Diabetes Medication Review & Update

Barbara Skinner, MS, RD, CDE

Types of Diabetes

- **Type 1**

  Autoimmune disease

  Destruction of beta-cells of pancreas

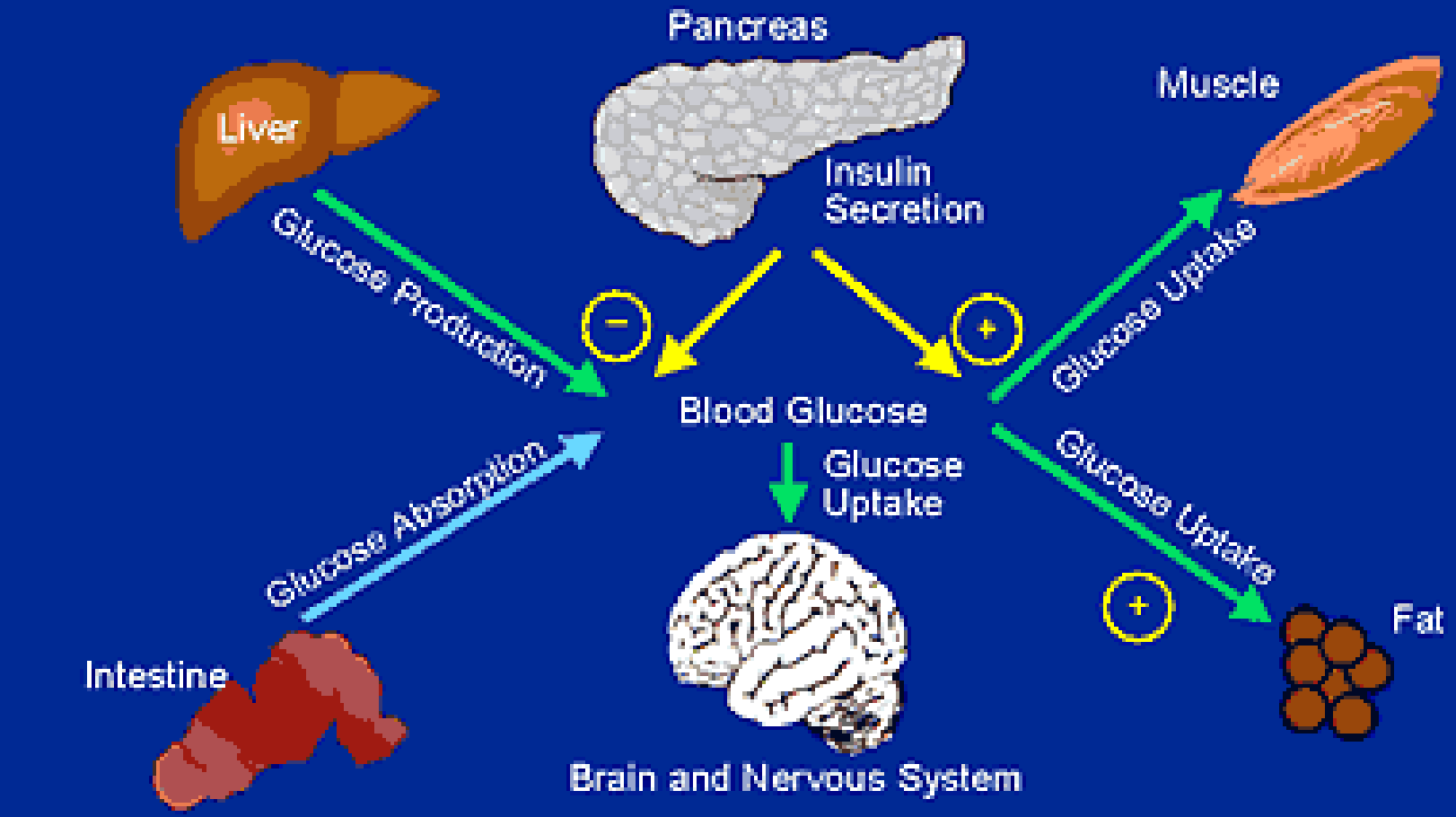
  Treatment = Insulin with syringes, pens or pumps

- **Type 2**

  90-95% of cases

- **Gestational**

Regulation of Blood Glucose



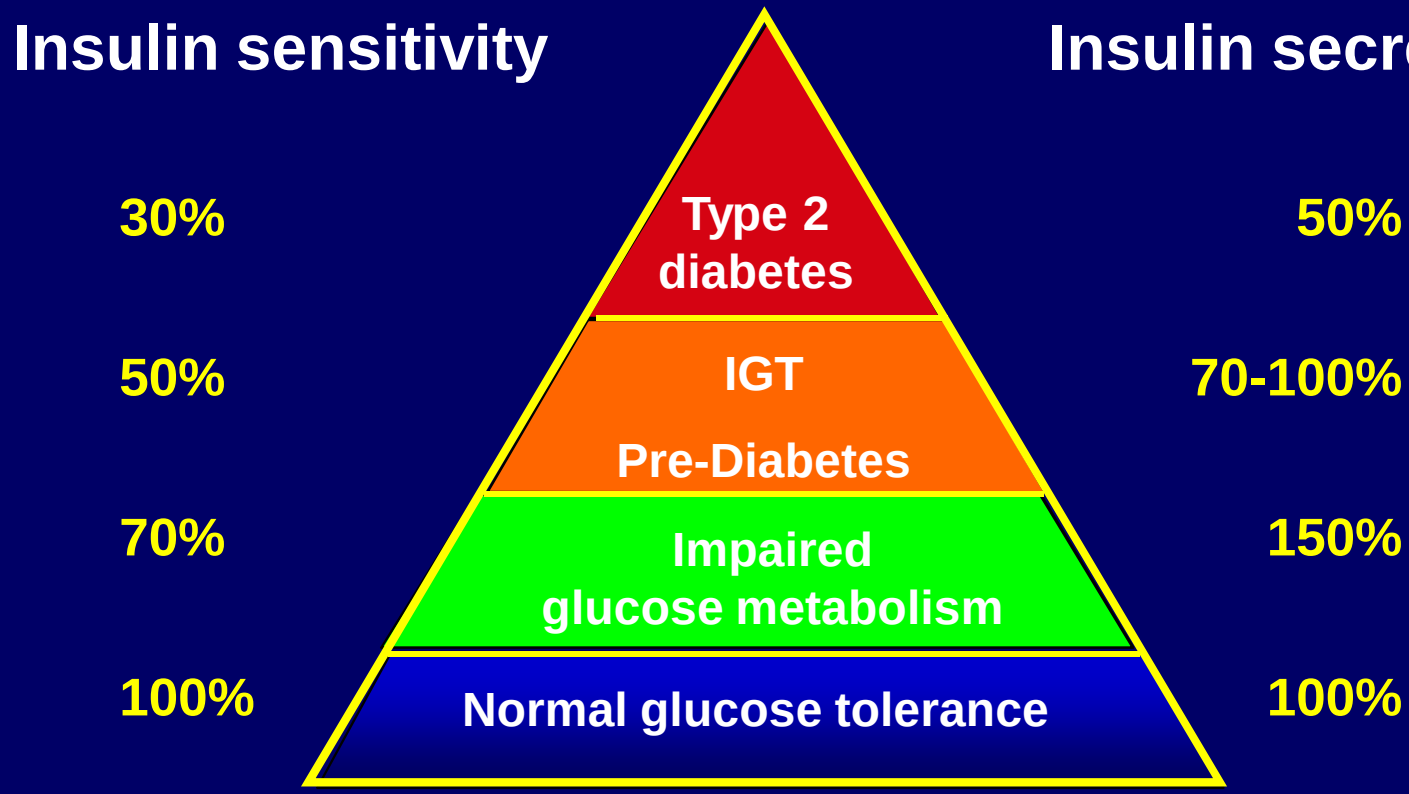
+/- Indicates effect of insulin on glucose production or uptake.

Type 2 Diabetes

Causes of Hyperglycemia

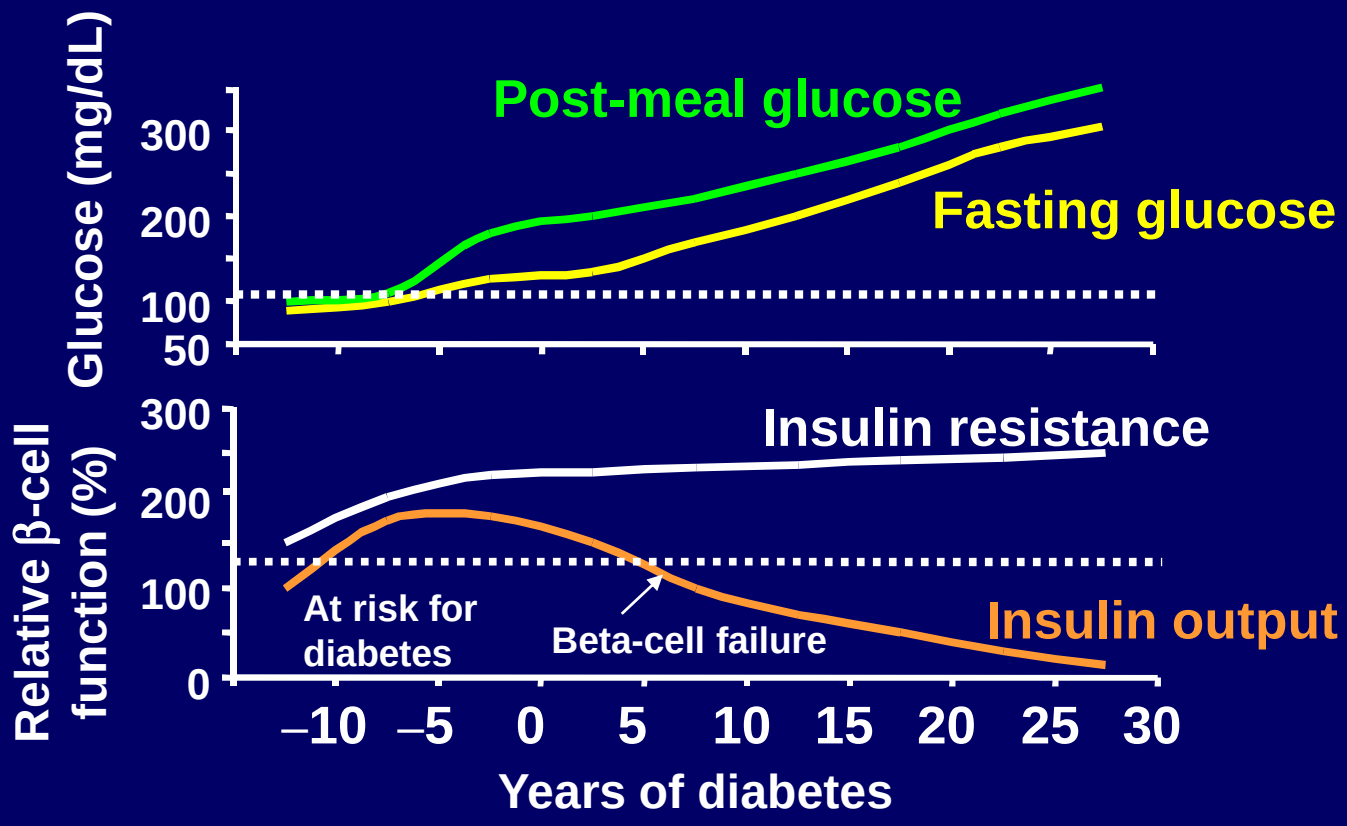
- Loss of 1st phase insulin response from pancreas
- Peripheral tissue insulin resistance
- Hepatic glucose overproduction
- Relative vs. absolute insulin deficiency
- Defective pancreatic beta cell function

Type 2 Diabetes Development



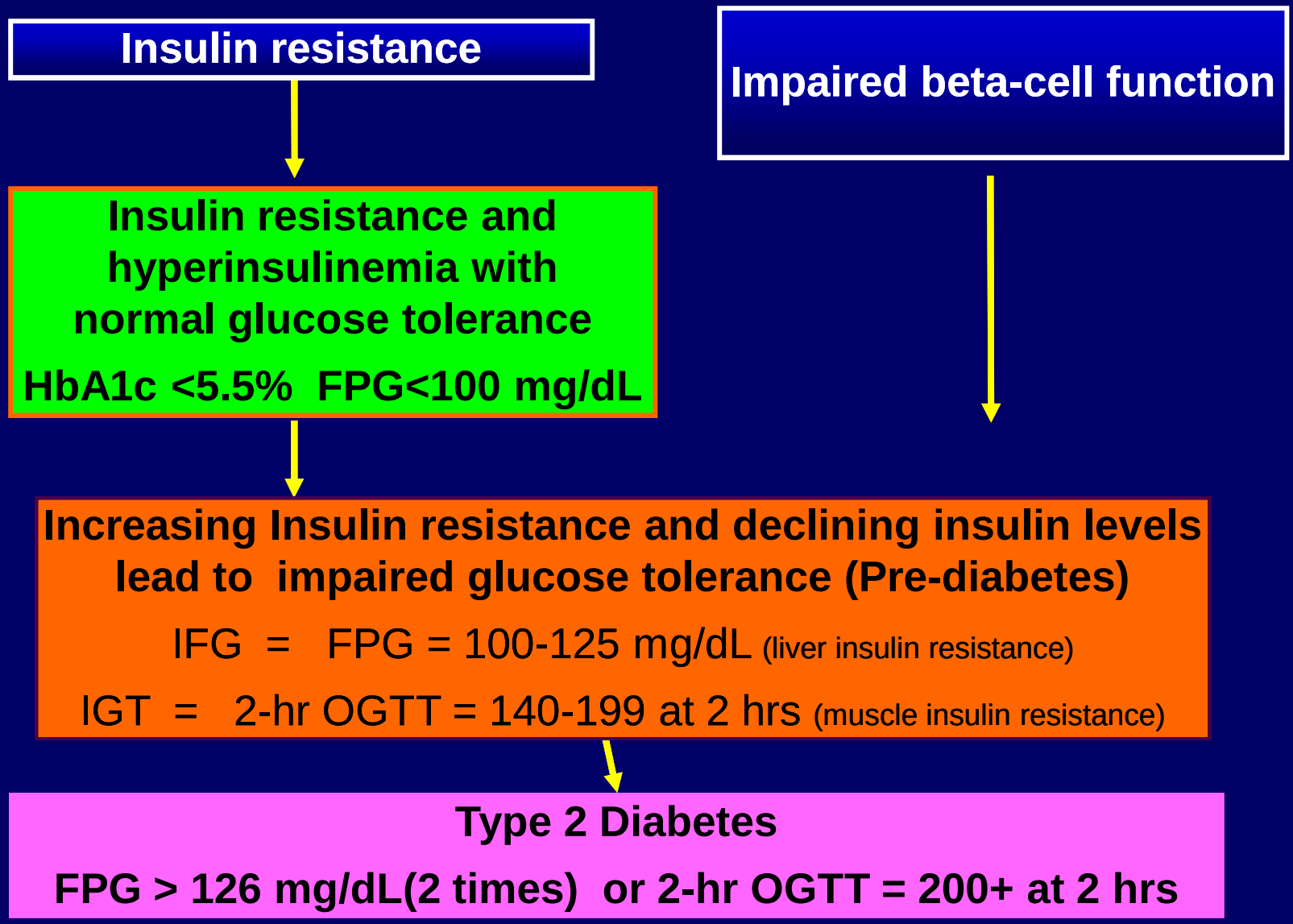
Groop L. Diabetes Obes Metab 1999;1(1):S1.

Natural History of Type 2 Diabetes



Adapted from Bergenstal R, et al.

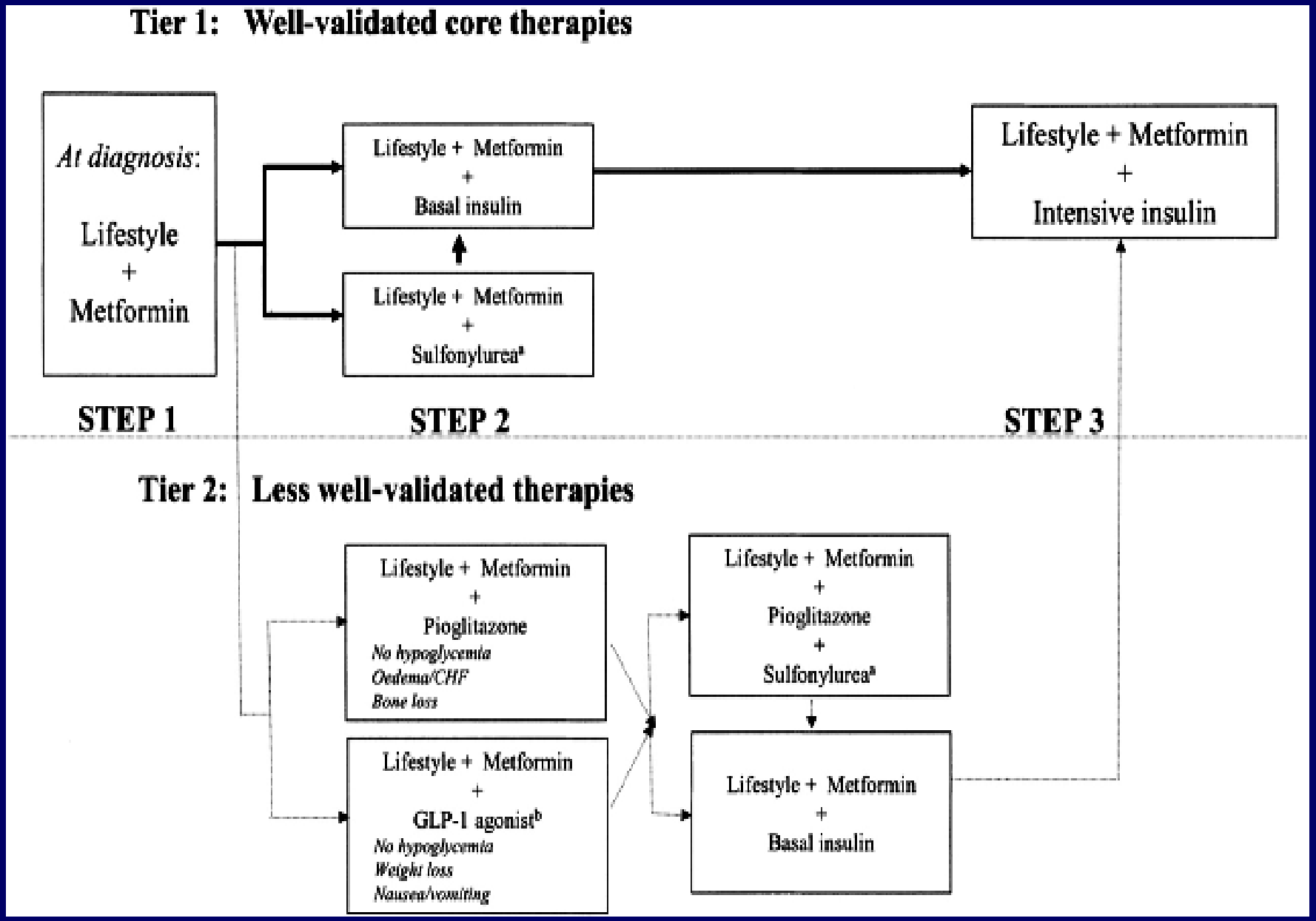
Presentation of Glucose Intolerance



Adapted from Diabetes 1996;45:1661.

Blood Glucose Goals

	ADA Goals (mg/dl)	AACE Goals (mg/dl)
Pre-meal	90-130	< 110
2-hour Post-meal	< 180	Less than or = 140 mg/dl
Hemoglobin A1C	Less than 7.0 %	Less than or = 6.5 %



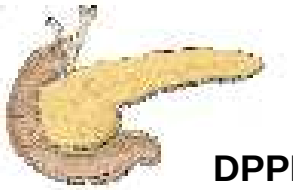
Diabetes Care 32: 193-203 Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

Oral Medications to Treat Type 2 Diabetes

Sites of Action

Pancreas

Impaired insulin secretion = *Insulin deficiency*



Sulfonylureas

Glitinides

DPPIV Inhibitors

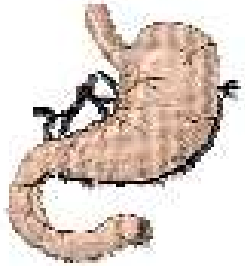
Gut

Carbohydrate absorption

Alpha glucosidase inhibitors

Acarbose

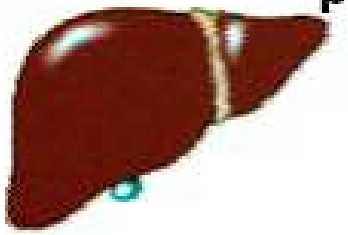
Miglitol



Hyperglycemia

Liver

↑ Hepatic glucose production



Metformin

TZD, DPPIV Inhibitors

Muscle

↓ Glucose uptake = ↑ *Insulin resistance*

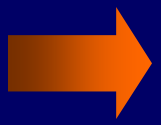
Rosiglitazone

Pioglitazone

Riddle M. *Am J Med*. 2000;108(6A):15S-22S.

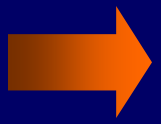
Major Classes of Oral Medications

1. Drugs that stimulate the pancreas to make more insulin



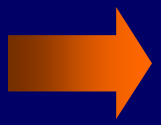
- Sulfonylureas
- Meglitinides
- DPPIV Inhibitors

2. Drugs that sensitize the body to insulin and/or control hepatic glucose production



- Thiazolidinediones
- Biguanides
- DPPIV Inhibitors

3. Drugs that slow the absorption of starches



- Alpha-glucosidase inhibitors

Sulfonylureas

- **Medications in this class:**

- **First Generation Agents**
  - chlorpropamide (Diabinese), tolazamide, acetohexamide (Dymelor), tolbutamide

- **Second Generation Agents**

  Glyburide (Micronase, Glynase, and DiaBeta)

  Glimepiride (Amaryl)

  Glipizide (Glucotrol, Glucotrol XL)

Sulfonylureas

Increase endogenous insulin secretion

- **Efficacy**
  - **Decrease fasting plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)**
  - **Reduce A1C by 1.0-2.0%**
  - **Established efficacy and track record; rapidly effective**
- **Other Effects**
  - **Hypoglycemia**
  - **Weight gain** (~ 2 kg after initiation)

Generally the least expensive class of medication

Sulfonylureas

- **Contraindications**
  - Sulfa allergy
  - Type 1 diabetes (no or little insulin production)
  - Severe impairment of renal or hepatic function
- **Caution**
  - Elderly and debilitated persons – severe episodes of hypoglycemia more common

Generally the least expensive class of medication in generic form

Sulfonylureas

- **Dosing**
  - Once or twice a day
  - Glucotrol (Glipizide) take on an empty stomach ½ hour before meal.

Most benefits are realized at 50% maximum dose.

Meglitinides (Glinides)

Medications in this Class:

- **Repaglinide (Prandin)**

  Appears to be somewhat more effective than nateglitinide.

- **Nateglinide (Starlix)**

Meglitinides (Glinides)

Stimulate insulin secretion (rapidly and for a short duration) in the presence of glucose.

- **Efficacy**
  - **Decreases peak postprandial glucose**
  - **Decreases plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)**
  - **Reduce A1C 1.0-2.0%**

Meglitinides

- **Other Effects and Points:**

  -Hypoglycemia (although may be less than with sulfonylureas)
  -Good if patient has a variable eating schedule
  -Weight gain (but probably less than w/ sulfonylurea)
  -- May be safer at higher levels of serum creatinine than sulfonylureas (shorter half-life)

Meglitinides

- **Dosing:**
  - .5 – 4mg TID (max 16 mg TID) for Prandin
  - 60 – 120 mg TID for Starlix
  - Taken with food (0-30 minutes before eating)
  - Can dose according to size of meal
  - If no meal, can skip pill

Biguanides

Medications in this Class:

- **Metformin hydrochloride (Glucophage)**
- **Metformin hydrochloride extended release (Glucophage XR)**
- **Also available in liquid form: Riomet**

Biguanides

Decrease hepatic glucose production and increase insulin-mediated peripheral glucose uptake.

- **Efficacy**
  - Decrease fasting plasma glucose 60-70 mg/dl
  - Reduce A1C ~ 1.5%
- **Other Effects**
  - Diarrhea and abdominal discomfort
  - Lactic acidosis if improperly prescribed
  - Cause small decrease in LDL cholesterol level and triglycerides
  - Interferes with B12 absorption; anemia rare
  - No weight gain, with possible modest weight loss
  - Contraindicated in patients with impaired renal function (Serum Cr > 1.4 mg/dL for women, or 1.5 mg/dL for men)

Biguanides

Dosing:

Gastrointestinal side effects may limit the dose that can be used.

1. Begin with low-dose metformin (500 mg) taken qd or BID with meals (breakfast and/or dinner) or 850 mg qd
2. After 5–7 days, if GI side effects have not occurred, advance to 850, or two 500 mg tablets, BID (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg BID per day but is often 850 mg BID.

Thiazolidinediones (TZDs/Glitazones)

Medications in this Class:

- Pioglitazone (Actos)
- Rosiglitazone (Avandia)

Thiazolidinediones (TZDs /Glitzones)

Decrease insulin resistance by making muscle, liver and adipose tissue more sensitive to insulin. They also suppress hepatic glucose production.

- **Efficacy**
  - **Decrease fasting plasma glucose ~35-40 mg/dl**
  - **Reduce A1C ~0.5-1.4%**
  - **6 weeks for maximum effect**

Thiazolidinediones (TZDs /Glitzones)

- **Other Effects or Points:**
  - **Weight gain (increased adiposity)**
  - **Peripheral edema**
  - **Hypoglycemia (if taken with insulin or agents that stimulate insulin release)**
  - **Contraindicated in patients with abnormal liver function, Class III or IV heart disease or CHF**
  - **Beneficial (pioglitazone) or neutral (rosiglitazone) effect on lipids.**
  - **LFTs prior to initiation and every 2 months**

Thiazolidinediones (TZDs/Glitzones)

Dosing:

Actos	Avandia
15 mg	2 mg
30 mg	4 mg
45 mg	8 mg

- Taken without regard to meals
- Initial effect ~ 3 weeks
- Full effect ~ 8-12 weeks

Thiazolidinediones

- **Caution:**

Several meta-analyses have shown a 30-40% relative increase in risk for MI with rosiglitazone (Avandia)

ADA Consensus Group advises against use of rosiglitazone.

Both pioglitazone (Actos) and rosiglitazone (Avandia) may be associated with increased fractures in women and possibly men.

Alpha-glucosidase Inhibitors

- **Medications in this Class:**

- **Acarbose (Precose)**

- **Miglitol (Glyset)**

Alpha-glucosidase Inhibitors

Block the enzymes that digest starches in the small intestine

- **Efficacy**
  - **Decrease peak postprandial glucose 40-50 mg/dl**
  - **Decrease fasting plasma glucose 20-30 mg/dl**
  - **Decrease A1C 0.5-1.0%**

Alpha-glucosidase Inhibitors

Other Effects or Points:

-Flatulence or abdominal discomfort
-No specific effect on lipids or blood pressure
-No weight gain
-Contraindicated in patients with inflammatory bowel disease or cirrhosis
-Must use GLUCOSE, FRUCTOSE or LACTOSE to treat hypoglycemia (Does not occur with monotherapy)

Alpha-glucosidase Inhibitors

Dosing:

- 25 mg TID starting dose
- Max dose- 60- 100 mg TID (based on weight)
- Take with 1st bite of food
- Monitor postprandial glucose to see how is working

DPP-IV Inhibitors

By blocking the degradation of the hormone GLP-1, enhances insulin production by the pancreas and reduces liver overproduction of sugar.

Medications in this class:

Januvia (sitagliptin)

DPP-IV Inhibitors

Efficacy:

–Decrease A1C 0.6-1.4%

Side Effects:

-No hypoglycemia when used alone
-URI, runny nose, headache, sore throat, diarrhea

Very costly.
Weight neutral.

DPP-IV Inhibitors

Dosing:

-Administer once daily without regard to meals
-Assess renal function prior to administration
and periodically thereafter

Daily doses:
100 mg qd if CrCl > 50
50 mg qd if CrCl 30 - < 50
25 mg qd if CrCl < 30

Combination Therapy

Fixed Combination Pills

Sulfonylurea + Biguanide

Glyburide + Metformin - *Glucovance*

Glipizide + Metformin - *Metaglip*

Sulfonylurea + TZD

Glimepiride + Rosiglitazone - *Avandaryl*

Glimepiride + Pioglitazone - *Duetact*

TZD + Biguanide

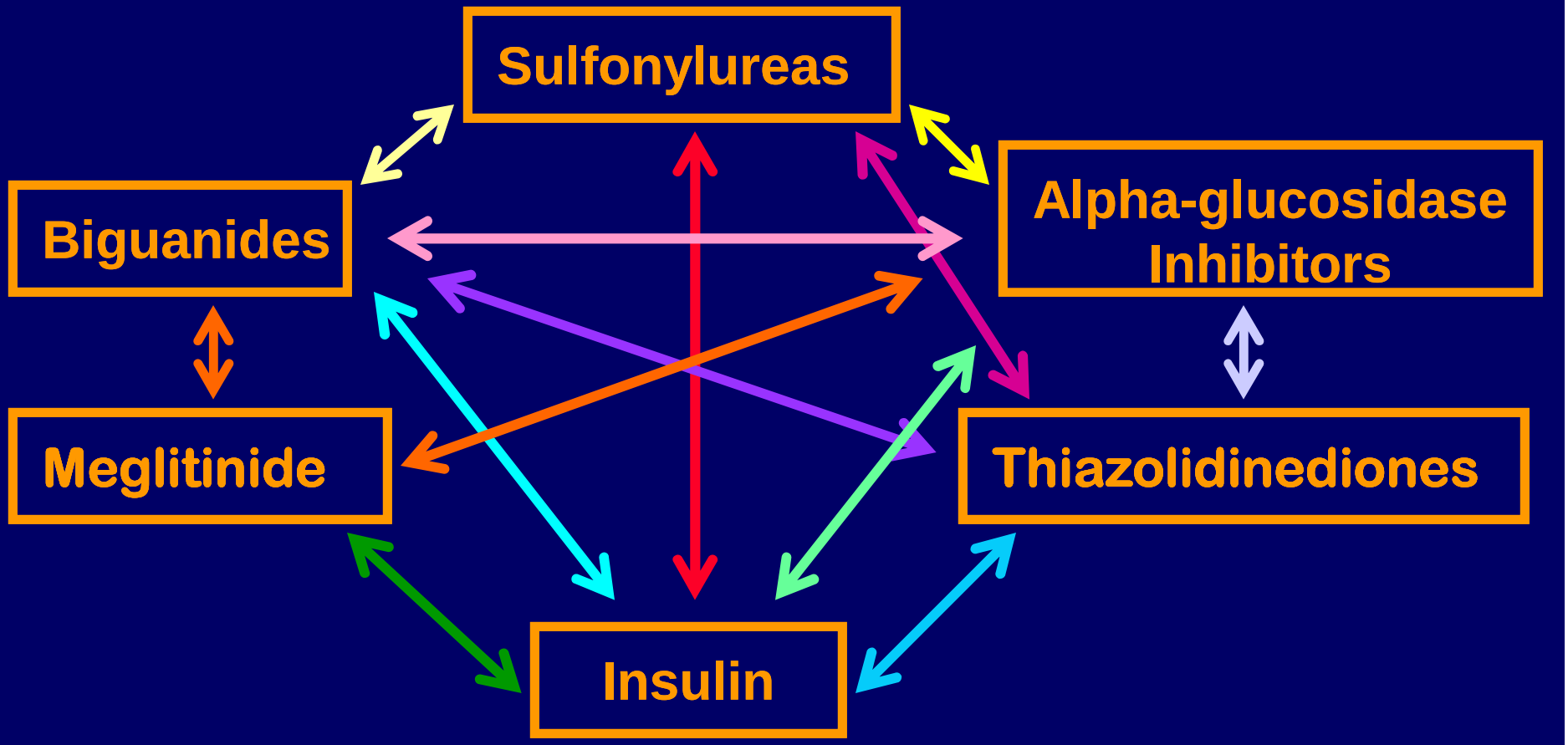
Rosiglitazone + Metformin - *Avandamet*

Pioglitazone + Metformin - *ACTOplusMET*

DPPIV Inhibitor + Biguanide

Sitagliptin + Metformin - *Janumet*

Commonly Used Combination Therapies for Type 2 Diabetes



Not all are FDA approved*

Nutritional Concerns

- **Hypoglycemia**

  Sulfonylureas, Meglitinides

- **Gastrointestinal Problems**

  Biguanides,

  Alpha-Glucosidase Inhibitors

- **Weight Gain**

  Sulfonylureas, TZDs

  (?) Meglitinides

Case Study Oral Meds

Our patient is a 48 year old female was diagnosed with type 2 diabetes one year ago. She has received MNT and over the past year has lost about 15 pounds and engaged in physical activity (walking 30 minutes daily).

At her last doctor's visit, she was advised that her glycemic control was suboptimal, and that she would likely benefit from a diabetes medication. He is treating her to the AACE targets of FBS < 140 mg/dl and A1C less than or = 6.5%.

What medication(s) might be appropriate?

What are the pro's and con's of each?

Clinical Data

- Fasting glucose = 165 mg/dl
- Hemoglobin A1c = 7.0 %
- BMI = 40
- Visceral adiposity
- Comorbidities: HTN, Dyslipidemia (both being treated with meds)
- Family hx of T2DM, CAD, Obesity

What Medications?

- **Biguanide**

Pros: No weight gain, may help lose weight
May help improve lipids
Available in generic – less costly
Can lower BG 60-70 mg/dl; A1C 1 -2 %

Cons: Could be problem if patient is binge drinker
May not tolerate GI side effects

- **Thiazolidinedione**

Pros: Can lower FBS 30-40 mg/dl; A1C .5 - 1 %
No GI side effects
May help improve lipids

Cons: Weight gain
Edema
Cost – no generic

- **Sulfonylurea or Meglitinide**

Pros: Sulfonylurea available in generic – less costly
Both can lower BG 60-70 mg/dl; A1C 1 -2 %

Cons: Hypoglycemia
Weight gain with Sulfonylurea
No effect on lipids

•Alpha Glucosidase Inhibitor

Pros: Do not cause weight gain

Can lower FBS 20-30 mg/dl and postprandial BG 40-50 mg/dl

Used alone do not cause hypoglycemia

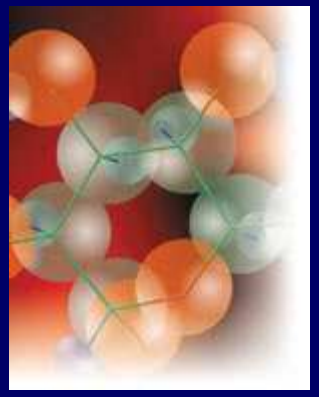
Cons: If used with insulin or secratagogue- contribute to hypoglycemia. If so,

must use GLUCOSE to treat.

No effect on lipids

Insulin

- Considered the most effective treatment agent for diabetes
- Absolute need for exogenous insulin in type 1 diabetes
- Within 6-10 years, many newly diagnosed patients will require exogenous insulin



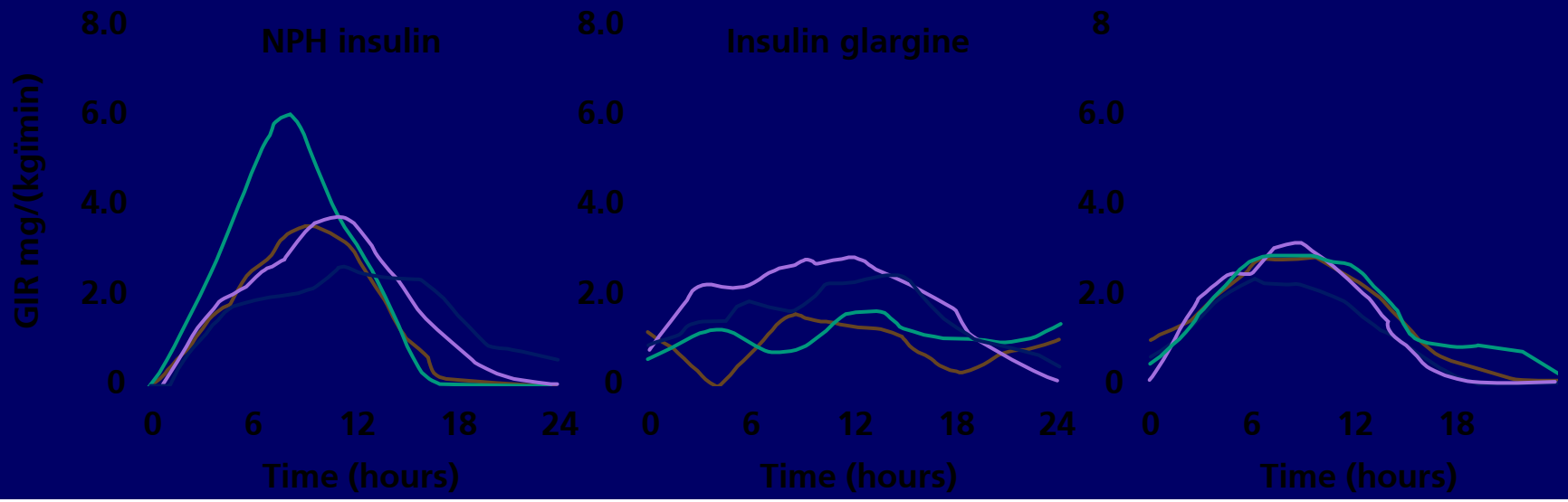
Insulin

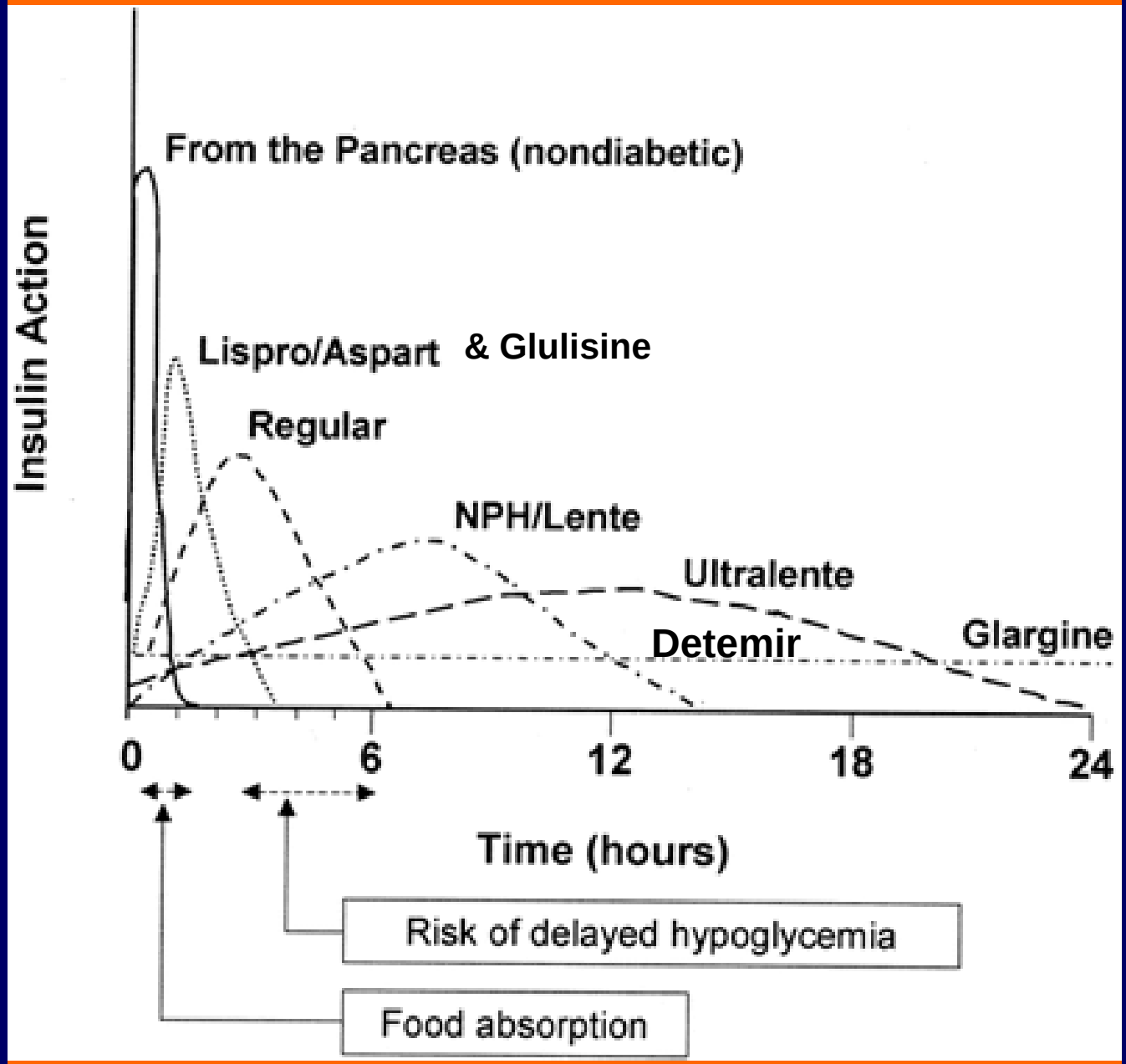
- Many types available
- Vary by characteristics, brand name and manufacturer
- All is made from recombinant DNA
- No more PORK or BEEF!
- Is almost identical to human insulin, unless contains modifier
- Risks – can cause severe hypoglycemia

Insulin

Characterized by action profile

- Rapid-acting
- Short-acting
- Intermediate-acting
- Long acting



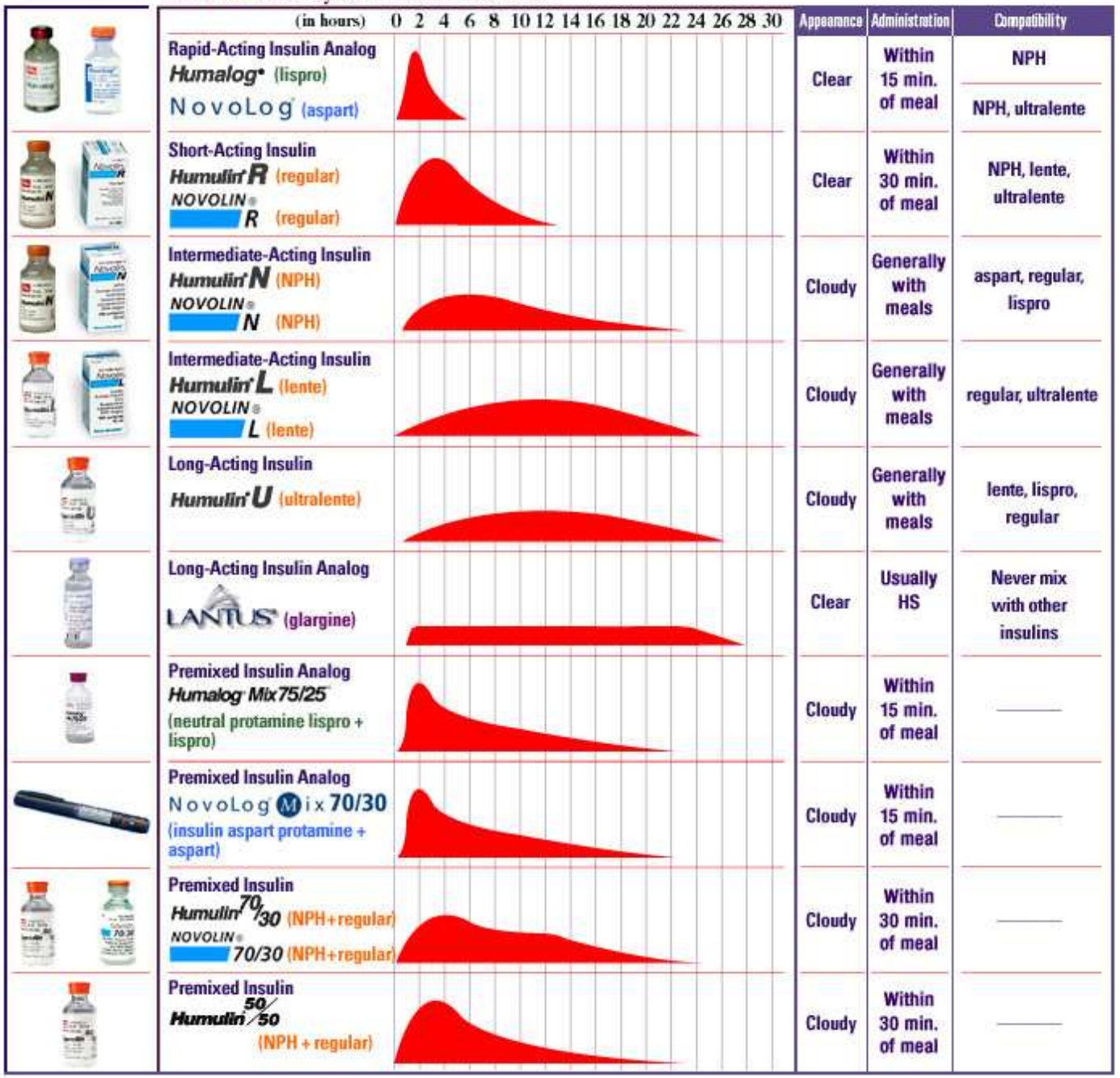


US Manufacturers

Three major brands in the US:

- **Lilly**
- **NovoNordisk**
- **Sanofi-Aventis**

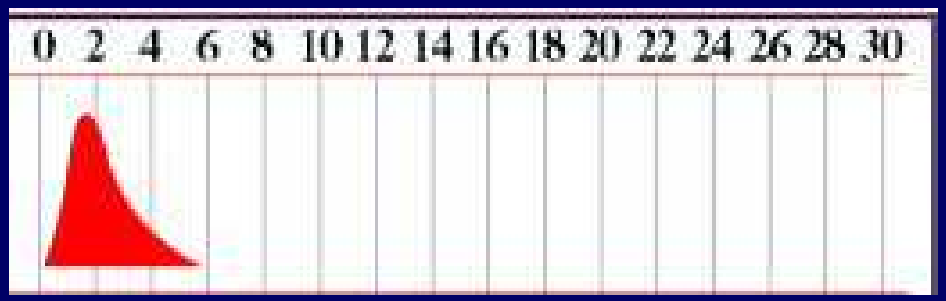
Time of Activity of Human Insulins*



	Appearance	Administration	Compatibility
Rapid-Acting Insulin Analog Humalog® (lispro) NovoLog® (aspart)	Clear	Within 15 min. of meal	NPH NPH, ultralente
Short-Acting Insulin Humulin® R (regular) NOVOLIN® R (regular)	Clear	Within 30 min. of meal	NPH, lente, ultralente
Intermediate-Acting Insulin Humulin® N (NPH) NOVOLIN® N (NPH)	Cloudy	Generally with meals	aspart, regular, lispro
Intermediate-Acting Insulin Humulin® L (lente) NOVOLIN® L (lente)	Cloudy	Generally with meals	regular, ultralente
Long-Acting Insulin Humulin® U (ultralente)	Cloudy	Generally with meals	lente, lispro, regular
Long-Acting Insulin Analog LANTUS® (glargine)	Clear	Usually HS	Never mix with other insulins
Premixed Insulin Analog Humalog® Mix 75/25™ (neutral protamine lispro + lispro)	Cloudy	Within 15 min. of meal	———
Premixed Insulin Analog NovoLog® Mix 70/30 (insulin aspart protamine + aspart)	Cloudy	Within 15 min. of meal	———
Premixed Insulin Humulin® 70/30 (NPH+regular) NOVOLIN® 70/30 (NPH+regular)	Cloudy	Within 30 min. of meal	———
Premixed Insulin Humulin® 50/50 (NPH + regular)	Cloudy	Within 30 min. of meal	———

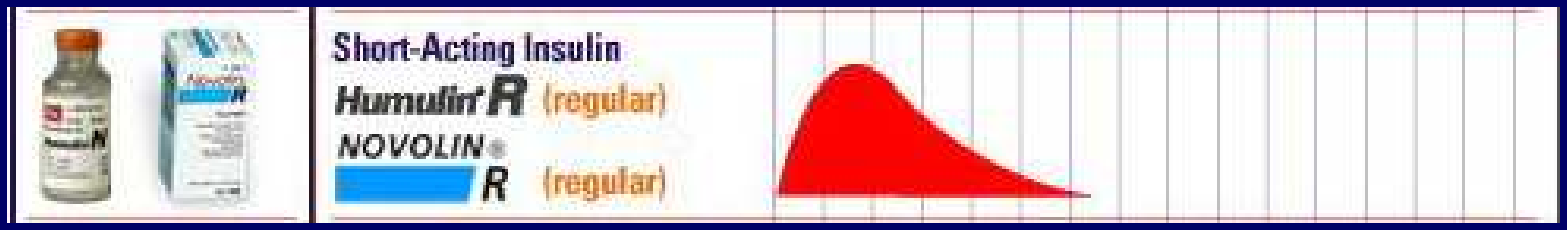
Rapid-Acting Insulins

- Lispro, Aspart, Glulisine (Humalog, Novolog, Apidra)
- Onset in 10-20 minutes
- Peak about 1-3 hrs after taking
- Duration 3-5 hours
- “Bolus” insulin
- Take 0-15 min. before meal
- Clear



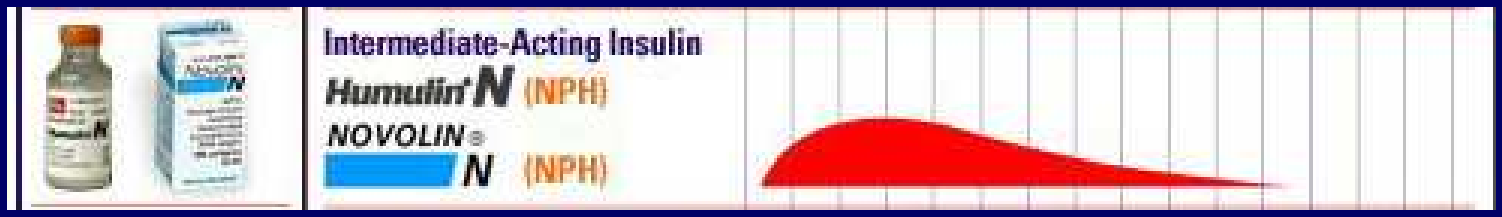
Short-Acting Insulins

- Humulin R, Novolin R
- Onset in 30-60 minutes
- Peak about 2-3 hours after taking
- Duration 6-8 hours
- Used at mealtimes
- Take 30-45 min. prior to meal



Intermediate-Acting Insulins

- Humulin N, Novolin N, NPH
- Onset in 2-4 hours
- Peak about 6-10 hours after taking
- Duration 14-18 hours
- Cloudy
- Used before AM +/or PM meals or HS

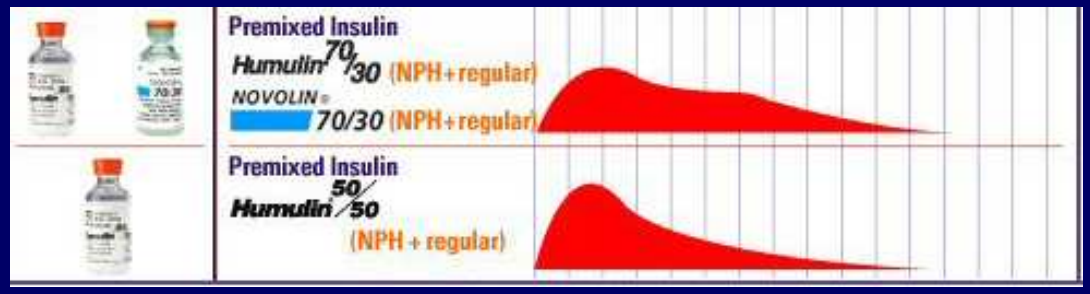


Long-Acting Insulins

- Glargine, Detemir (Lantus, Levemir)
- Onset in ~ 1 hour and Peakless (?)
- Duration up to 24 hours*
- Clear
- Used once or twice daily
- Do not mix with or inject into same area as other insulins
- “Basal” insulin

Combinations

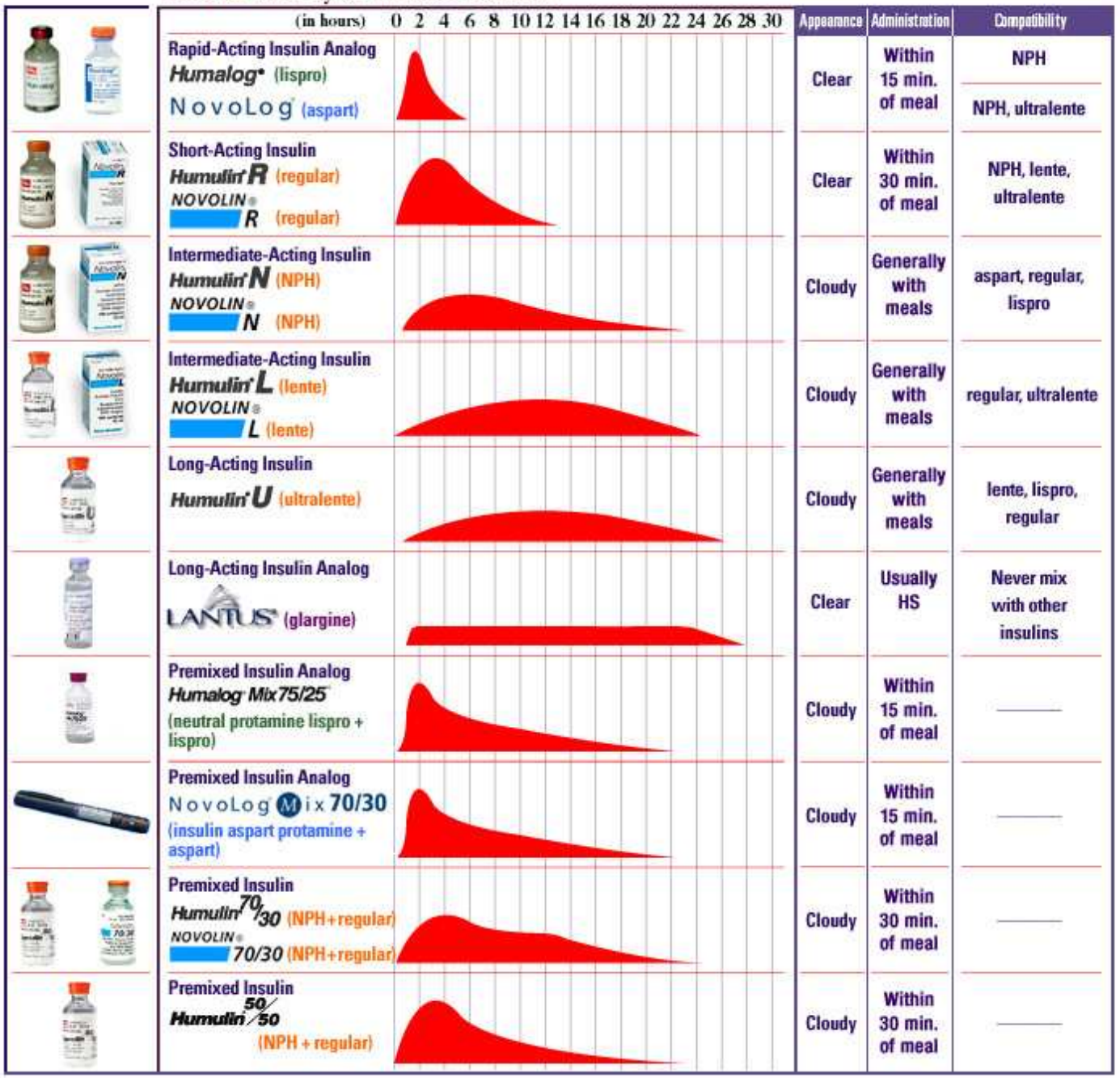
- Humulin 50/50 (50%NPH 50%R)
- Humulin 70/30 & Novolin 70/30 (70%NPH 30%R)
- Combination of R and NPH insulins
- Two peaks with 70/30
- Onset ½ - 1 hour & Duration 18-24 hours
- Cloudy
- BID – 30-45 min. before breakfast & dinner



Combinations

- Humalog Mix 75/25
- Novolog Mix 70/30
- Onset less than ½ hour
- Peak 1-6.5 hours & Duration 22-34 hrs
- Cloudy
- BID – 0-15 min. before breakfast & dinner

Time of Activity of Human Insulins*



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Short-Acting Insulin Humulin® R (regular) NOVOLIN® R (regular)	Clear	Within 30 min. of meal	NPH, lente, ultralente
Intermediate-Acting Insulin Humulin® N (NPH) NOVOLIN® N (NPH)	Cloudy	Generally with meals	aspart, regular, lispro
Intermediate-Acting Insulin Humulin® L (lente) NOVOLIN® L (lente)	Cloudy	Generally with meals	regular, ultralente
Long-Acting Insulin Humulin® U (ultralente)	Cloudy	Generally with meals	lente, lispro, regular
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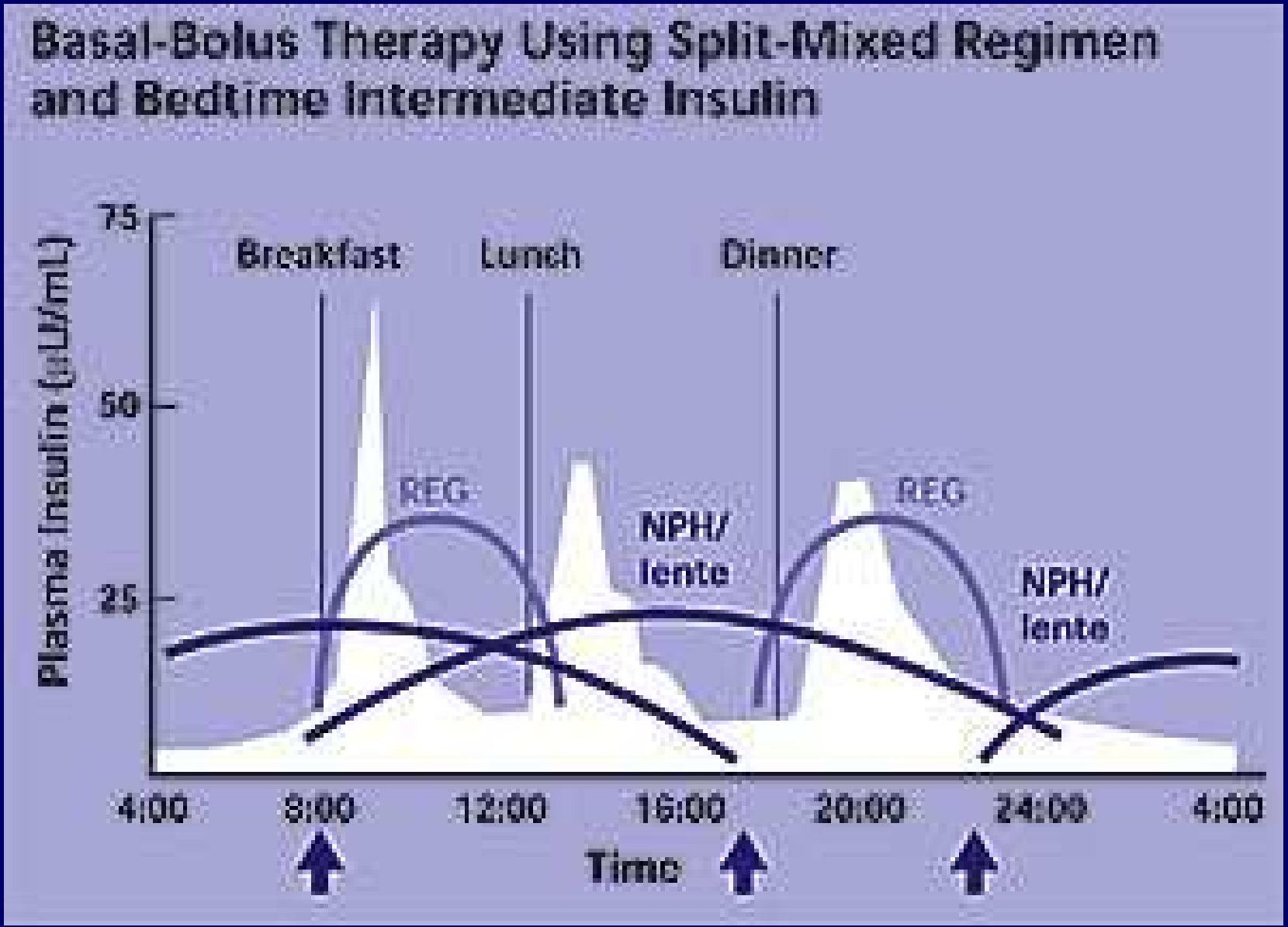
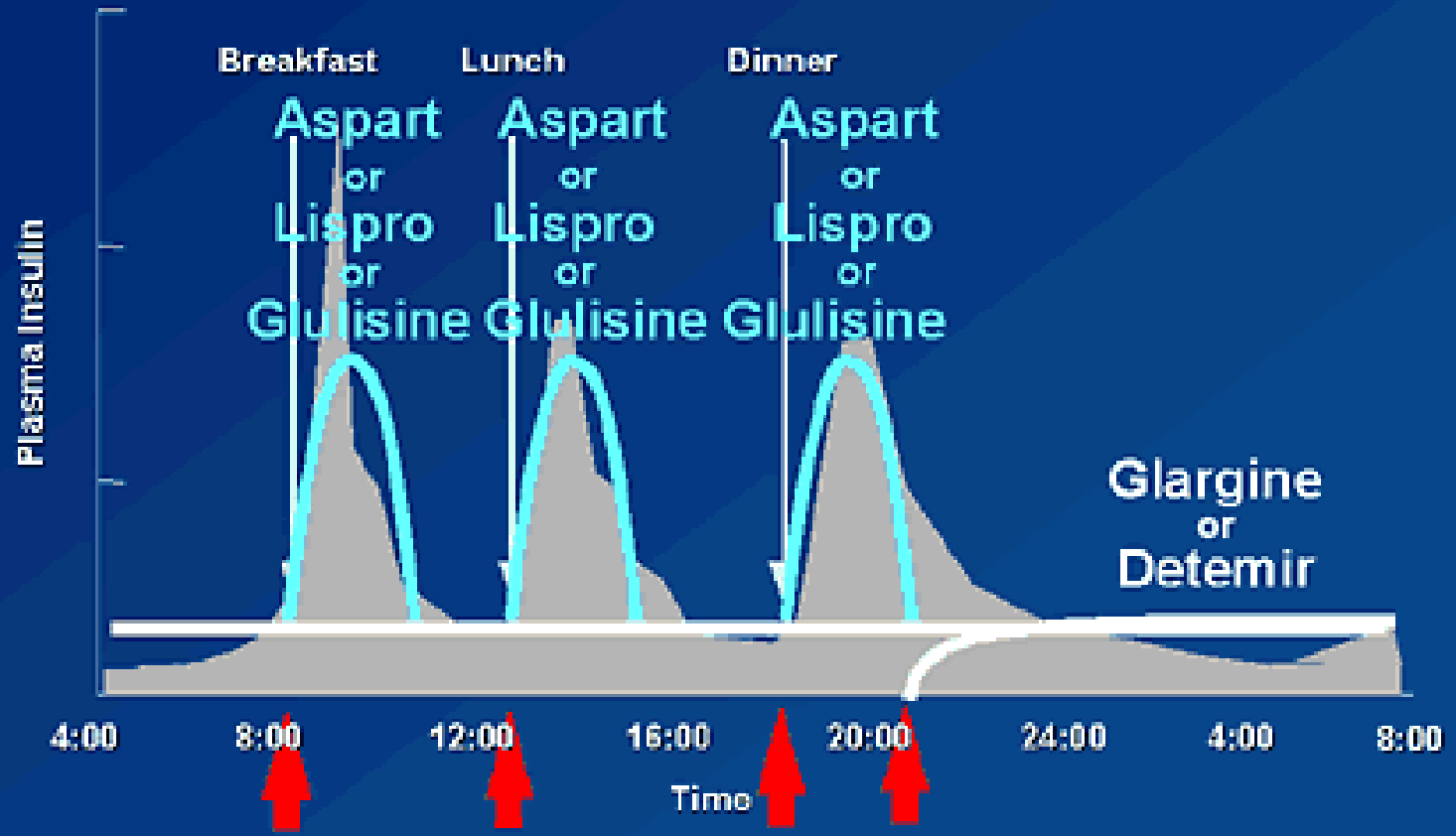
Premixed Insulin Humulin® 50/50 (NPH + regular)	Cloudy	Within 30 min. of meal	———

Insulin Regimens



Basal-Bolus Treatment Program With Rapid Acting and Long Acting Analogues



Normal insulin secretion... Covers fasting plasma glucose (FPG) and postprandial glucose (PPG) levels in healthy subjects

Normal insulin secretion in nondiabetic subjects

Theoretical representation of insulin profile

Basal insulin alone is only half of the story...

Covers only FPG levels in patients with diabetes

Basal insulin alone

Theoretical representation of insulin profile

NovoLog® Mix 70/30...

Covers FPG and PPG levels in patients with diabetes*

NovoLog Mix 70/30

Normal insulin secretion

Theoretical representation of insulin profile

Insulin Delivery Devices

- **Vial and syringe**

Disposable syringe and vial of insulin

- **Insulin Pens**

- **Insulin Pumps**

Use rapid acting insulin

Case Study - Insulin

Our patient is a 15 year old male with Type 1 diabetes. John Q. attends high school. He plays sports after school. Currently he is playing softball.

John is on a "split-mixed" insulin regimen of NPH and Regular insulin BID – before breakfast and dinner.

Lately, John has been experiencing low blood sugar reactions on his way home from practice.

What could be the cause?

What might you recommend in terms of MNT and/or insulin regimen?

Recommendations

- Evaluate AM dose of NPH (and/or Regular)
- Consider decrease in AM NPH on sports days
- Eat snack before practice. Test blood sugar before, during and after.
- Change to basal-bolus or pump

Exenatide (Byetta)

- Twice daily injection using pen device
- Incretin Mimetic
  - Mimics the intestinal hormone GLP-I (glucagon like peptide I) and extends its activity
  - Enhances insulin secretion (?1st phase release), reduces liver release of sugar, delays gastric emptying and release of sugars into bloodstream
- For Type 2 Diabetes only

The Incretin Effect

	Abnormalities leading to elevated glucose levels[1,3,4]	BYETTA: 5 distinct benefits	BYETTA: Key results
	Diminished insulin secretion	Enhances glucose-dependent insulin secretion	Sustained A1C control
	Loss of first-phase insulin response	Restores first-phase insulin response	
	Glucagon stimulates an increase in hepatic glucose output	Suppresses glucagon toward normal for reduced glucose output	
	Accelerated gastric emptying	Slows accelerated gastric emptying	Weight loss
	Increased food intake	Decreases food intake*	

*This effect is postulated to be mediated through the central nervous system.

Exenatide (Byetta)

- Effective in lowering A1C .5 -1.0 %
- Especially good at lowering postprandials
- Weight loss ~ 2-3 kg in 6 months in trials
- Side Effects:

  Nausea, Vomiting, Diarrhea

  Possible hypoglycemia if used with insulin secretagogue, insulin, Januvia (sitagliptin)

- Dosing – 5 mcg BID X 30 days

  then 10 mcg BID. Prefilled pen.
- Must be taken within 0-60 min. prior to meal.

Pramlintide (Symlin)

- Hormone injected at mealtime to improve postprandial blood sugars.
- Type 1 or 2 can use (usually with insulin)
- Synthetic form of “amylin”
- Hormone from pancreatic beta-cells
- Decreases appetite
- Decreases glucagon release postmeal – decreasing sugar from liver
- Regulates gastric emptying

Pramlintide (Symlin)

- Type 2 – A1C drop from baseline was 0.6% in 26 weeks
- Type 1 – A1C drop 0.4% in 26 weeks
- Dosing: Titration Needed
- Delivery: Syringe or pen
- Cannot be mixed with insulin

Side Effects

- Hypoglycemia – can be severe with type 1 diabetes (usually 3 hours after taking)
- GI complaints – N/V

Long term safety not established; expensive

Discussion

What is role of RD?