Controlling Diabetes:
Successfully Using Oral Agents, Insulins, Exenatide and Pramlintide

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U.S. Diabetes Prevalence

- 18+ Million
- 41+ million have Prediabetes
- 1.3 million new cases each year
- #1 cause of blindness
- 45% all new cases ESRD
- 60% all amputations
- 70% of people have neuropathy
- 70% die of MI or CVA
- Prevalence is increasing, but control is deteriorating


2 ADA. Diabetes Care. 2003;26:917-932.
Glycemic Control Has Not Improved

Percent of Patients with A1c < 7.0%

- NHANES 1988-1994
- NHANES 1999-2000

Adapted from Koro CE, et al. Diabetes Care 2004;27:17
Management of T2DM Has Not Improved

Risk Factor Control
Saydah SH et al. *JAMA* 2004;291:335-342

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>A1c &lt;7%</td>
<td>44%</td>
<td>37%</td>
</tr>
<tr>
<td>BP &lt;130/80</td>
<td>29%</td>
<td>36%</td>
</tr>
<tr>
<td>TC &lt;200</td>
<td>34%</td>
<td>50%</td>
</tr>
<tr>
<td><em>All 3 at Goal</em></td>
<td>5%</td>
<td>7%</td>
</tr>
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</table>
Therapeutic Trends In The USA For Patients With T2DM

A single oral agent is started when the average A1c is 8.7%, and the A1c had been >8% for 9 months!

A second oral agent is started when the average A1c is 8.8% and the patient had been a single-agent failure for 15 ~21 months!!

Insulin is started when the average A1c is 9.6% and the A1c had been >8% for almost 2 years!!!
Objective:
Investigate the relationship between physicians' beliefs on tight control of T2DM versus FPS & A1c in their patients

456 physicians were surveyed:
“For your average patient with T2DM, what do you think the fasting glucose should be?”

Data on glycemic control was later collected

The QuED Study Group Results

Relationship Between Patient’s A1c and Physician’s Target FPG

Barriers To Achieving Control of T2DM

- Physician’s attitudes
  - Hypoglycemia
  - Weight gain
  - Starting insulin

- Patient’s fears
  - Hypoglycemia
  - Weight gain
  - Insulin

- Overcoming Inertia
  - Patient does not believe T2DM is a problem
  - Physician does not believe tight control is necessary
EPIC-Norfolk Study:
HbA$_{1c}$ and Risk of CV Events or Death

Therapeutic Goals

- A1c < 6.5%
- Fasting glucose < 110 mg/dL
- 2 h postprandial < 140-180 mg/dL
- Blood pressure < 130/80 mmHg
- LDLc < 100 mg/dL
  (<70 mg/dL if very high risk)
- Triglyceride < 150 mg/dL
What Should Be The First Therapy?

First therapy can be determined based on the A1c

- **A1c ≤ 6.5%**: Continue course
- **A1c ≤ 8.5%**: Monotherapy¹,²
  - Combination therapy
- **A1c ≥ 8.5%**: Combination therapy³

**Combination therapy**
- Metformin + TZD
- Metformin + SU
- Metformin or SU + Exenatide
- Metformin + SU + Exenatide

¹ Monotherapy with SU or Metformin does not sustain A1c reductions (UKPDS)
² Glipizide ER and glimepiride have a lower incidence of hypoglycemia
³ If glucose is >260 mg% and the patient is symptomatic, insulin is required
Should Combination Therapy Be The First Intervention?

Ideal Intervention:
- Reduce A1c to <6.5%
- No hypoglycemia
- No weight gain
- Improve Beta-cell function
- Durability

Should metformin +TZD be the first intervention?
Should Metformin &/or SU + Exenatide be the first intervention?
Rosiglitazone Increases Islet Insulin In db/db Mice*

* Clinical significance of the preclinical findings is unknown.
28 days’ treatment with rosiglitazone 1.42 mg/kg, metformin 100 mg/kg, glyburide 49.4 mg/kg.

Patient F.T.N.

40-year-old white male had an acute onset diabetes age 34. He had always been treated with insulin and the A1c ~12% (non-adherence)

Lab C-peptide: 3.7 ng/mL
GAD antibody negative

Therapeutic changes
a. Stop insulin
   Begin sulfonylurea + metformin
   → A1c decreased to 6.9%

b. TZD later added to SU + metformin
   → Increased C-peptide and ↓A1c

### C-Peptide & Thiazolidinediones

<table>
<thead>
<tr>
<th>Patient F.T.N.</th>
<th>C-Peptide</th>
<th>A1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>3.7 ng/mL</td>
<td>12.0%</td>
</tr>
<tr>
<td>d/c insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Begin SU + Met</td>
<td>3.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Add TZD (Rezulin)</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>18 mo</td>
<td>6.3</td>
<td>10.0</td>
</tr>
<tr>
<td>24 mo</td>
<td>9.4</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Effects Of Rosiglitazone Plus Metformin On A1c and Weight

**HbA1c (%) Change**

-2.0  -1.5  -1.0  -0.5  0.0  0.5  1.0  1.5  2.0

- Placebo + MET (N=34)
- RSG 4 mg + MET (N=35)
- RSG 8 mg + MET (N=36)

**Weight**

-2.0  -1.5  -1.0  -0.5  0.0  0.5  1.0  1.5  2.0

- Placebo + MET (N=29)
- RSG 4 mg + MET (N=29)
- RSG 8 mg + MET (N=32)

*Significant difference from screening. †Significant difference from metformin.

Change in Mean Weight With Dual and Triple Therapy

Options For Combination Therapy In Patients Who Cannot Use Metformin or a TZD: Incretins

- Use Exenatide (GLP-1 analog incretin mimetic)
- Options include
  - SU + Exenatide
  - Metformin + Exenatide
  - SU + Metformin + Exenatide
- Exenatide is not yet approved for use with TZD’s
The Incretin Effect in Healthy Subjects

Data from Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498
Exenatide: The Synthetic Analog of GLP-1

<table>
<thead>
<tr>
<th>Effect</th>
<th>GLP-1</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-dependent insulin secretion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatic glucose output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Glucose absorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food intake (induces satiety)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Postprandial glucose to near-normal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Weight loss</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Resistant to DPP-IV degradation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Half-life after SQ injection</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>
Exenatide Restores the 1\textsuperscript{st} Phase Insulin Response

Exenatide Lowers A1c

Exenatide Lowers Postprandial Glucose

Prior to Treatment

Week 30

Glucose (mg/dL)

Time (min)

Placebo bid
5 μg exenatide bid
10 μg exenatide bid

Data on file, Amylin Pharmaceuticals, Inc.
Exenatide: Effect on Weight

What Is The Next Step For The Patient Who Has Failed Dual Therapy?

If Glycemic goals have not been met after 3 months on dual therapy:

Add a 3 oral agent or Exenatide if A1c is < 8.5%

OR

Add insulin for any A1c above goal
TYPE 2 DIABETES..... A PROGRESSIVE DISEASE

Over Time, Most Patients Will Need Insulin To Control Glucose

ACE Position Statement*

Early use of insulin therapy is frequently needed for timely achievement of glycemic goals. In type 2 diabetes, targets may be achieved by basal insulin plus oral agents or basal-bolus insulin regimens; pre-mixed insulin preparations can be used in special situations.

*Implementation Conference for ACE Outpatient Diabetes Mellitus Consensus Conference Recommendations, February 2, 2005
Progression of T2DM Reflects an Increasing Imbalance Between Insulin Supply and Demand

Adapted from *Type 2 Diabetes BASICS*. International Diabetes Center; 2000.
Why Is Basal-Bolus Insulin Therapy Recommended?

Safety: There are now more than 30 studies demonstrating that glucose can be managed to goal with about 50% less hypoglycemic events using glargine rather than NPH

The Basal - Bolus Concept

- **Basal Insulin**
  - Suppresses glucose production between meals and overnight fasting
  - Produced at nearly constant levels
  - Supplies about 50% of daily needs

- **Bolus Insulin (Mealtime or Prandial)**
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of total daily insulin requirement at each meal
Glargine vs NPH Insulin: Action Profiles by Glucose Clamp

Fast Analogues Aspart, Glulisine & Lispro: Plasma Insulin Profiles

What Is The Role of Oral Therapy, ± Exenatide, When A Patient Starts Insulin?

When starting insulin after oral therapy failure:
   a. Continue ALL oral agent!
   b. Stop exenatide (not approved with insulin)
   c. After glycemic control is achieved, determine if the SU may be weaned
Initiating Once-Daily Insulin Therapy

- Begin 10 units glargine q a.m. (or NPH, 10 units h.s.)

- Alternative:
  0.1-0.25 units per Kg per day (weight-based dose)

- Titrate every 2 days until fasting glucose is <110
  - >180 mg/dL + 6 units
  - 141-180 + 4 Add 2 units
  - 121-140 + 2 OR every 2 days until FPG <110
  - 100-120 + 1
  - <80 - 2

www.texasdiabetescouncil.org
Advancing Insulin Therapy

Bolus insulin may be started several ways

a. Arbitrarily give 5 units a.c.

b. Give bolus based on carbohydrate counting
   i. 1 unit/15 grams carbohydrate
   ii. “Rule 500”
   \[
   \frac{500}{\text{TDD}} = \text{Number grams of carbohydrate}
   \]
   1 unit of insulin will cover

c. Give correction dose to cover hyperglycemia
   “Rule of 1800”
   \[
   \frac{1800}{\text{TDD}} = \text{How much 1 unit of insulin will decrease the blood glucose}
   \]

www.texasdiabetescouncil.org
A patient using 35 units basal insulin glargine reports

<table>
<thead>
<tr>
<th>Time</th>
<th>Fasting Blood Sugar</th>
<th>2h Postprandial Breakfast</th>
<th>2h Postprandial Lunch</th>
<th>2h Postprandial Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.m.</td>
<td>95</td>
<td>140</td>
<td>140</td>
<td>230</td>
</tr>
</tbody>
</table>

Options:

a. Arbitrarily add 5 units bolus insulin before dinner

b. Add bolus insulin based on “Carb Counting”
   i. Give 1 unit per 15 grams carb or
   ii. $\frac{500}{35} = 1$ unit per 14 grams carbohydrate

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Advancing Insulin Therapy

A patient uses 35 units basal insulin glargine reports:

- a.m. 2 h pp brkfst 2 h pp lunch 2 h pp dinner
- 95 140 140 240

Titrate the bolus insulin:

a. Monitor 2 h postprandial glucose
b. Increase the dinner time insulin by 2 units every 1-2 days until the 2 h postprandial glucose that is <140-180

Correct hyperglycemia (Rule 1800): $1800/35 = \sim 50$
Add 1 extra unit bolus insulin for every 50 mg% glucose >150

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Advancing Insulin Therapy

A patient using 50 units basal insulin glargine reports

<table>
<thead>
<tr>
<th>Time</th>
<th>2h pp brkfst</th>
<th>2 h pp lunch</th>
<th>2 h pp dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.m.</td>
<td>95</td>
<td>140</td>
<td>190</td>
</tr>
<tr>
<td>2h pp</td>
<td>140</td>
<td>190</td>
<td>240</td>
</tr>
</tbody>
</table>

Options:

a. Arbitrarily add 5 units bolus insulin before lunch and before dinner

b. “Carb Count” bolus before lunch and dinner
   i. Give 1 unit per 15 grams carb or
   ii. 500/50 = 1 unit per 10 grams carbohydrate

www.texasdiabetescouncil.org
**Advancing Insulin Therapy**

A patient using 50 units basal insulin glargine reports

<table>
<thead>
<tr>
<th>a.m.</th>
<th>2h pp brkfst</th>
<th>2 h pp lunch</th>
<th>2 h pp dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>140</td>
<td>190</td>
<td>240</td>
</tr>
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</table>

- **Titrate the bolus insulins**
  - a. Monitor 2 h postprandial glucose
  - b. Independently increase each bolus dose of insulin by 2 units every 1-2 days to reach the 2 h postprandial goals of $<140-180$

- Correct hyperglycemia: $1800/50 = \sim 35$
  - Add 1 extra unit bolus insulin for every 35 mg% glucose $>135$

www.texasdiabetescouncil.org
Advancing Insulin Therapy

An 80 Kg patient using 30 units glargine reports

<table>
<thead>
<tr>
<th>a.m.</th>
<th>2h pp brkfst</th>
<th>2 h pp lunch</th>
<th>2 h pp dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>190</td>
<td>240</td>
<td>240</td>
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Options: Add bolus or begin Physiologic Insulin

Physiologic Insulin: Give 0.5 units insulin per Kg

- 50% = basal glargine
- 50% = bolus fast analog ÷ t.i.d.

Example: 80 Kg x 0.5 units/Kg = 40 U insulin

- Give 20 units glargine each morning
- Give ~7 units bolus before each meal

Titrate and add correction doses. Recalculate the Rule 500 and Rule 1800 values as TDD increases

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A patient is using 40 units of NPH insulin at bedtime. The morning glucose is 110 mg/dL, but hypoglycemia occurs frequently in the early a.m.

How you convert once daily NPH to glargine?

→ Conversion is “unit-for-unit”

Give 40 units glargine each morning

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A patient is using NPH twice-daily: 40 units each a.m. and 25 units each p.m.

Fasting and evening glucose are controlled, but hypoglycemia occurs ~0200 and when the patient is active.

How do you convert a patient from multi-dose intermediate to basal insulin?

→ Glargine dose is 80% of the total NPH dose, or
80% (40 +25) = 52

Give 52 units glargine each morning

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Advancing Insulin Therapy

A patient is using 70/30 premix twice-daily: 30 units q a.m. + 20 units q p.m. Glycemic excursions occur.

How do you convert from twice-daily premix to basal:bolus insulin?

→ Glargine is 80% of the total intermediate insulin
  Total intermediate = 70% (30 + 20) = 35 units
  Glargine = 80% x 35 units = 28 units
  Give 28 units glargine each morning

→ Bolus is “unit-for-unit” of the fast-acting insulin
  Total fast-acting = 30% (30 +20) =15 units ÷ t.i.d.
  Give 5 units bolus insulin before each meal

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Options For Insulin-Managed Patients Who Cannot Obtain Postprandial Control

- Repeat education!
  - Medical Nutrition Therapy and Carb Counting
  - Diabetes Education
  - Insulin Management

- Insulin pump therapy is appropriate for some patients..... *but not for all patients*

- Consider Pramlinitide, a synthetic amylin analog, for postprandial control
Amylin Is A Neuroendocrine Hormone

Amylin → Brain → Satiety

Brain → Liver ↓ Glucagon

Liver ↓ Gastric Emptying

Liver → Stomach ↓ Gastric Emptying

Stomach → Brain

Stomach → Pancreas

Pancreas → Insulin ↑ Glucose Disposal

Insulin → Tissues

Tissues → Plasma Glucose

Plasma Glucose → Amylin

Amylin → Amylin
The Amylin Analog Pramlintide Plus Insulin: Effect on Postprandial Glucose Concentration

Data on file, Amylin Pharmaceuticals Inc.
Effects of Pramlintide Therapy in T2DM

Change in % HbA$_{1c}$

Baseline: 9.3  9.1

Week 4  Week 13  Week 26

Change in % HbA$_{1c}$

Change in Insulin Use (%)

Week 4  Week 13  Week 26

Change in Weight (lb)

Week 4  Week 13  Week 26

- Placebo + Insulin (N=284)
- Pramlintide + Insulin (N=292)

Data on file, Amylin Pharmaceuticals, Inc.
Options For Insulin-Managed Patients Who Cannot Obtain Postprandial Control

- Continue basal glargine, same dose
- Decrease each bolus dose ~50%
- Begin Pramlintide
  - T1DM 15 mcg a.c. and titrate
  - T2DM 30 mcg a.c. ± titrate