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

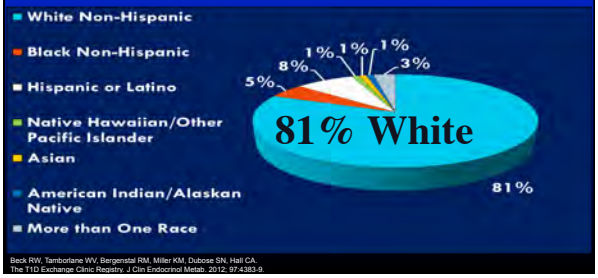
- Misperceptions and Physical Appearance
- Incidence and Prevalence
- Hereditary Influence
- Etiology and "Natural History"
- Characteristics and Associated Conditions
- Treatment Strategies
- Approaches to basal insulin management strategies

Incidence and Prevalence of Type 1 vs Type 2 Diabetes

	Type 1	Type 2
Number in the US	1,250,000	31,000,000
Diagnosed Every Day in the US	110	6,000

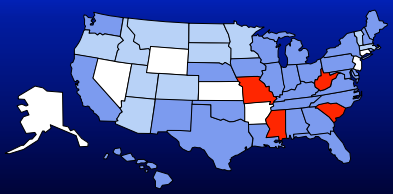
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2017.

Type 1 Race/Ethnicity



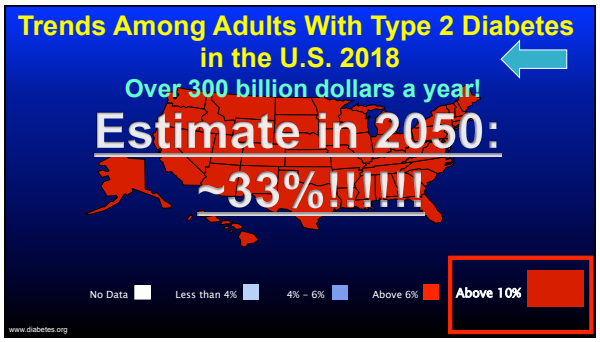
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

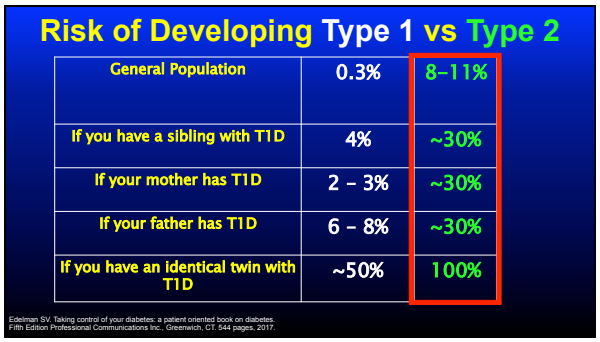
Trends Among Adults With Type 2 Diabetes in the U.S. 1990

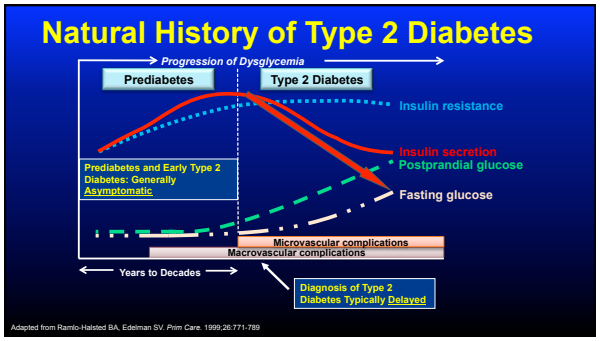


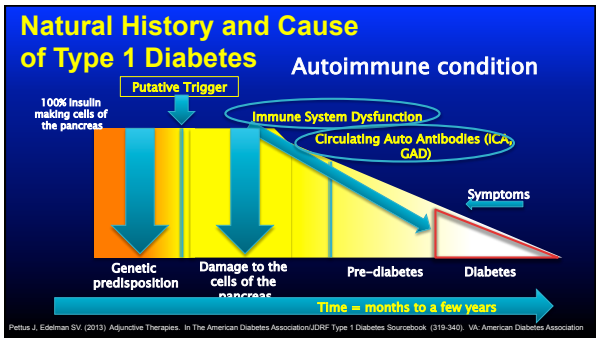
No Data | Less than 4% | 4% – 6% | Above 6%

Mokdad et al., Diabetes Care 2000;23:1278-83.

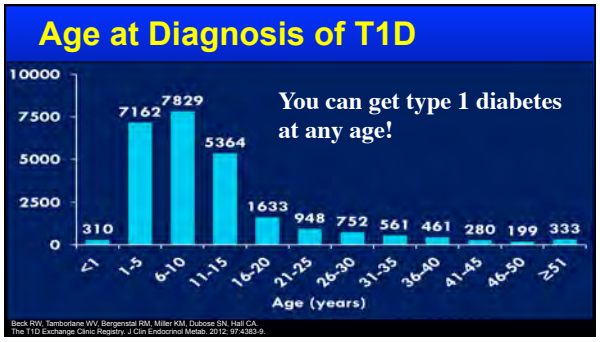

Trends Among Adults With Type 2 Diabetes in the U.S. 2018
Over 300 billion dollars a year!
Estimate in 2050:
~33%!!!!!!
No Data
Less than 4%
4% – 6%
Above 6%
Above 10%
www.diabetes.org


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%
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2017.


Natural History of Type 2 Diabetes
Progression of Dysglycemia
Prediabetes
Type 2 Diabetes
Insulin resistance
Insulin secretion
Postprandial glucose
Fasting glucose
Prediabetes and Early Type 2 Diabetes: Generally Asymptomatic
Microvascular complications
Macrovascular complications
Years to Decades
Diagnosis of Type 2 Diabetes Typically Delayed
Adapted from Ramlo-Halsted BA, Edelman SV. Prim Care. 1999;26:771-789


Natural History and Cause of Type 1 Diabetes
Autoimmune condition
Putative Trigger
100% insulin making cells of the pancreas
Immune System Dysfunction
Circulating Auto Antibodies (ICA, GAD)
Symptoms
Genetic predisposition
Damage to the cells of the pancreas
Pre-diabetes
Diabetes
Time = months to a few years
Pettus J, Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association


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!
10000
7500
5000
2500
0
310
7162
7829
5364
1633
948
752
561
461
280
199
333
<1
1-5
6-10
11-15
16-20
21-25
26-30
31-35
36-40
41-45
46-50
≥51
Age (years)
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

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)

Gary Hall Jr.
Olympic Gold Medalist
World Record Holder

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. 9th Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2017.

Generic and Trade Names: Insulin

	Generic Name	Trade Name
Fast-Acting Insulin	Regular U-500 Regular Aspart Faster Acting Aspart Glulisine Lispro (U-100 and U-200) Follow on biologic lispro Inhaled Insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Fiasp Apidra Humalog Admelog Afrezza
Basal Insulin	Intermediate-Acting: NPH Long-Acting: Detemir Glargine (U-100) Glargine (U-300)* Degludec (U-100/200)* Follow on biologic glargine (U-100)	 Humulin N Novolin NPH Levemir Lantus Toujeo* Tresiba* Basaglar

Information taken from the PDR Guide and Package Inserts

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

Expert Opin. Biol. Ther. (2014) 14(6):7909-88

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

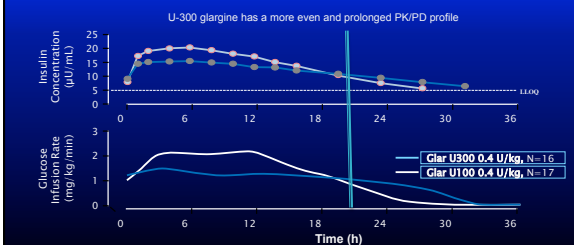
Toujeo prescribing information. Bridgewater, NJ: sanofi, US; 2015 http://products.sanofi.us/toujeo/toujeo.pdf
Tresiba prescribing information 2015. http://www.novo-pi.com/tresiba.pdf

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

Riddle MC *et al. Diabetes Care.* 2014;37:2755-2762; Yki-Järvinen H *et al. Diabetes Care.* 2014; Published ahead of print: doi: 10.2337/dc14-0990
Bolli GB *et al.* Poster presented at EASD 2014: P947; Bajaj H. Oral presentation at CDA 2014: #14; Home P *et al.* Abstract presented at EASD 2014: 0148
Bajaj H *et al.* Poster presented at CDA 2014: P112; Matsuhisa M *et al.* Poster presented at EASD2014: P975; Terauchi Y *et al.* Poster presented EASD 2014: P976

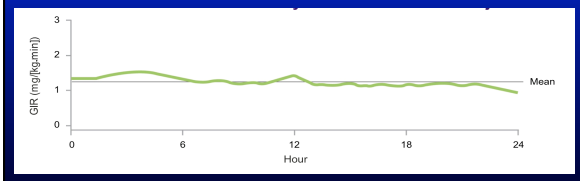
PK/PD Profile with Glar U-300 vs Glar U-100



May need 13 to 17% more than previous dose of glargine

Becker RH, et al. *Diabetes Care.* 2015;4:639-643.

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

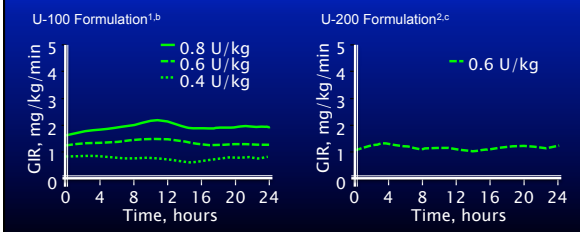
Becker RHA, et al. Diabetes Obes Metab. 2015; 17(3): 261-267

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(units)
- 160 units can be given at one time.

Owens et al. Diabetes Metab Res Rev. 2014;30:104-119.
Heise T et al. Diabetes Obes Metab. 2012;14:944-950.
Heise T et al. Diabet Med. 2002;19:490-495.
Jonassen I et al. Pharm Res. 2012;29:2104–2114.
Press release. http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=a1b5d012-c7cb-4b56-9525-b9c779d01dde Accessed December 15, 2014.

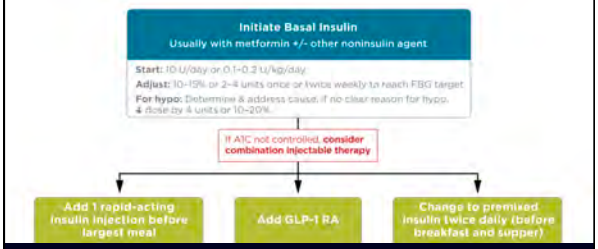
Pharmacodynamics of Insulin Degludec[a] U-100 and U-200 in Patients with T2DM: Same time course of action



1. Heise T, et al. *Diabetes Obes Metab*. 2012;14:944-950.
2. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].

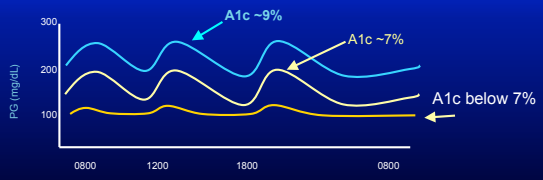
[a,b] Glucose clamp study in patients with T2DM (n = 49).
[c] Glucose clamp study in patients with T2DM (n = 16).

2018 ADA Basal Insulin Recommendations



American Diabetes Association Dia Care 2018

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)

Adapted with permission from Cefalu WT. In: Leahy J, Cefalu W, eds. Insulin Therapy. New York: Marcel Dekker; 2002:1-11.

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 glycemic control by suppressing hepatic glucose production

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages. 2014.

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

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

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

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

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

*Adjust dose subsequently to patient's need.
†Dosage was not increased that week if there were any episodes of documented hypoglycemia (<72 mg/dL) during the preceding week. FPG, fasting plasma glucose.
Gerstein HC et al. Diabet Med. 2006;23:736-742.

Starting/Adjusting Long-Acting Basal Insulin

1. Give Basal insulin once a day at Morning
2. Starting dose: 20 units
3. Every 1 day(s), adjust your dose based on your fasting blood sugar that morning before eating or drinking:
   a. If fasting blood sugar is over 140, then increase your dose by 2
   b. If fasting blood sugar is under 90, then decrease your dose by 2
   c. If fasting blood sugar is between 90 and 140, then keep the same Lantus dose

Important:
The purpose of long active basal is to provide a background amount of insulin throughout the day and at night while you sleep. It is not meant to treat high blood sugars caused by eating food, so you should not change your dose based on blood sugar numbers during the day when you are eating.

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"

Case continued

- Staggered testing results (asked to test one to two times a day at different times)

Time	Blood glucose range	Blood glucose average
Pre-Breakfast	148 - 229 mg/dL	(~175 mg/dL)
Pre- Lunch	111 - 182 mg/dL	(~147 mg/dL)
Pre- Dinner	91 - 155 mg/dL	(~139 mg/dL)
Bedtime	148 - 231 mg/dL	(~184 mg/dL)
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

Pre-Breakfast	82 - 155 mg/dL	(~122 mg/dL)
Pre- Lunch	----	----
Pre- Dinner	----	----
Bedtime	128 - 183 mg/dL	(~145 mg/dL)

- 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!

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2017.

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:

	Pre–Breakfast	Pre–Lunch	Pre–Dinner	Bedtime
Monday	243	----	----	---
Tuesday	221	----	---	----
Wednesday	54	----	----	---
Thursday	267	----	---	----

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

A	She did an unusual about 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

	Pre–Breakfast	Pre–Lunch	Pre–Dinner	Bedtime
Friday	201	----	----	244
Saturday	192	----	---	154
Sunday	82	----	----	239
Monday	212	----	---	267

- 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

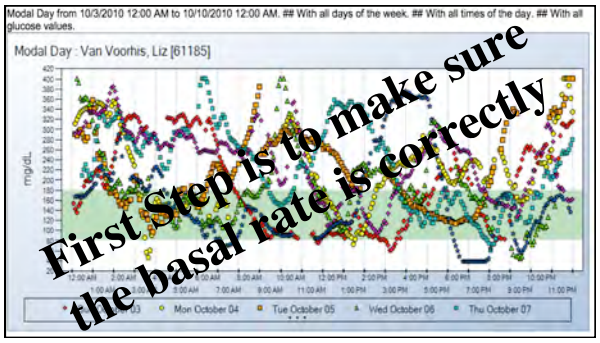
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

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

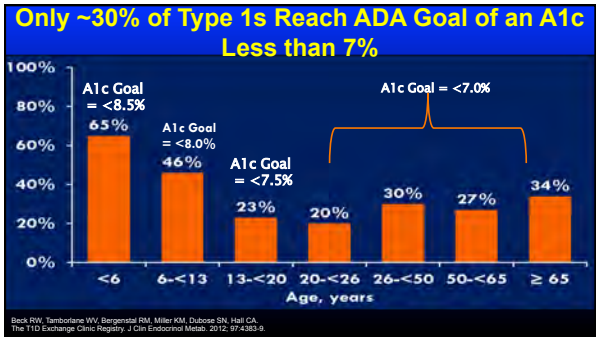
swipe

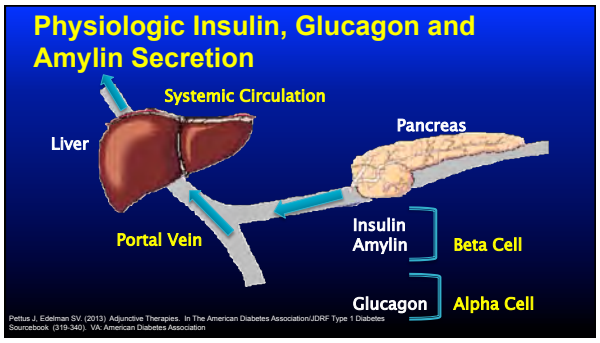
Every Day Is Different For A Person With Type 1 Diabetes

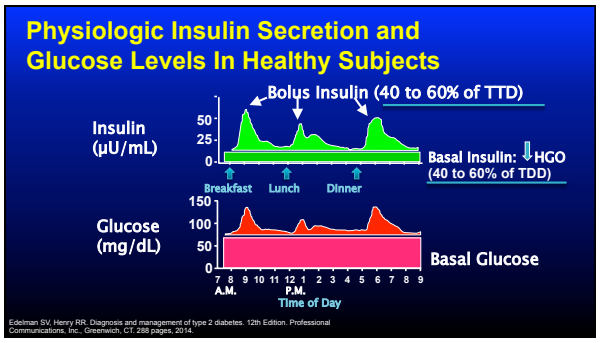


Despite Following all of the Rules

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

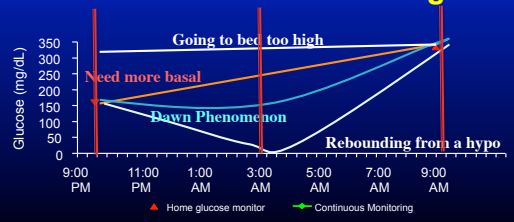



Physiologic Insulin, Glucagon and Amylin Secretion
Systemic Circulation
Liver
Pancreas
Portal Vein
Insulin
Amylin
Beta Cell
Glucagon
Alpha Cell
Pettus J, Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association


Physiologic Insulin Secretion and Glucose Levels In Healthy Subjects
Bolus Insulin (40 to 60% of TTD)
Insulin (µU/mL)
50
25
0
Basal Insulin: ↓HGO (40 to 60% of TDD)
Breakfast
Lunch
Dinner
Glucose (mg/dL)
150
100
50
0
Basal Glucose
7 8 9 10 11 12 1 2 3 4 5 6 7 8 9
A.M.
P.M.
Time of Day
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.


Continuous Glucose Monitoring Devices Currently Available in the United States

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

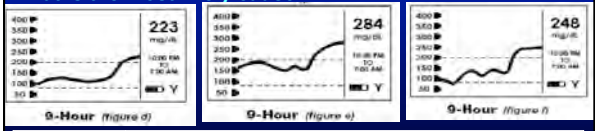
Testing During The Day (different day than testing pm)

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

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2017.

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?



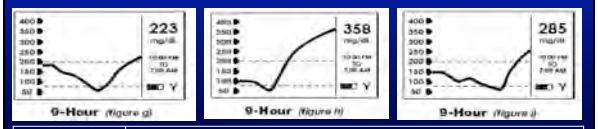
A	Not bolusing enough for her bedtime snack
B	Early morning resistance to insulin (dawn phenomenon)
C	Eating a snack at 3am without any insulin
D	Gastroparesis

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)

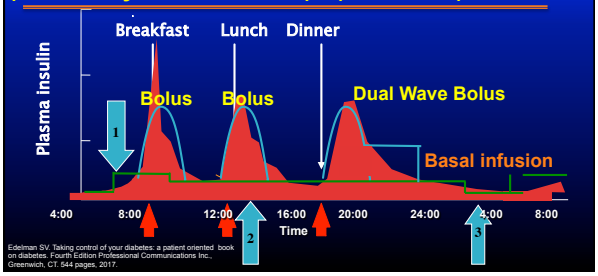
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. 544 pages. 2017.
Walsh JA, Roberts R. Pumping Insulin 5th edition. 2011.

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?

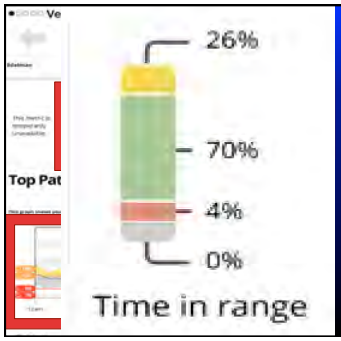


A	Bolusing fast-acting insulin at bedtime
B	Too much basal insulin
C	Going to the 24 hour gym at midnight
D	All of the above

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



Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages. 2017.



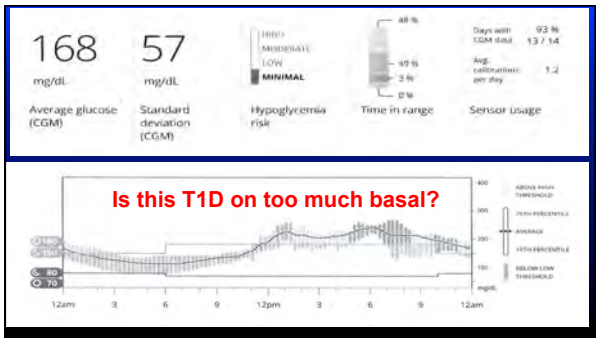
Smart Phone Clarity App

Mean glucose value

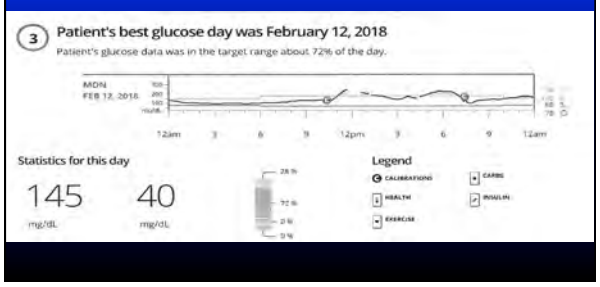
Standard Deviation

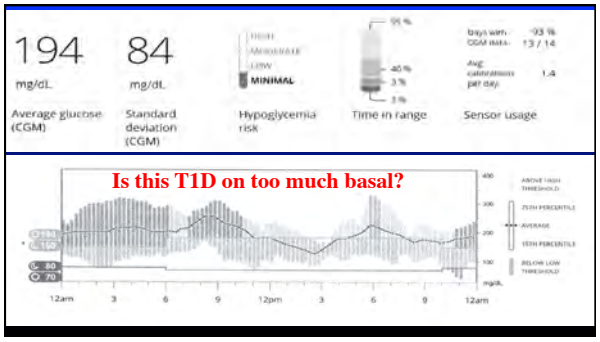
Time in Range

24 hour multiday profile

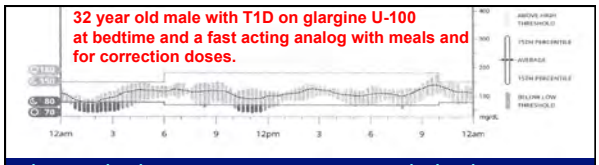


Testing the overnight basal dose





Testing the overnight basal dose



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 o 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

BeAM Value In Type 2 Diabetes

BeAM is defined as the difference between **be**dtime and **AM** glucose value as an indicator of the need to target the post prandial glucose value

BeAM Value = **Be**dtime glucose value minus the prebreakfast (**AM**) glucose value

BeAM value greater than 30 to 40mg/dl (higher at bedtime and lower in the morning) indicates that the post prandial glucose needs to be targeted

BeAM value of greater than – 30 to –40 mg/dl (lower at bedtime and higher in the morning) means your patient may need more basal

Diabetes Research and Care 2016;4:e000171