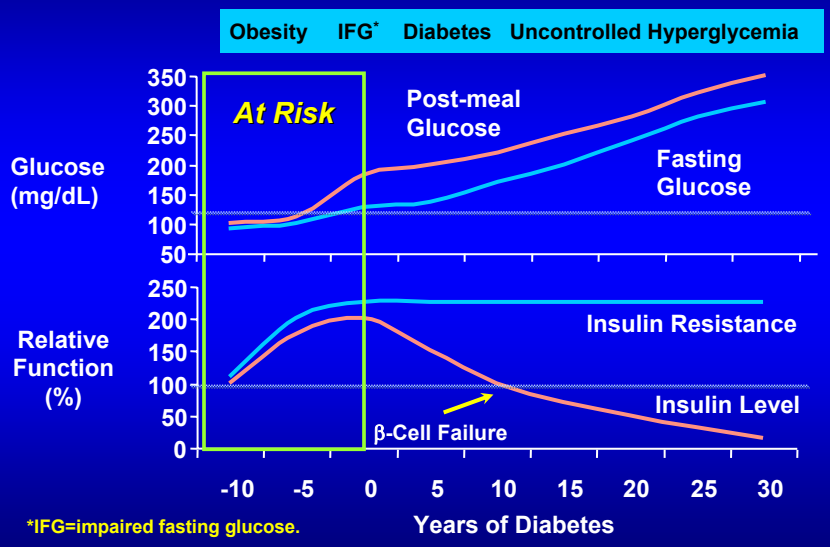
Achieving Optimal Control In Type 2 Diabetes

Case Study

- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- HbA1C 7.3%

Natural History of Type 2 Diabetes

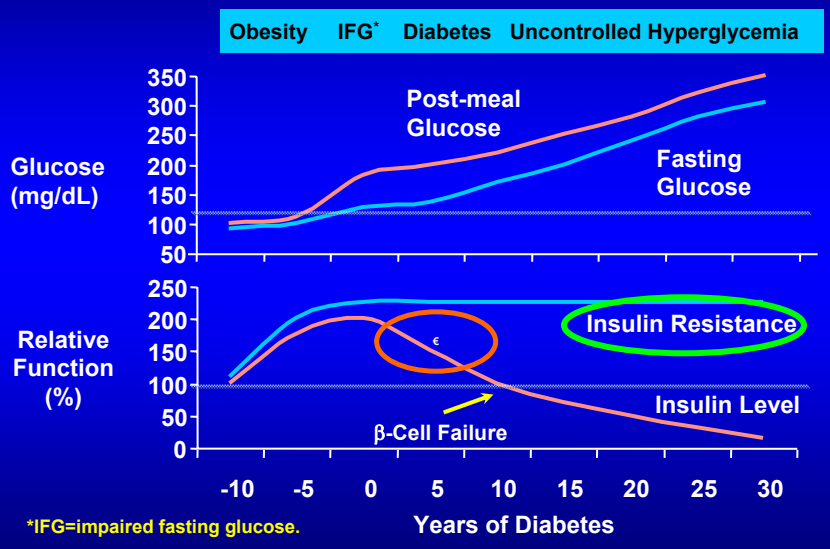


*IFG=impaired fasting glucose.

Therapy of Diabetes

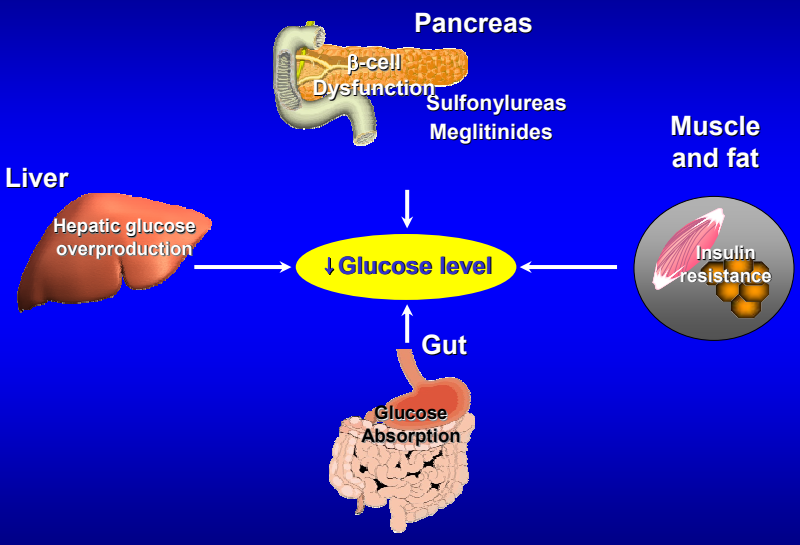
- Diet
- Exercise
- Medications

Natural History of Type 2 Diabetes



*IFG=impaired fasting glucose.

Major Targeted Sites of Drug Classes



Therapeutic Options
Sulfonylureas

Positives	Negatives
➥Efficacious	➥Hypoglycemia
➥Long Experience	➥Weight Gain
➥Inexpensive	➥Primary + Secondary Failure

Therapeutic Options
Meglitinides

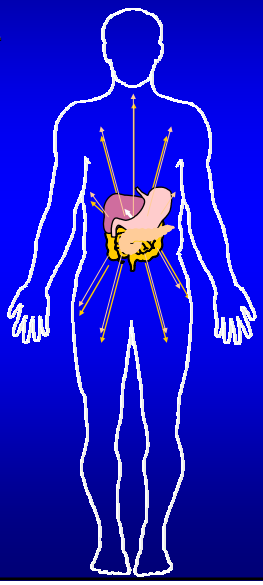
Positives	Negatives
➥Efficacious	➥Hypoglycemia, Less Than SU
➥Fairly Long Experience	➥Weight Gain
	➥TID Dosing
	➥Expensive

GLP-1 Modes of Action in Humans

Upon Ingestion of Food…

GLP-1 Is Secreted From the L-cells In the Intestine

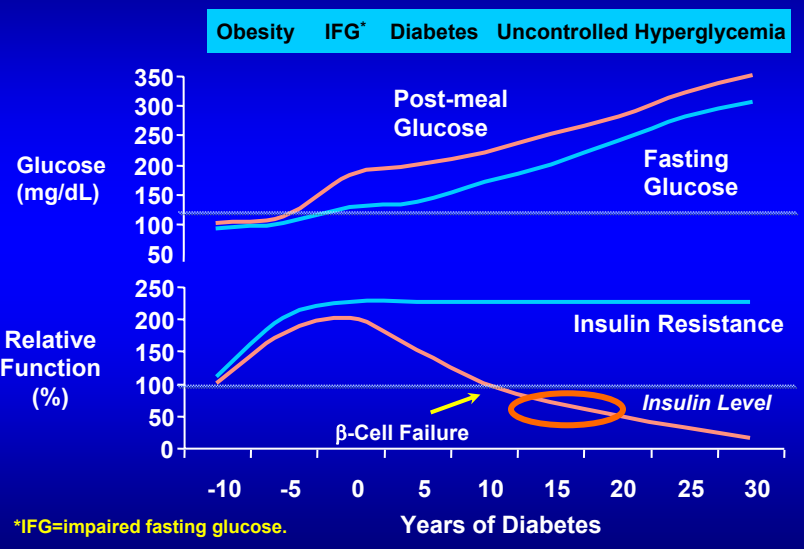
This in Turn…



- ✓ Stimulates Insulin Secretion
- ✓ Suppresses Glucagon
- ✓ Slows Gastric Emptying
- ✓ Reduces Food Intake

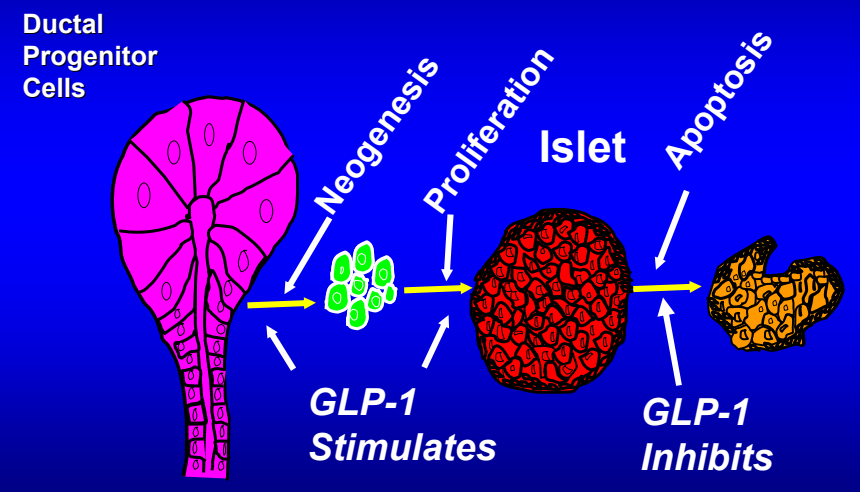
One More Point Going Back to Those β Cells….

Natural History of Type 2 Diabetes



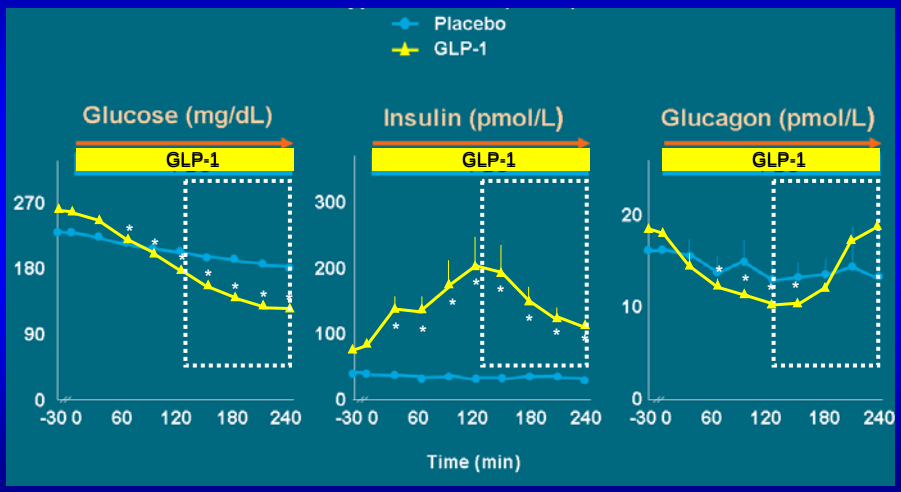
*IFG=impaired fasting glucose.

β-cell Neogenesis, Proliferation and Apoptosis



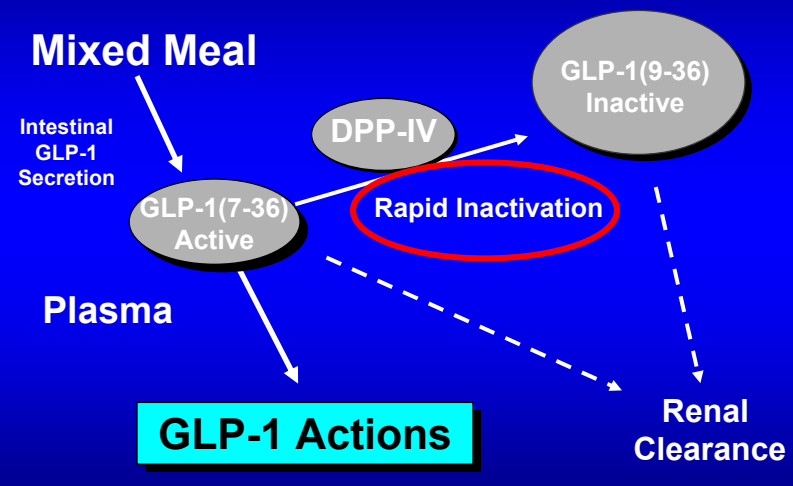
Glucose Dependent Effects of GLP-1

Type 2 Diabetics (n=10)



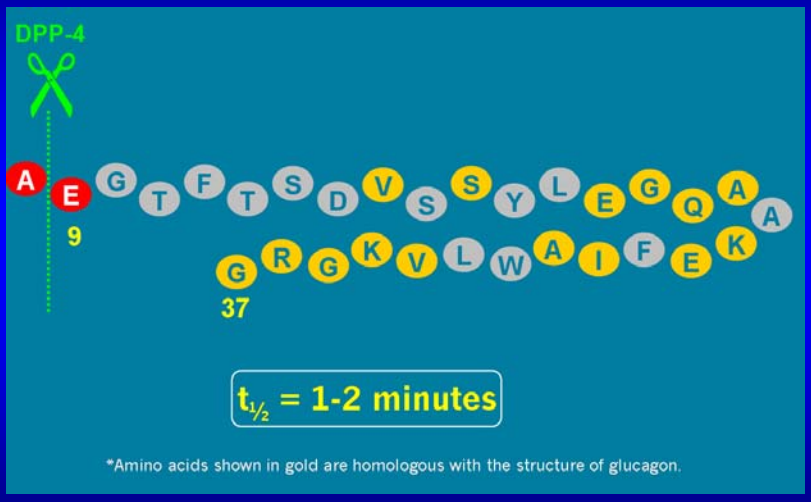
Mean (se) <p.05

GLP-1 Effect : Blocked By DPP-4



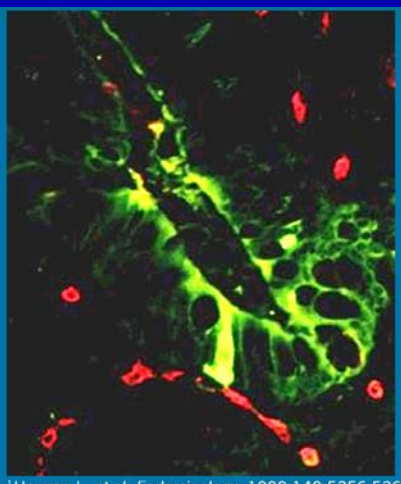
Deacon *et al.* Diabetes 1995; 44:1126

GLP-1: Rapidly Degraded by DPP-4



Mentlein, R *Regulatory Peptides* 85:9-24, 1999

Secreted GLP-1 Rapidly Degraded



- GLP-1 (green) released into intestinal capillaries is immediately exposed to DPP-4 (red)[1]
- >50% of secreted GLP-1 is already degraded before it reaches the general circulation[2]
- >40% of circulating GLP-1 is already degraded before it reaches β-cells[2]

[1]Hansen L, *et al. Endocrinology.* 1999;140:5356-5363;
[2]Deacon CF, *et al. Am J Physiol.* 1996;271(3 pt 1):E458–E464.

Enhance GLP-1 Effect By…

GLP-1 AGENTS

- Exenatide sc (Byetta)
- Liraglutide (Victoza) sc
- Albglutide sc

GLP-1 Agents

The Good:

- ✓ Decrease Post-Prandial Glucose
- ✓ No Hypoglycemia
- ✓ Potential For Weight Loss
- ✓ Perhaps ß Cell Preservation

The Not So Good:

- ✓ *GI Upset*
- ✓ *Injection*
- ✓ *Rare Reports Of Pancreatitis*
- ✓ *Cost*

Enhance GLP-1 Effect By…

GLP-1 AGENTS

- Exenatide sc (Byetta)
- Liraglutide sc (Victoza)
- Albglutide sc

DPP-4 INHIBITORS

- Sitagliptin (Janvuia) po
- Saxagliptin (Onglyza) po
- Linagliptin (Tradjenta) po
- Vildagliptin (Galvus) po
- Alogliptin po

DPP-4 Inhibitors

The Good:

- ✓ Decrease Post-Prandial Glucose
- ✓ No Hypoglycemia
- ✓ Weight Neutral
- ✓ Safe In Renal Disease
- ✓ No GI Upset
- ✓ Perhaps ß Cell Preservation

The Not So Good:

- ✓ *Short Experience*
- ✓ *Cost*

Therapeutic Options
Biguanide

Positives	Negatives
➥Efficacious	➥GI Upset
➥Long Experience	➥Caution With Renal Disease
➥Inexpensive	➥Hold For Dye Procedures/Surgery
➥Weight Loss	

Therapeutic Options
TZDs

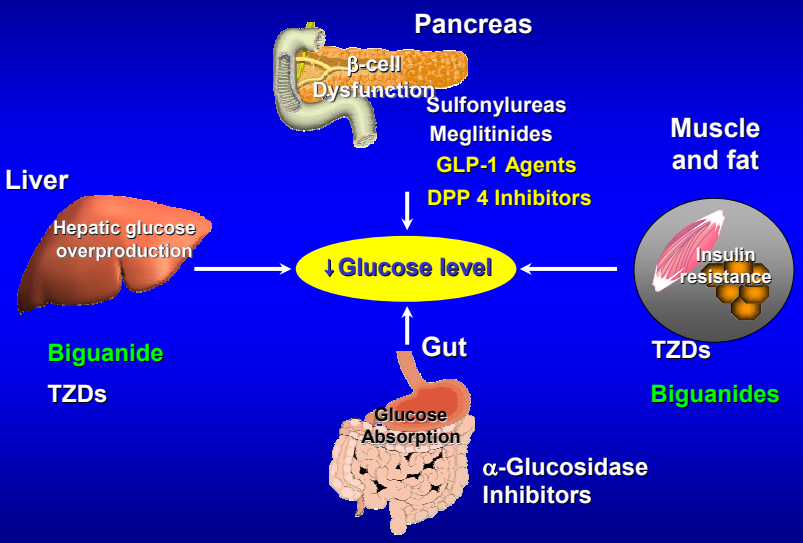
Positives	Negatives
➥Efficacious	➥Increased CV Risk?
➥Reasonably Long Experience	➥Edema
➥No Hypoglycemia	➥Weight Gain
➥β Cell Preservation	➥Fractures

TZD's…Be Careful In Patients With CHF

Another TZD Concern ⇨⇨

Increased Fractures In Women (Extra-Vertebral)

Major Targeted Sites of Drug Classes



Therapeutic Options

α Glucosidase Inhibitors

Positives	Negatives
➥Reasonably Long Experience	➥Only Mildly Efficacious
➥No Hypoglycemia	➥GI Intolerance
➥No Weight Gain	

New Oral Agents For Diabetes

Dopamine Receptor Agonists

Sodium-Glucose Transport Inhibitors (SGLT's)

Low Dose Rapid Acting Bromocriptine

- Dopamine Receptor Agonist (Cycloset)
- Increases Brain Dopamine To Reduce Insulin Resistance→ Reduces Glucose, BP and Lipids
- Lowers A1C, BP and CV Risk

New Oral Agents For Diabetes

Sodium-Glucose Transport Inhibitors (SGLT's)

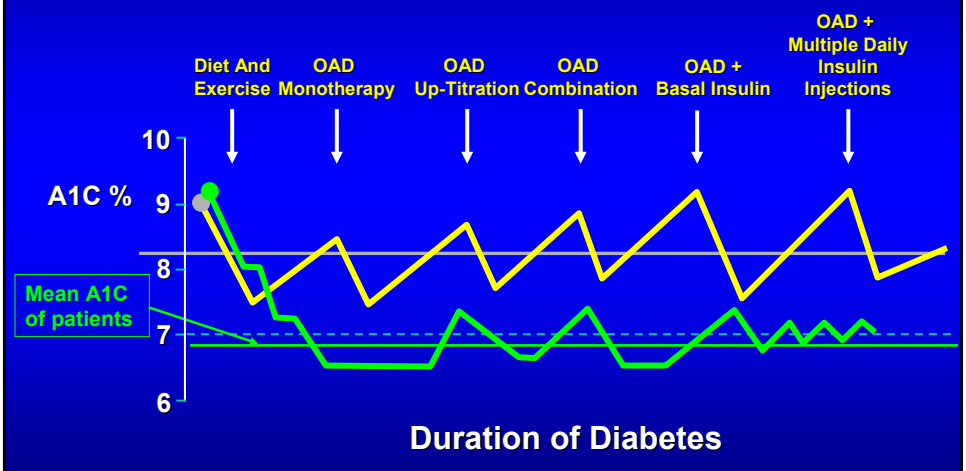
Inhibit Sodium Glucose Co-transporter-2

↓

↓

Prevent Reabsorption Of Glucose In Renal Tubules

Therapeutic Progression



Del Prato S et al. Int J Clin Pract. 2005;59:1345–1355.

Combination Pills for Type 2 Diabetes

Glyburide/Metformin (Glucovance)
Glipizide/Metformin (Metaglip)
Pioglitazone/Metformin (ActoPlusMet)
Glimepiride/Pioglitazone (DuetAct)
Sitagliptin/Metformin (Janumet)
Saxaglitin/Metformin (Kombiglyze)

Case Study

- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- HbA1C 7.3%
- Metformin Started

Case Study

3 Months Later

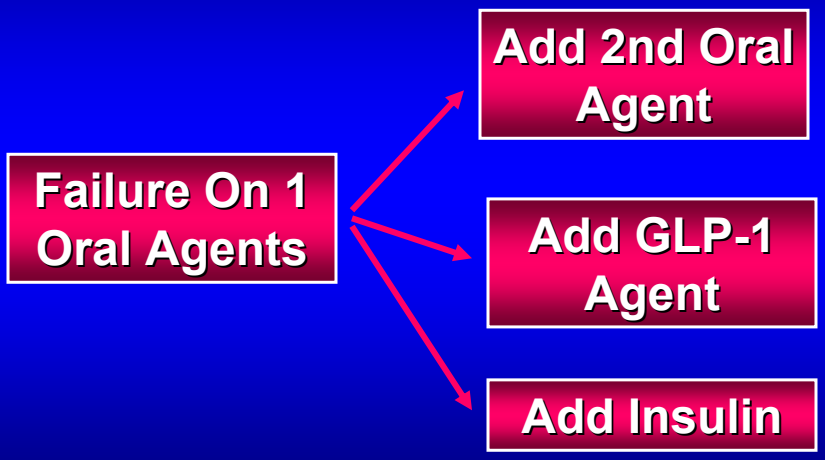
- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- On Metformin
- Hb A1C 6.2%

Case Study

3 Years Later

- 61 Year Old Journalist
- Type 2 DM X 3 Years
- On Metformin
- Hb A1C 8.9%

Decisions, Decisions…



Case Study

- 61 Year Old Journalist
- Type 2 DM X 3 Years
- On Metformin
- Hb A1C 8.9%
- Second Oral Agent Added

Case Study

3 Months Later

- 61 Year Old Journalist
- Type 2 DM x 3 Years
- On Metformin + Second Oral Agent
- Hb A1C 6.9%

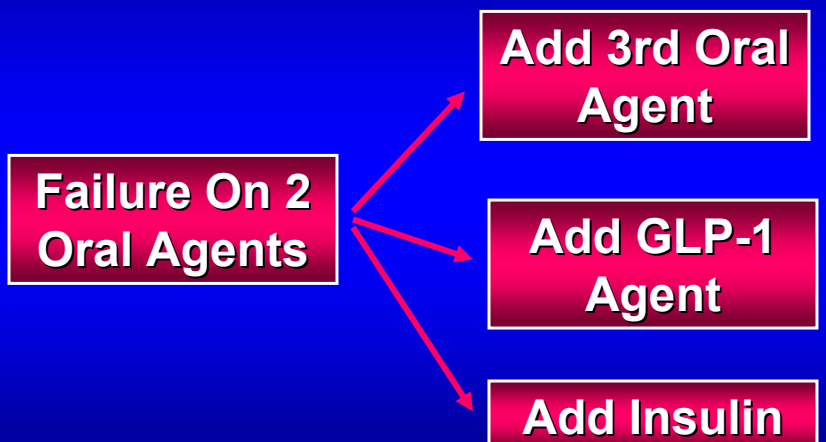
Case Study

1 Year Later

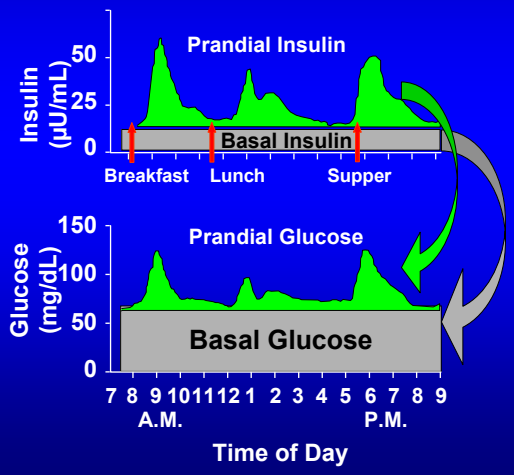
- 62 Year Old Journalist
- Type 2 DM X 4 Years
- On Metformin + Second Oral Agent
- HbA1C 9.6%

What To Do If/When Two Oral Agents Are Not Enough?

Decisions, Decisions…



Physiologic Insulin Secretion : Basal/Bolus Concept



- Suppresses Glucose Production Between Meals & Overnight
- *Basal ≅ 50% of Daily Needs*

50/50 Rule

A Basic Principle:

Fix The Fasting First

Currently Available Basal Insulins

- Neutral Protamine Hagedorn (1946)
- Insulin Glargine (2001)
- Insuin Detemir (2006)

Keep The Sulfonylurea, Tide, or The Gliptin On Board To Drive The β Cell For Mealtime Coverage!

Starting Basal Insulin

Continue Oral Agent(s) at Same Dosage (Eventually Reduce)

Add Single Insulin Dose (~ 15 units)

- ✓Glargine (Anytime)
- ✓ Increase Insulin Dose 1 unit Daily Until FBS<100mg &/or HbA1C < 7%

Starting Basal Insulin

Continue Oral Agent(s) at Same Dosage (Eventually Reduce)

Add Single Insulin Dose (~ 15 units)

- ✓Glargine (Anytime)
- ✓Detemir (Evening)
- ✓NPH (Bedtime)
- ✓Premix (Evening Meal)

Case Study

- 62 Year Old Journalist
- Type 2 DM x 4 Years
- On Metformin + Second Oral Agent
- Hb A1C 9.6%
- Basal Insulin Added

Case Study

4 Months Later

- 62 Year Old Journalist
- Type 2 DM X 4 Years
- On Metformin + Second Oral Agent + Basal Insulin
- Hb A1C 6.9%

Case Study

2 Years Later

- 64 Year Old Journalist
- Type 2 DM x 7 Years
- On Metformin + Second Oral Agent + Basal Insulin
- HbA1C 7.8% With Fasting Sugars Between 100 and 110 mg%

What's Going On?

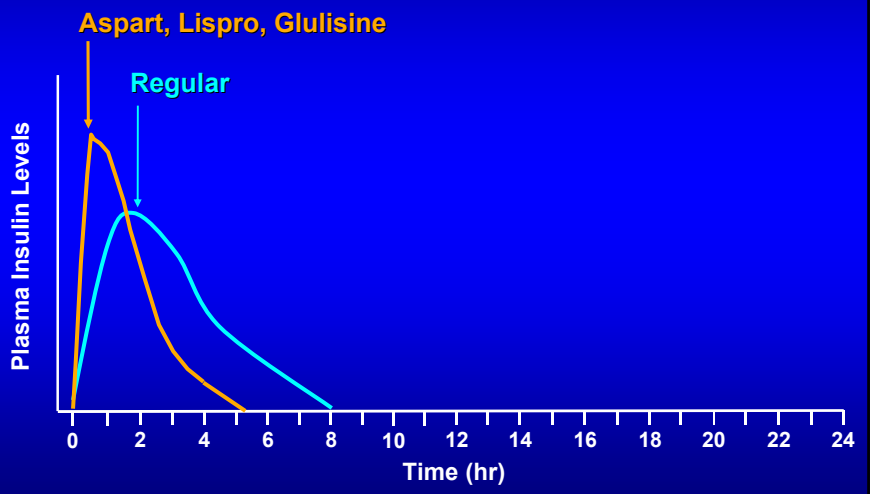
Postprandial Glucose Must Be Elevated

BOLUS INSULIN…

Currently Available Bolus Insulins

- Regular (1921)
- Insulin Lispro (1996)
- Insulin Aspart (2000)
- Insulin Glulisine (2006)

Insulin Profiles

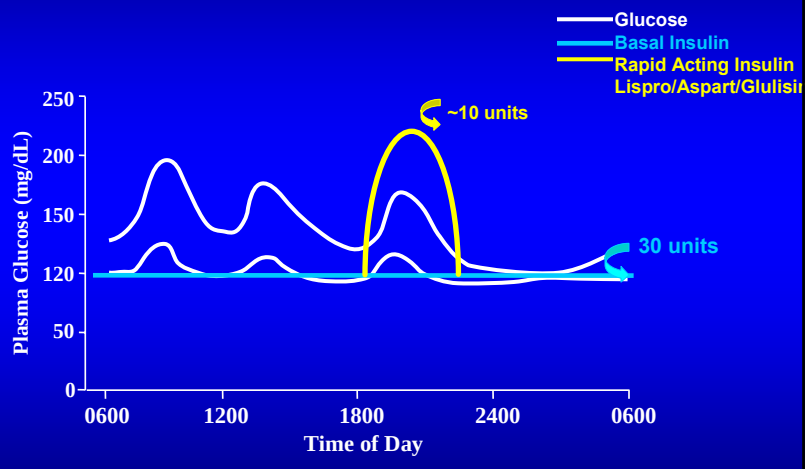


Rosenstock J. Clin Cornerstone. 2001;4:50

Bolus Insulin

- ✓ Add Rapid Acting Insulin For Mealtime Coverage
- ✓ *Rule Of Thumb For Glargine:*
  - 50% Basal
  - 50% Prandial, Divided Over 3 Meals

Glucose Patterns in Type 2 Diabetes Mellitus



Continue SU/Tide/DPP-4 Inhibitor, Metformin, TZD

Case Study

3 Months Later

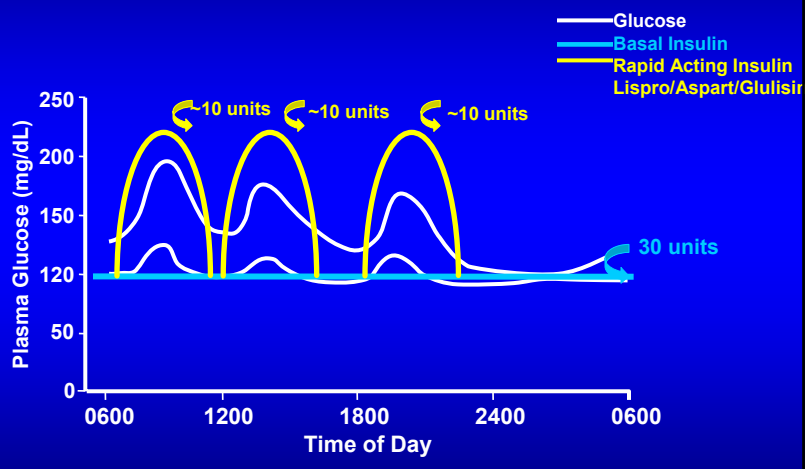
- 64 Year Old Journalist
- Type 2 DM x 7 Years
- On Metformin + Second Oral Agent + Basal Insulin + 1 Shot Bolus Insulin
- HbA1C 6.7%

Case Study

2 Years Later

- 66 Year Old Journalist
- Type 2 DM X 9 Years
- On Metformin + Second Oral Agent + Basal Insulin + 1 Shot Bolus Insulin
- Hb A1C 9.8%

Glucose Patterns in Type 2 Diabetes Mellitus



Discontinue SU/Tide/DPP-4 Inhibitor; Continue Metformin, TZD

Fine Tuning The Bolus

The Bolus Has 2 Components:

Prandial→

Fine Tune By Carbohydrate Counting

Correction Factor →

Adjustment For Pre-Meal Hyperglycemia

Case Study

- **66 Year Old Journalist**
- **Type 2 DM x 9 Years**
- **On Metformin + Second Oral Agent* + Basal Insulin + Bolus Insulin Before Each Meal**
- **HbA1C 6.9%**

***If 2nd oral agent is SU, it should be discontinued.**