

# Updates in Diabetes

Mae Sheikh-Ali, M.D.  
 Assistant Professor of Medicine  
 Division of Endocrinology  
 University of Florida College of Medicine-  
 Jacksonville

---

---

---

---

---

---

---

---

## Presentation Outline

- Pathogenesis of DM
- Criteria for the diagnosis of DM
- DM Complications
- Treatment Goals for A<sub>1</sub>C, FPG, and PPG
- DM Management -the new and the old
- Insulin therapy

---

---

---

---

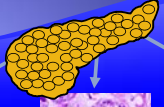
---

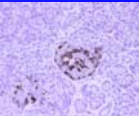
---

---

---

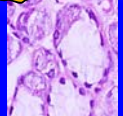
## The Role of the Pancreas in Blood Sugar Regulation





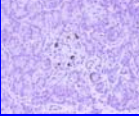
**Alpha Cells**

- Glucagon
- Acts on liver to release glycogen
- Increases blood sugar



**Beta Cells**

- Insulin
- Decreases blood sugar



**Delta Cells**

- Somatostatin
- Stops glucagon and growth hormone
- Decreases blood sugar

Colorado State University  
<http://arbl.cvmbs.colostate.edu/hbooks/pathophys/endocrine/pancreas/anatomy.html>  
 Accessed December 3, 2003.

---

---

---

---

---

---

---

---

## Diabetes Mellitus

- 10% of diabetes is Type 1<sup>1</sup>
  - Genetic link (chromosome 6HLA region)
  - Presence of islet cell autoantibodies
  - Autoimmune destruction of the beta cells
- 80% of diabetes is Type 2<sup>2</sup>
  - Genetic predisposition
  - Obesity
  - Impairment of insulin secretion and defects in insulin action

1. Atkinson MA and Eisenbarth GS. Lancet. 2001;358:221-229.  
2. CDCP. December 2003. Atlanta, GA: US Dept. of Health and Human Services, CDCP, 2003.

---

---

---

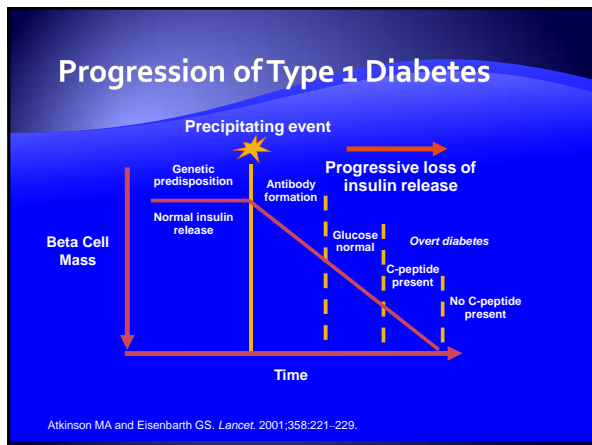
---

---

---

---

---




---

---

---

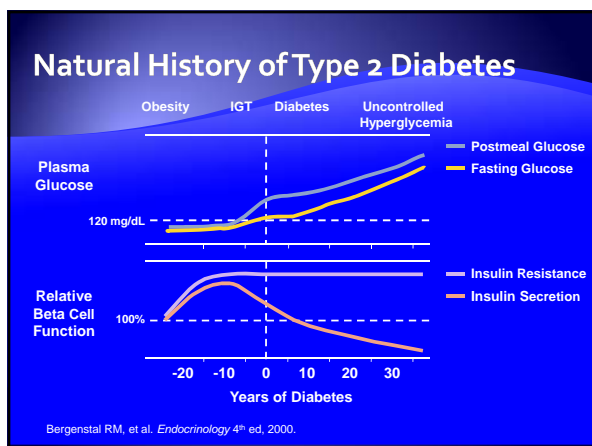
---

---

---

---

---




---

---

---

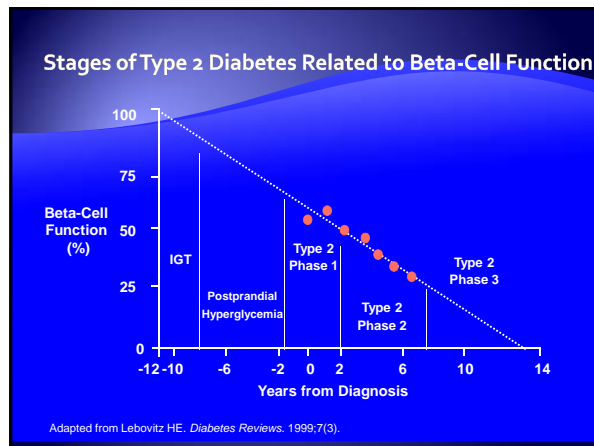
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

## MODY

- Accounts for about 5 % of type 2 DM
- Single gene defects
  - Autosomal dominant inheritance
  - Multiple generations affected
- Early age at onset < 25 years
- Characterized by absence of obesity, no ketosis, no evidence of beta cell autoimmunity
- Genetic defects of beta cell function

---

---

---

---

---

---

---

---

---

---

Criteria for the Diagnosis of Diabetes Mellitus <sup>†</sup>		
Normoglycemia	IFG and IGT	Diabetes mellitus*
FPG <100 mg/dL	FPG ≥100 mg/dL and <126 mg/dL (IFG)	FPG ≥126 mg/dL
2-h PG● <140 mg/dL	2-h PG● ≥140 mg/dL and <200 mg/dL (IGT)	2-h PG● ≥200 mg/dL
—	—	Symptoms of DM and casual plasma glucose concentration ≥200 mg/dL
DM, diabetes mellitus; FPG, fasting plasma glucose; 2-h PG, 2-h postload glucose.		
* In the absence of unequivocal hyperglycemia, a diagnosis of diabetes must be confirmed on a subsequent day by any one of the three methods included in the chart. In clinical settings, the FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no caloric intake for at least 8 h.		
● This test requires the use of a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.		
<sup>†</sup> Copyright © 2004 American Diabetes Association From <i>Diabetes Care</i> Vol 27, Supplement 1, 2004. Reprinted with permission from The American Diabetes Association.		

---

---

---

---

---

---

---

---

---

---

Standards of Medical Care in Diabetes—  
2011  
AMERICAN DIABETES ASSOCIATION

A1C 6.5%  
or  
FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.  
or  
2-h plasma glucose 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.  
or  
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/dl (11.1 mmol/l)

---

---

---

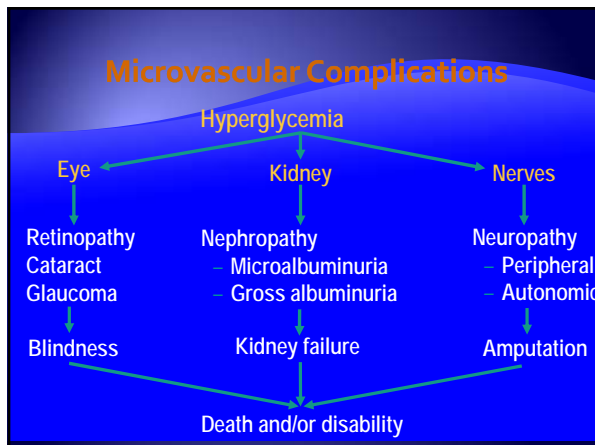
---

---

---

---

---




---

---

---

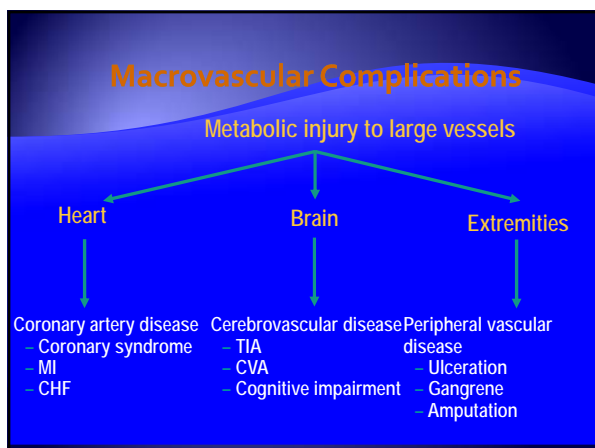
---

---

---

---

---




---

---

---

---

---

---

---

---

### ADA and AACE/ACE Guidelines: Treatment Goals for A1C, FPG, and PPG

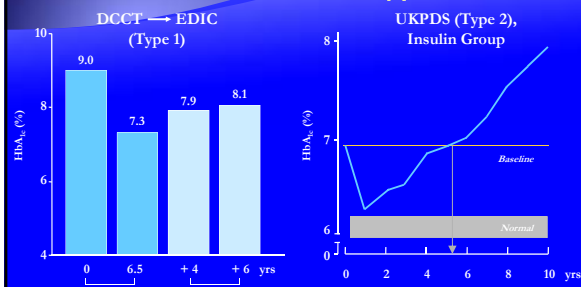
	Normal <sup>1,2</sup>	ADA <sup>3</sup>	AACE/AC E <sup>2</sup>
Parameter	Level	Goal	Goal
FPG, mg/dL	<100	90–130	<110
PPG, mg/dL	<140	<180	<140
A1C, %	4–6	<7 <sup>a</sup>	≤6.5

<sup>a</sup>The goal for an individual patient is to achieve an A1C as close to normal (<6%) as possible without significant hypoglycemia.

FPG=fasting plasma glucose; PPG=postprandial glucose; ADA=American Diabetes Association; AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology.  
1. Adapted from Buse J et al. In: Williams Textbook of Endocrinology, 10th ed. 2003. Permission requested.  
2. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. Endocr Pract 2007;13(suppl 1):3–68.  
3. ADA. Diabetes Care 2007;30:S4–S11.

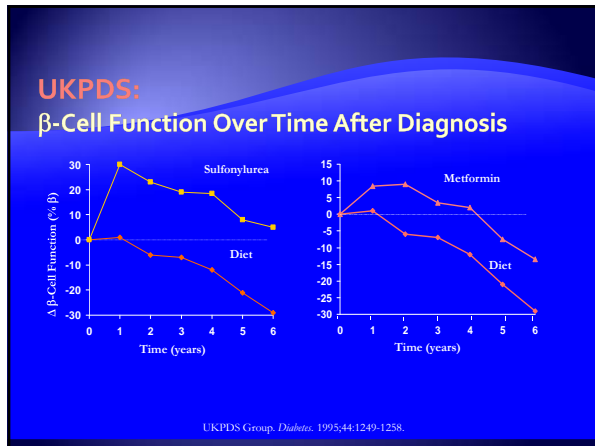
### Management strategy to achieve the glycemic goals

### Lessons from the DCCT and UKPDS: Sustained Intensification of Therapy is Difficult



DCCT/EDIC Research Group. New Engl J Med 2001;342:359–369.  
Hoffert et al. Diabetes 2001 (suppl 2):S46–S47.

UK Prospective Diabetes Study Group (UKPDS) 33.  
Lancet 1998;352:837–853.




---

---

---

---

---

---

---

---

---

---

**IN LIGHT OF THESE RESULTS MORE THERAPEUTIC OPTIONS WERE DEVELOPED**

Lower A1c  
Preserve Beta cell function  
Lower CVD events

---

---

---

---

---

---

---

---

---

---

Efficacy in Lowering A1c  
Ability to Preserve Beta cell function  
Lower CVD events

**IN THE LAST DECADE, 7 NEW CLASSES OF DRUGS HAVE BEEN INTRODUCED**

---

---

---

---

---

---

---

---

---

---

****	Mechanism of action	Typical Change in A1C
Insulin		1.5-3.5
Metformin	Decrease hepatic gluconeogenesis	1.0-2.0
Sulfonylurea	Stimulate insulin secretion	1.0-2.0
<b>Glinides</b> (Repaglinide, Nateglinide)	Stimulate insulin secretion (short acting)	1.5
<b>TZDs</b> (Rosiglitazone, Pioglitazone)	Insulin sensitizer potentiate peripheral glucose uptake	<1.0
<b>Alpha-glycosidase Inhibitors</b> (Acarbose, Miglitol)	Inhibit digestion and absorption of carb in small intestine	<1.0
<b>GLP-1 analogue</b> Exenatide (byetta)	↑ insulin, ↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0
<b>DPP-4 Inhibitors</b> (sitagliptine)	Inhibit the degradation of GLP-1	<1.0
<b>Amylin analogue</b> Pramlintide (Symlin)	↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0

---

---

---

---

---

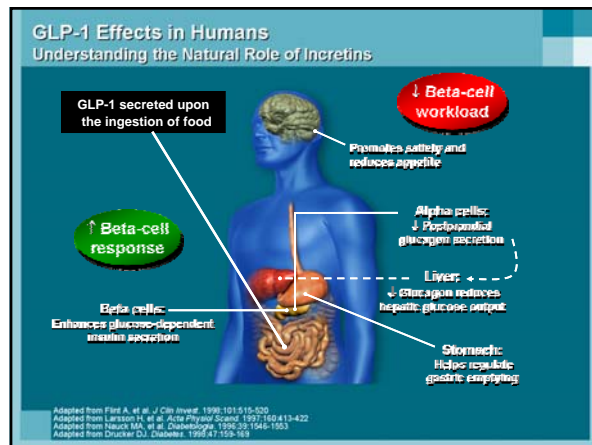
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

**More Than 50% of Secreted GLP-1 Is Degraded Before Plasma Absorption**

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

Histochemistry by C. Orskov, Panum Institute, Copenhagen. Copyright © 1999, The Endocrine Society.  
1. Hansen L, et al. Endocrinology. 1999;140:5396-5393.  
2. Deacon CF, et al. Am J Physiol. 1996;271(3 pt 1):E458-E464.

---

---

---

---

---

---

---

---

---

---

	Mechanism of action	Typical Change in A1C
Insulin		1.5-3.5
Metformin	Decrease hepatic gluconeogenesis	1.0-2.0
Sulfonylurea	Stimulate insulin secretion	1.0-2.0
Glinides (Repaglinide, Nateglinide)	Stimulate insulin secretion (short acting)	1.5
TZDs (Rosiglitazone, Pioglitazone)	Insulin sensitizer potentiate peripheral glucose uptake	<1.0
Alpha-glycosidase Inhibitors (Acarbose, Miglitol)	Inhibit digestion and absorption of carb in small intestine	<1.0
GLP 1 analogue Exenatide (byetta)	↑ insulin, ↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0
DPP-4 Inhibitors (sitagliptine)	Inhibit the degradation of GLP 1	<1.0
Amylin analogue Pramlintide ( Symlin)	↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0

---

---

---

---

---

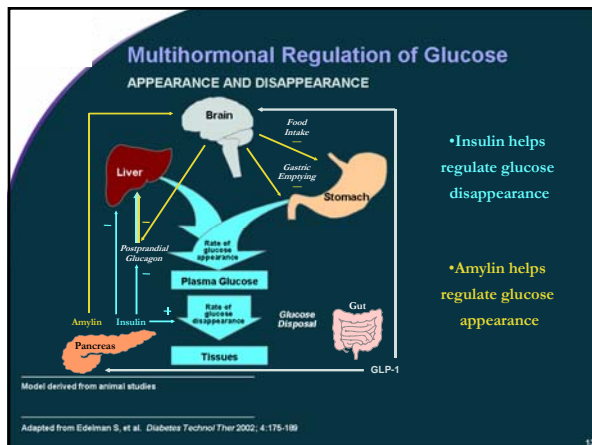
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

	Mechanism of action	Typical Change in A1C
Insulin		1.5-3.5
Metformin	Decrease hepatic gluconeogenesis	1.0-2.0
Sulfonylurea	Stimulate insulin secretion	1.0-2.0
Glinides (Repaglinide, Nateglinide)	Stimulate insulin secretion (short acting)	1.5
TZDs (Rosiglitazone, Pioglitazone)	Insulin sensitizer potentiate peripheral glucose uptake	<1.0
Alpha-glycosidase Inhibitors (Acarbose, Miglitol)	Inhibit digestion and absorption of carb in small intestine	<1.0
GLP 1 analogue Exenatide (byetta)	↑ insulin, ↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0
DPP-4 Inhibitors (sitagliptine)	Inhibit the degradation of GLP 1	<1.0
Amylin analogue Pramlintide ( Symlin)	↓ glucagon, ↓ gastric emptying, ↓ appetite	<1.0

---

---

---

---

---

---

---

---

---

---



## INSULIN HAS THE MOST POTENT EFFECT ON A<sub>1</sub>C

The newer drugs are less potent than insulin

---

---

---

---

---

---

---

---

## Preservation of Beta Cell Mass?

- In animal models some drug classes such as TZD and GLP<sub>1</sub> preserve beta cell mass
- We do not have clinical data to demonstrate beta cell preservation in humans
  - however studies with TZD have shown that they have better durability of efficacy compared to metformin and glyburide

---

---

---

---

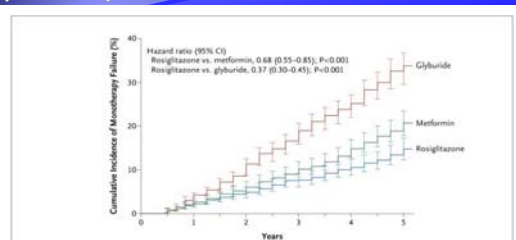
---

---

---

---

## A Diabetes Outcome Progression Trial (ADOPT)



Treatment was considered to have failed if a patient had a confirmed or adjudicated level of fasting plasma glucose of more than 180 mg per deciliter.

Kahn et al. 355 (23): NEJM 2006

---

---

---

---

---

---

---

---

## Cardiovascular Outcome?

---

---

---

---

---

---

---

---

## THE FIRST INTERVENTIONAL TRIAL TO LOOK AT CVD MORTALITY FOR THE NEWER AGENTS

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive Trial)

---

---

---

---

---

---

---

---

## PROactive Trial Results

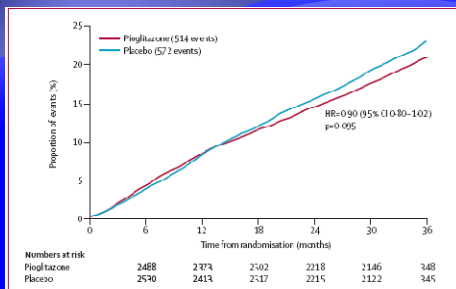


Figure 2: Kaplan-Meier curve of time to primary endpoint\*  
 \*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

Dormandy JA Lancet 366:1279-89,2005.

---

---

---

---

---

---

---

---




---

---

---

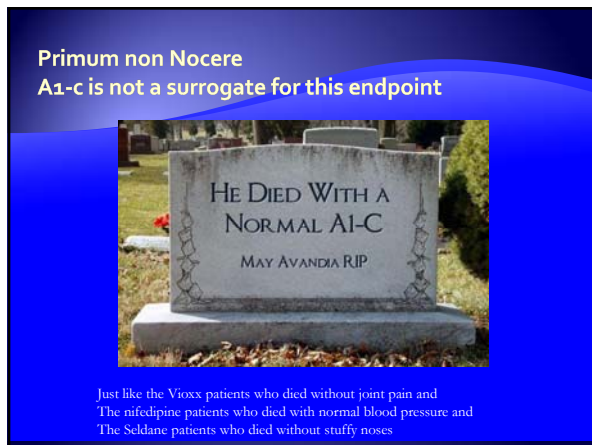
---

---

---

---

---




---

---

---

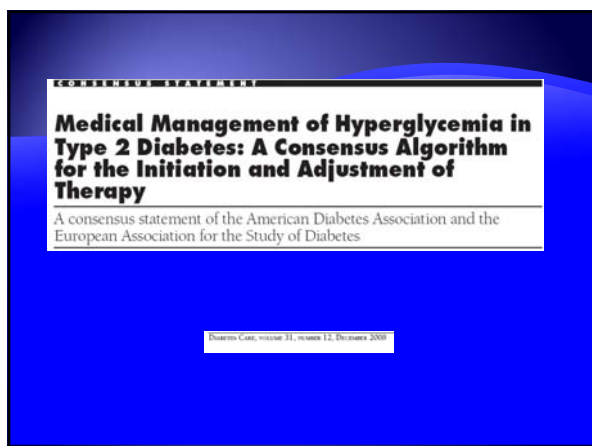
---

---

---

---

---




---

---

---

---

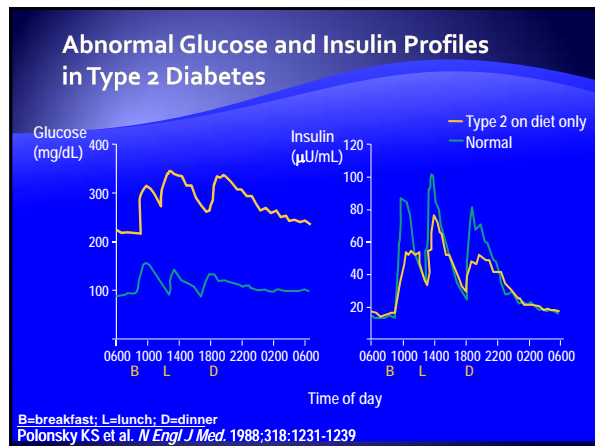
---

---

---

---






---

---

---

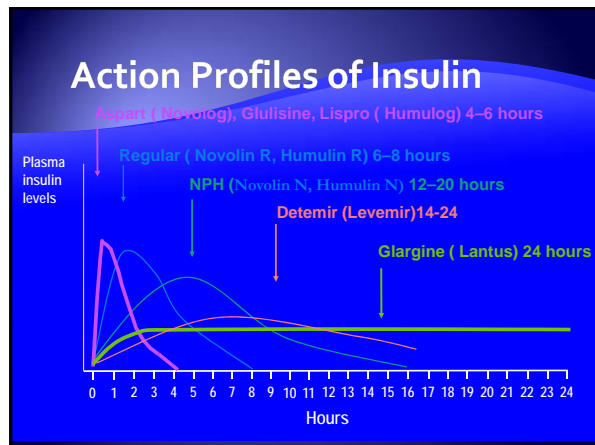
---

---

---

---

---




---

---

---

---

---

---

---

---

Insulin Preparations	Action Profile (hours)		
	Onset	Peak	Duration
<b>Ultra-Rapid acting analogues</b>	15-30 minutes	0.5-2 hours	3-4 hours
•Lispro	15-30 minutes	0.5-2 hours	3-4 hours
•Aspart	15-30 minutes	0.5-2 hours	3-4 hours
•Glulisine			
<b>Short Acting Insulin (Human)</b>	30-60 minutes	2-3 hours	6-8 hours
•Regular	1-3 hours	6-12 hours	12-18 hours
•U-500			
<b>Intermediate-Acting (Human)</b>	1.5 hours	4-10 hours	16-24 hours
•NPH			
<b>Intermediate-Acting Analogues</b>	1-2 hours	6-8 hours	14-24 hours
•Detemir			
<b>Long Acting Analogues</b>	1-1.5 hours	No peak	20-24 hours
•Glargine			

---

---

---

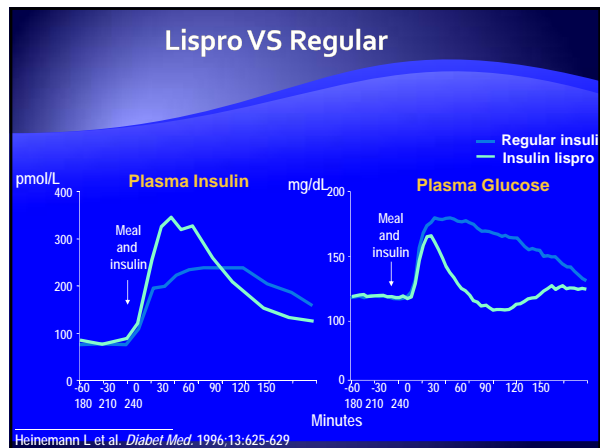
---

---

---

---

---




---

---

---

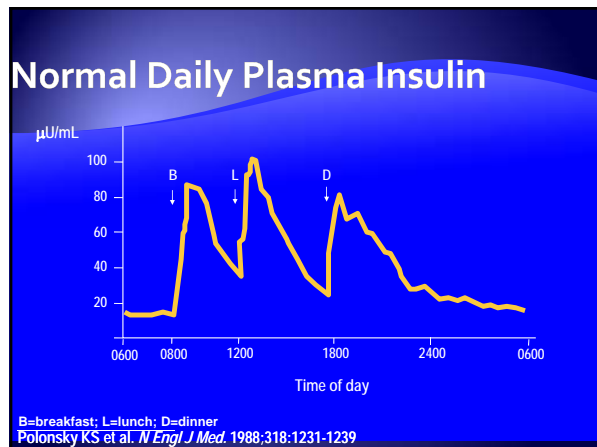
---

---

---

---

---




---

---

---

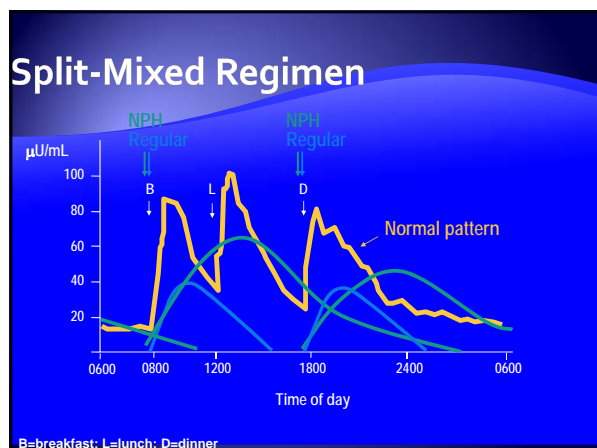
---

---

---

---

---




---

---

---

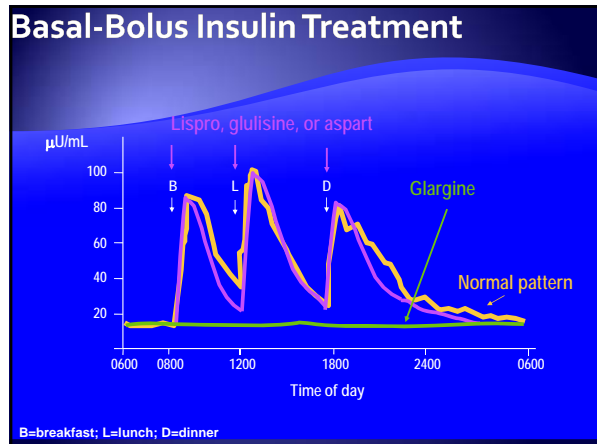
---

---

---

---

---




---

---

---

---

---

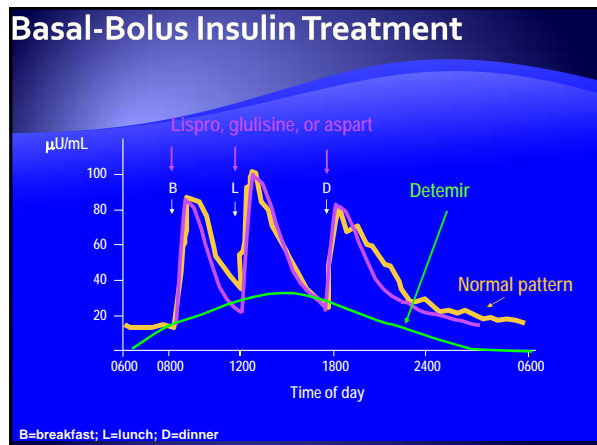
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

### Insulin Delivery: Spectrum of Options

Durable and Disposable Options  
For accurate, consistent dose

Current Standard Insulin Therapy

Intensive Delivery System Therapy

Intensive Insulin Pump Therapy

---

---

---

---

---

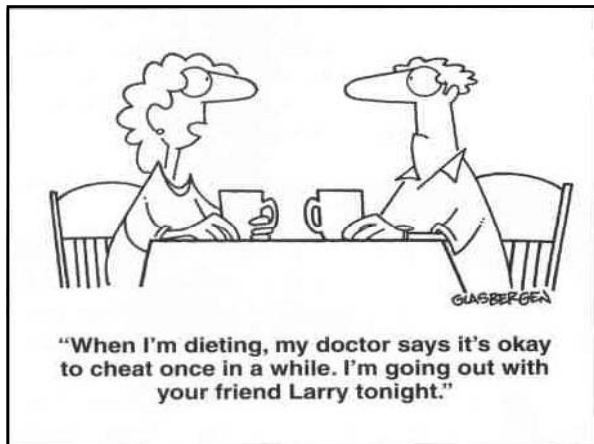
---

---

---

---

---



---

---

---

---

---

---

---

---