinic or follow up in some other manner (phone, fax, email, telehealth, etc.) relatively soon
4. You can usually limit SMBG to only once a day in the morning but check at bedtime once in awhile to make sure the pt. does not need pre dinner fast acting insulin or a GLP1-RA

IS or Intermittent Sensing Is Excellent For Type 2s
- Goes on easily
- 12 hour warm up time
- Lasts 10 days
- Swipe to get a number
- Has trend arrows
- No calibration
- No alerts or alarms
- No sharing feature

Every Day Is Different For A Person With Type 1 Diabetes
First Step is to make sure the basal rate is correctly set.

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

Despite Following all of the Rules

- Unexpected highs
- Unexpected lows
- Carb:Insulin ratio not working consistently
- Correction Factor not working consistently
- Not responding to insulin and exercise consistently

Only ~30% of Type 1s Reach ADA Goal of an A1c Less than 7%

A1c Goal = <8.5%
A1c Goal = <8.0%
A1c Goal = <7.5%
A1c Goal = <7.0%

Only ~30% of Type 1s Reach ADA Goal of an A1c Less than 7%

Basal Insulin T1 & T2
Physiologic Insulin, Glucagon and Amylin Secretion

Liver ➔ Portal Vein ➔ Pancreas ➔ Systemic Circulation

- Insulin
- Amylin
- Glucagon

Beta Cell ➔ Alpha Cell


Physiologic Insulin Secretion and Glucose Levels in Healthy Subjects

Insulin (µU/mL) vs. Glucose (mg/dL) vs. Time of Day

- Basal Glucose
- Basal Insulin HCO (40 to 60% of TDD)
- Bolus Insulin (40 to 60% of TDD)

Breakfast, Lunch, Dinner


Continuous Glucose Monitoring Devices Currently Available in the United States

- Medtronic Guardian
- Dexcom G6
- Abbott FreeStyle

Basal Insulin T1 & T2 15
Reasons For A High FBS: Single vs. Continuous Glucose Monitoring

Testing The Basal Rate In Type 1 Diabetes

Testing Overnight
1. Ask the patient have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

Testing During The Day (different day than testing pm)
1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140–180mg/dl with a horizontal trend arrow

Testing A Basal Segment in T1D: Foundation of any Insulin Regimen

39 year female with T1D for 2 years on an insulin pump (0.6 U/hr). Her main problem is that she goes to bed with a good BS level and then wakes up with a high value. What is the most likely cause?

- A Not bolusing enough for her bedtime snack
- B Early morning resistance to insulin (dawn phenomenon)
- C Eating a snack at 3am without any insulin
- D Gastroparesis

Insulin Pumps: Advantages

- Improved glycemic control
  - More precise, physiologic insulin delivery
  - Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
- In some situations (but not all) freedom and flexibility in lifestyle
  - Eliminate multiple daily injections (1 stick every 3 days) Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)
25 y/o male with T1D on insulin detemir. Good values at bedtime and high in the morning. He also c/o occasional night sweats.
What is/are the possible cause for the high morning BS?

- Bolusing fast-acting insulin at bedtime
- Too much basal insulin
- Going to the 24 hour gym at midnight
- All of the above

Variable Basal Rate Capability
(Total daily basal dose/24) - (10 to 20%)

Smart Phone Clarity App
Mean glucose value
Standard Deviation
Time in Range
24 hour multiday profiles
Is this T1D on too much basal?

Testing the overnight basal dose
Same patient fasting from 6pm until 9am

Patient's best glucose day was February 12, 2018
Patient's glucose data was in the target range about 75% of the day.

Statistics for this day
145 mg/dL
40 mg/dL

Is this T1D on too much basal?
Same pt. fasting from 9pm until 7am

Patient's best glucose day was March 14, 2018

Patient's glucose data was in the target range about 70% of the day.

32 year old male with T1D on glargine U-100 at bedtime and a fast acting analog with meals and for correction doses.

What is the best treatment option to help this patient with his overnight values?
A. Decrease the basal insulin
B. Switch the U-100 glargine for U-300 glargine or degludec
C. Have a larger bedtime snack
D. Do not exercise after 7pm

Summary and Conclusions

Type 1 and Type 2 Diabetes are very different conditions including the approach to basal insulin therapy

In Type 2 diabetes self titration is important to reach an adequate FBS and paired testing is important to make sure the bedtime glucose value is in range

In Type 1 diabetes the basal dose should be tested by overnight and daytime fasting.

CGM is the standard of care in T1D and will shortly be used more and more in Type 2 Diabetes