Glucose Homeostasis

The body must control glucose levels because all cells use glucose to make ATP, the energy currency of cells. Some tissues like brain almost never burn any other fuel molecule. But too much glucose damages cells by getting attached to certain proteins and changing their function. Key tissues in this balancing act are:

Liver
Fat
Muscle
Brain
Pancreas (endocrine cells)

Diabetes Mellitus

Increase of blood glucose due to an imbalance between regulating factors

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

Two-hour PG (OGTT) ≥200 mg/dL (11.1 mmol/L)

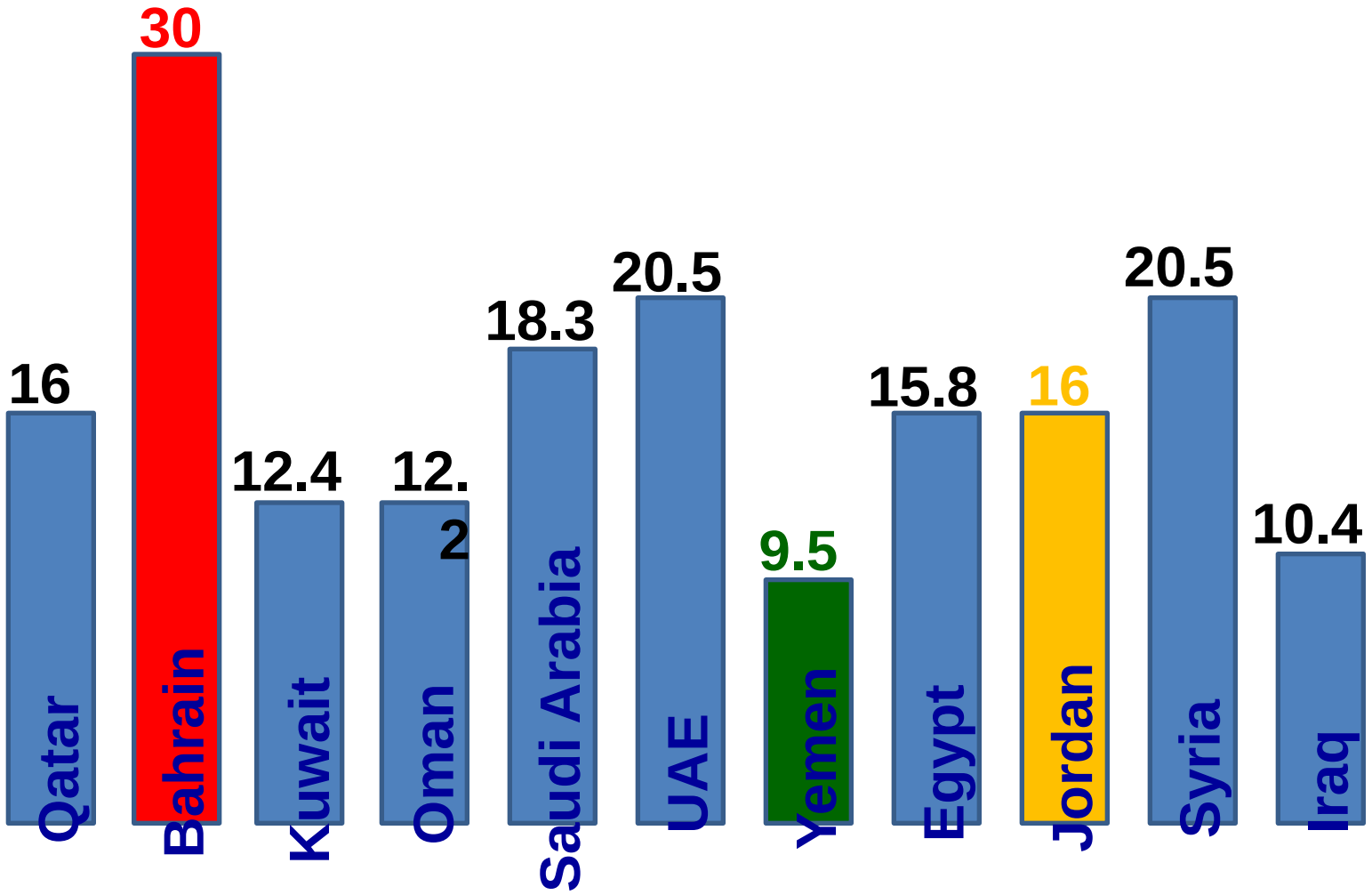
(The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water)

Treatment

No treatment or cure, the only possible so far is to keep the serum glucose level within normal.

Prevalence of Diabetes

in adults 20 years and older



Dept. of Non Communicable Disease Surveillance and Control, Ministry of Health, Oman 2012

	Smoking	Insufficient physical activity	Overweight	Obesity
	>15 years of age		>20 years of age	
Kuwait	17.0	64.5	79.3	42.8
Oman	3.4	NA	57.5	22.0
S. Arabia	6	68.8	71.3	35.2
UAE	7.2	62.5	72.0	33.7
Jordan	26.3	NA	68.8	34.3
Palestine	19.3	46.5	57.8	26.8
Lebanon	37.6	46.8	62.8	28.2
Iraq	14.8	58.4	65.2	29.4
Syria	NA	NA	66.4	31.6
Yemen	29.3	8.0	18.6	NA

Diabetes Mellitus

Gestational diabetes

Type 1 diabetes

Type 2 diabetes

Complications

Cardiovascular Disorders

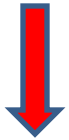
Kidney Disease

Neuropathy and Nerve Damage

Eye Complications

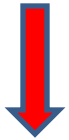
Ketoacidosis

Relative or absolute deficiency of insulin



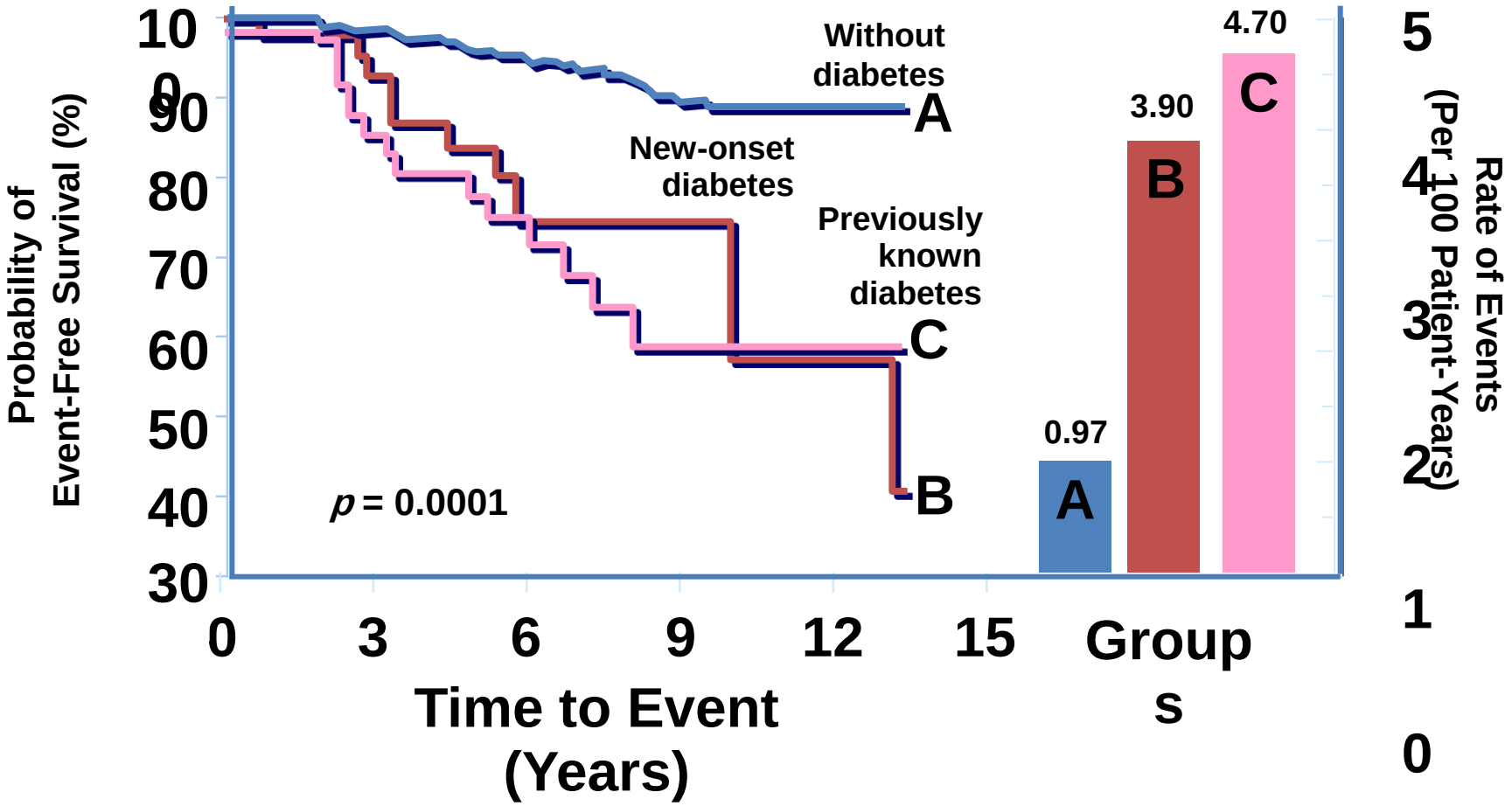
Increased delivery of fatty acids to the liver

Oxidation of fatty acids by the liver



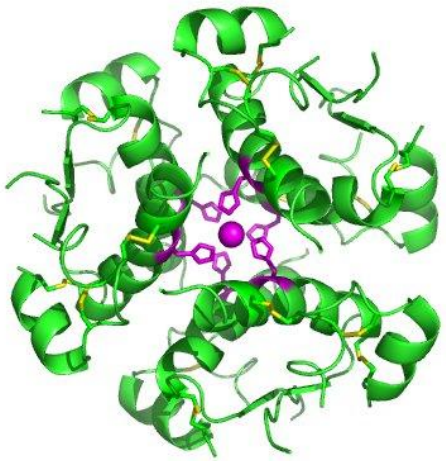
Accelerated production of ketone bodies

Cardiovascular Events in Treated Hypertensive Diabetic Patients



Verdecchia P, et al. *Hypertension.* 2004;43:963-969,

Insulin



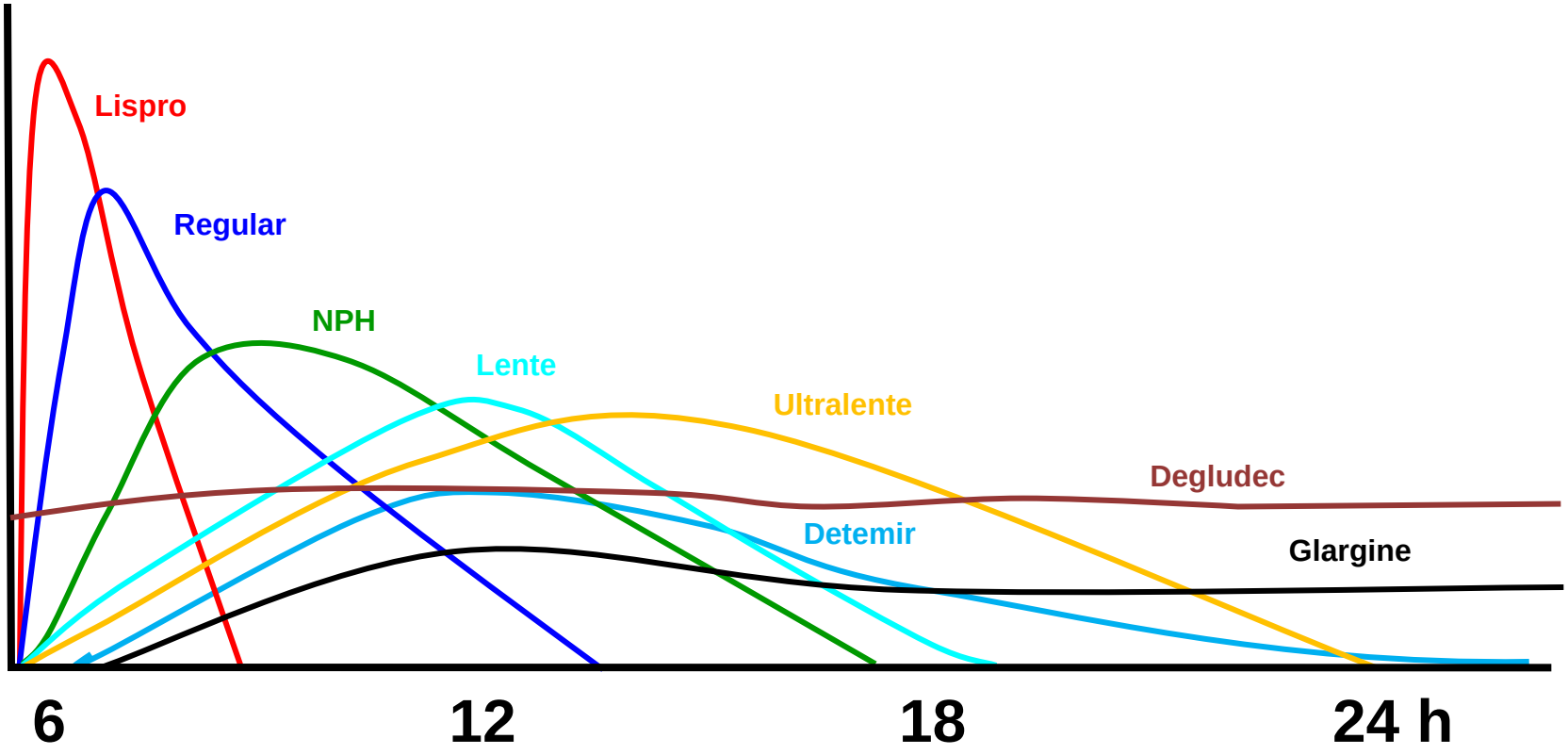
Insulin is a hormone produced by the beta cells of the pancreas which is responsible for regulating carbohydrates and fat metabolism in the body.

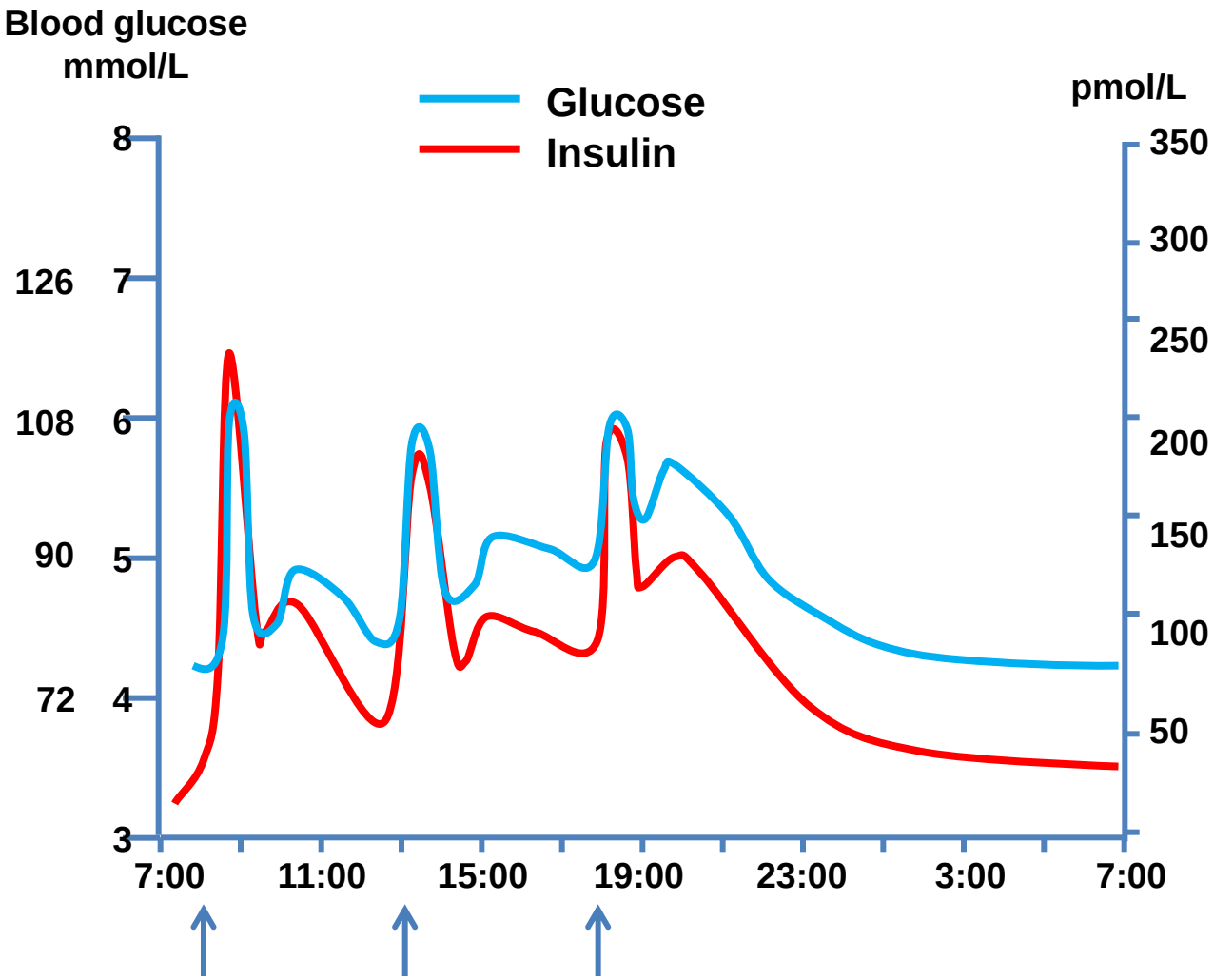
Insulin causes cells in the liver, muscles, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscles.

Insulin stops the use of fat as an energy source by inhibiting the release of glucagon.

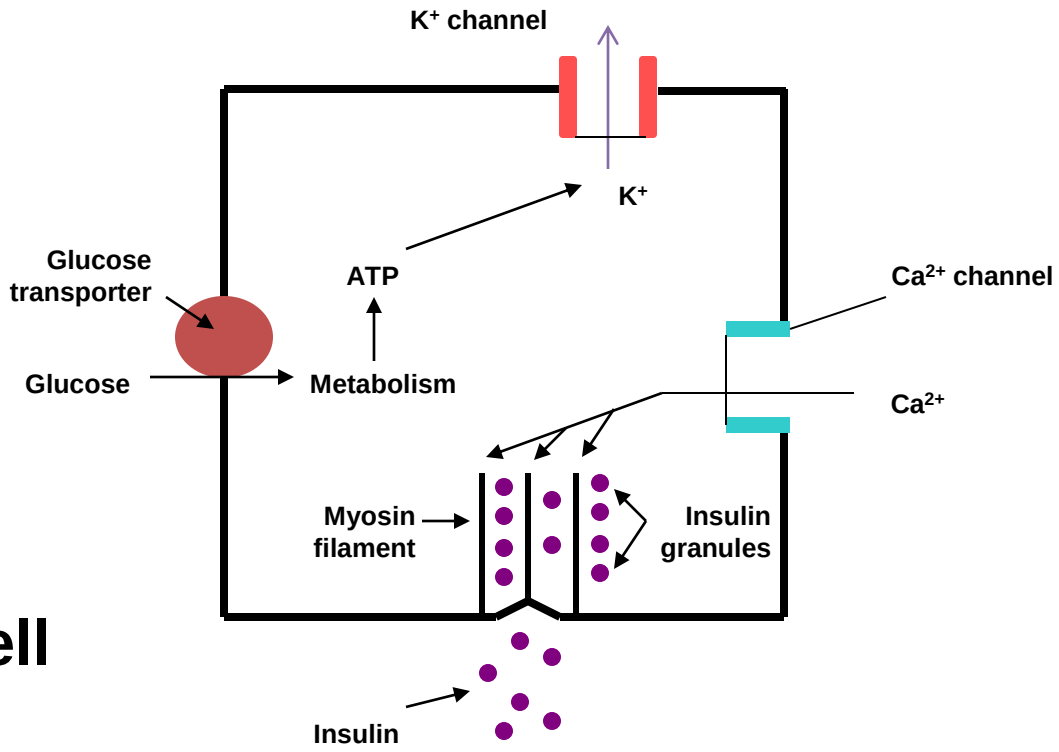
In addition, it has several other anabolic effects throughout the body.

Insulin duration of action



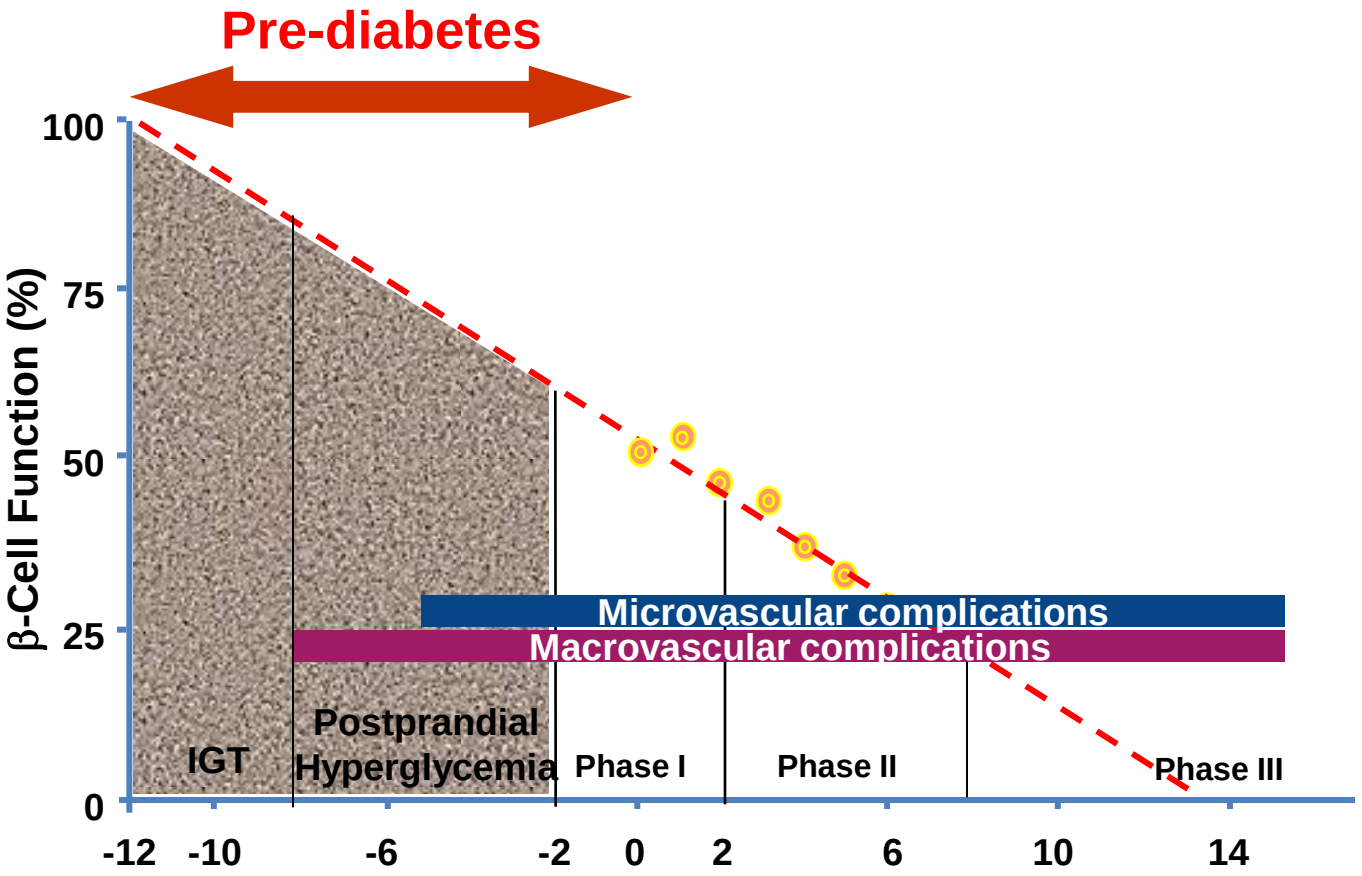

Blood glucose
mmol/L
Glucose
Insulin
pmol/L
8
7
6
5
4
3
126
108
90
72
350
300
250
200
150
100
50
7:00
11:00
15:00
19:00
23:00
3:00
7:00

Beta cell



B-cell

β-cell function



Lebovitz H, Diabetes Review 1999.

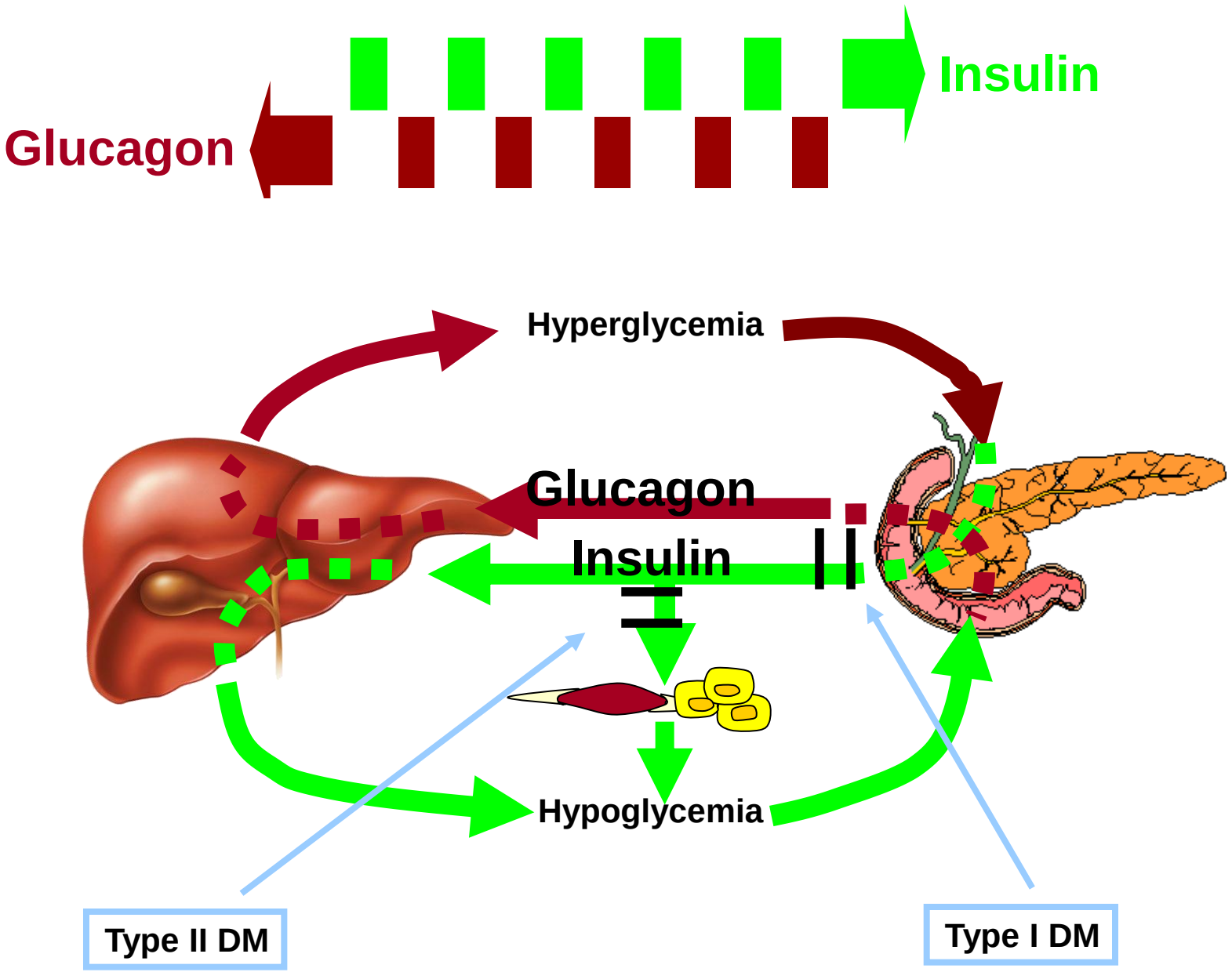
Glucagon

Glucagon, a hormone secreted by the alpha cells of the pancreas, raises blood glucose levels. Its effect is opposite that of insulin which lowers blood glucose levels.

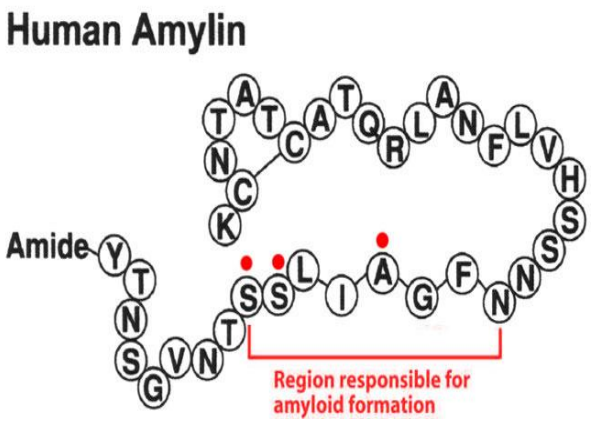
The pancreas releases glucagon when blood glucose levels fall too low.

Glucagon causes the liver to convert stored glycogen into glucose.

glucagon and insulin are part of a feedback system that keeps blood glucose levels at a stable level.

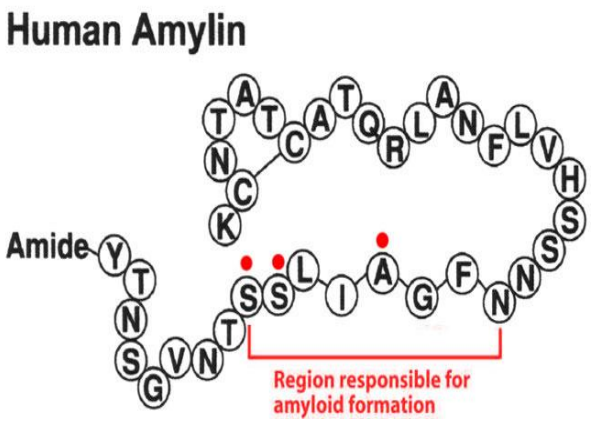

Insulin
Glucagon
Hyperglycemia
Glucagon
Insulin
Hypoglycemia
Type II DM
Type I DM

Amylin



Amylin, or Islet Amyloid Polypeptide is cosecreted with insulin from the pancreatic β-cells in a ratio of approximately 100:1 Amylin plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing post prandial spikes in blood glucose levels.

Hyperamylinemia



Hyperamylinemia, a common pancreatic disorder in obese and insulin resistant patients, is known to cause amylin oligmerization and cytotoxicity in pancreatic islets leading to β-cell mass depletion and development of type-2 diabetes.

Annals of Neurology (Jun 2013)

Insulin

- Sources of insulin:

  human insulin has largely replaced the insulin isolated from cows or pigs pancreas for therapeutic uses.

  Human insulin is produced by recombinant DNA technology using Escherichia coli or yeast that have been genetically alter to contain the gene for human insulin.

Insulin

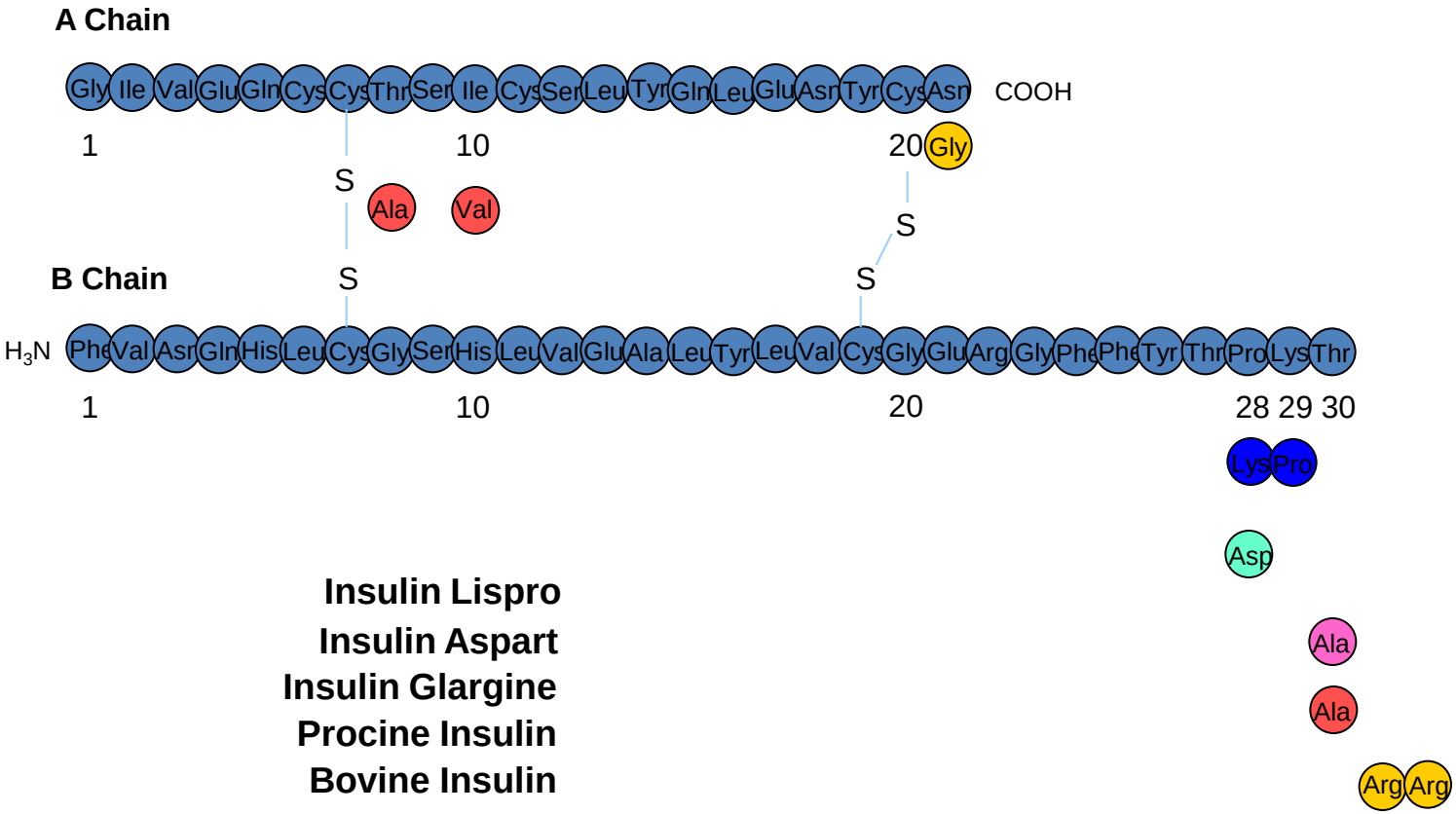
- Modification of the amino acid sequence of human insulin have produced insulins with different pharmacokinetic properties.

- For example: insulin-Lispro, and -Aspart have faster onset and shorter duration of action than the regular insulin.

- On the other hand, Insulin Glargine and insulin Detimir are long-acting insulins and show prolonged flat level of the hormone following a single injection.

- Because of the fact that insulin is a polypeptide, it is degraded in the GI tract if taken orally. It therefore is generally administered by subcutaneous injection.

Insulin analogs



TYPES OF INSULIN PREPARATIONS

1. Ultra-short-acting

2. Short-acting (Regular)

3. Intermediate-acting

4. Long-acting

	Short-acting (regular) insulins e.g. Humulin R, Novolin R	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	Designed to control postprandial hyperglycemia & to treat emergency diabetic ketoacidosis	Similar to regular insulin but designed to overcome the limitations of regular insulin
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
Chemical structure	Hexameric analogue	Monomeric analogue
Route & time of administration	S.C. 30 – 45 min before meal I.V. in emergency (e.g. diabetic ketoacidosis)	S.C. 5 min (no more than 15 min) before meal I.V. in emergency (e.g. diabetic ketoacidosis)
Onset of action	30 – 45 min (S.C)	0 – 15 min (S.C)
Peak serum levels	2 – 4 hr	30 – 90 min
Duration of action	6 – 8 hr	3 – 4 hr
Usual administration	2 – 3 times/day or more	2 – 3 times / day or more

3. Intermediate - acting insulins

e.g. isophane (NPH)

Turbid suspension

Injected S.C.(Only)

Onset of action 1 - 2 hr

Peak serum level 5 - 7 hr

Duration of action 13 - 18 hr

Insulin mixtures

75/25 70/30 50/50 (NPH / Regular)

4. Long – acting insulins

e.g.Insulin glargine

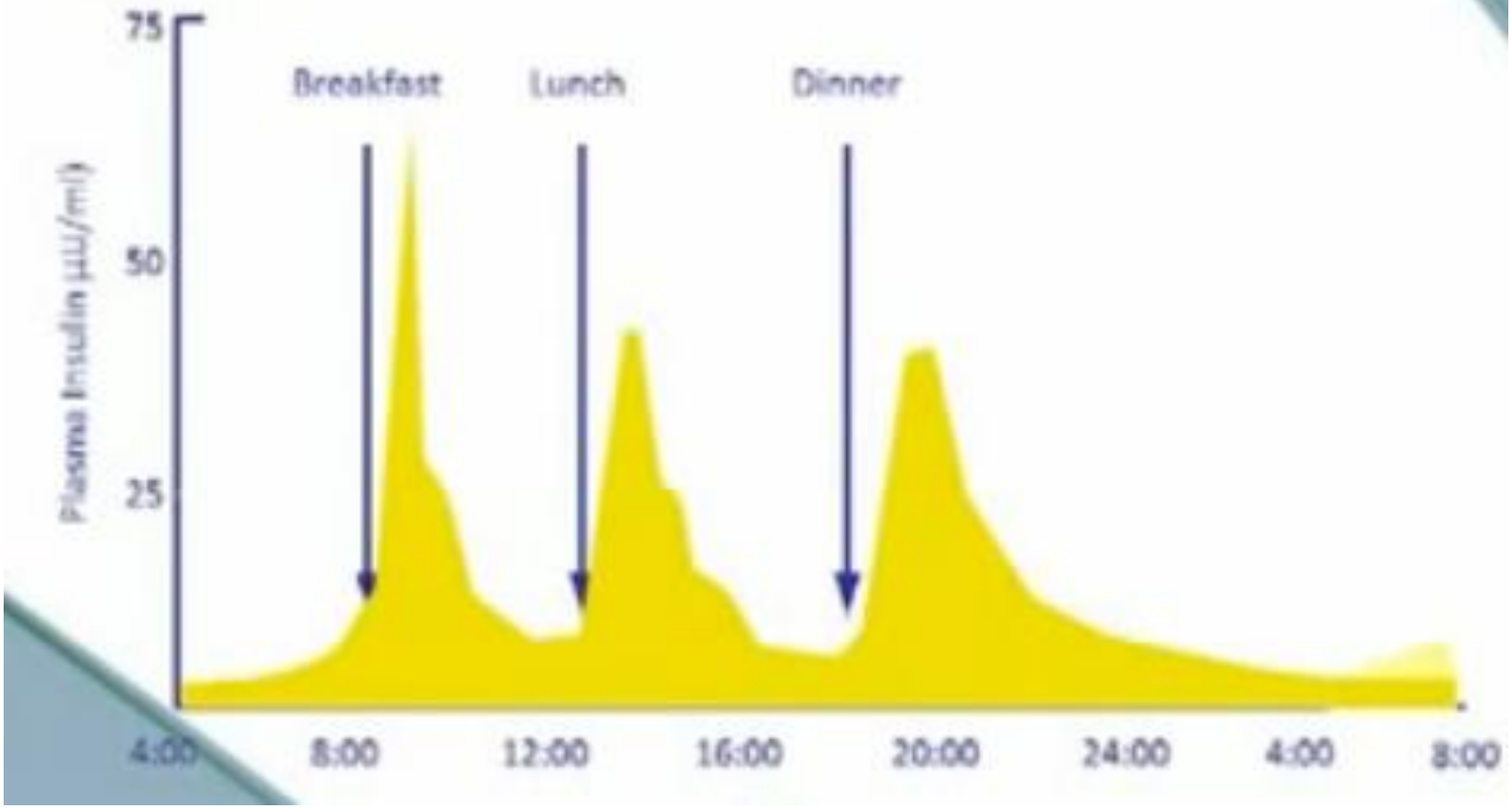
- Onset of action 2 hr
- Absorbed less rapidly than NPH & Lente insulins.
- Duration of action upto 24 hr
- Designed to overcome the deficiencies of intermediate acting insulins
- Advantages over intermediate-acting insulins:

Constant circulating insulin over 24hr with no pronounced peak.

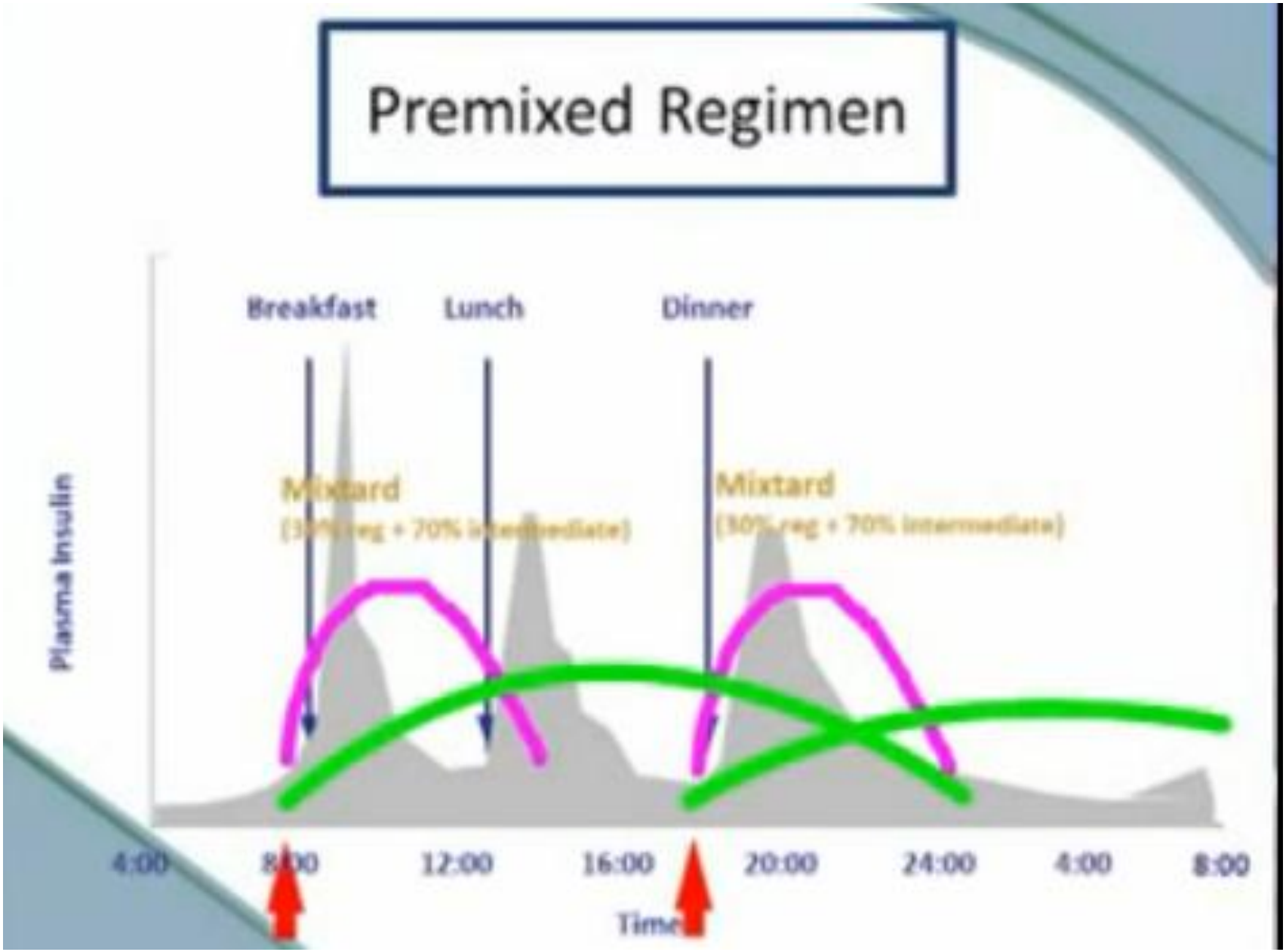
More safe than NPH & Lente insulins due to reduced risk of hypoglycemia(nocturnal hypoglycemia).

Clear solution that does not require resuspention before administration.

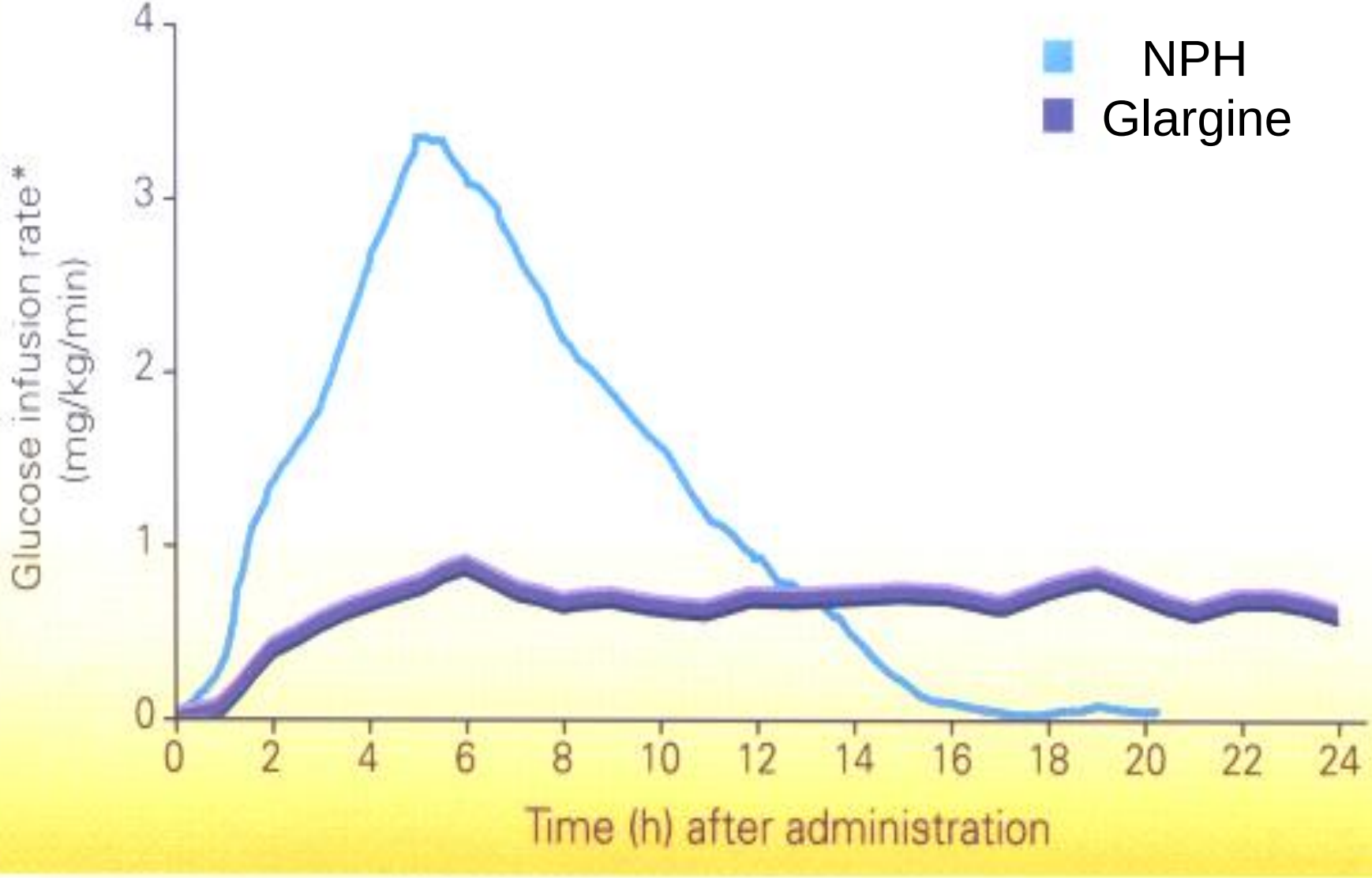
Normal Physiological secretion of Insulin

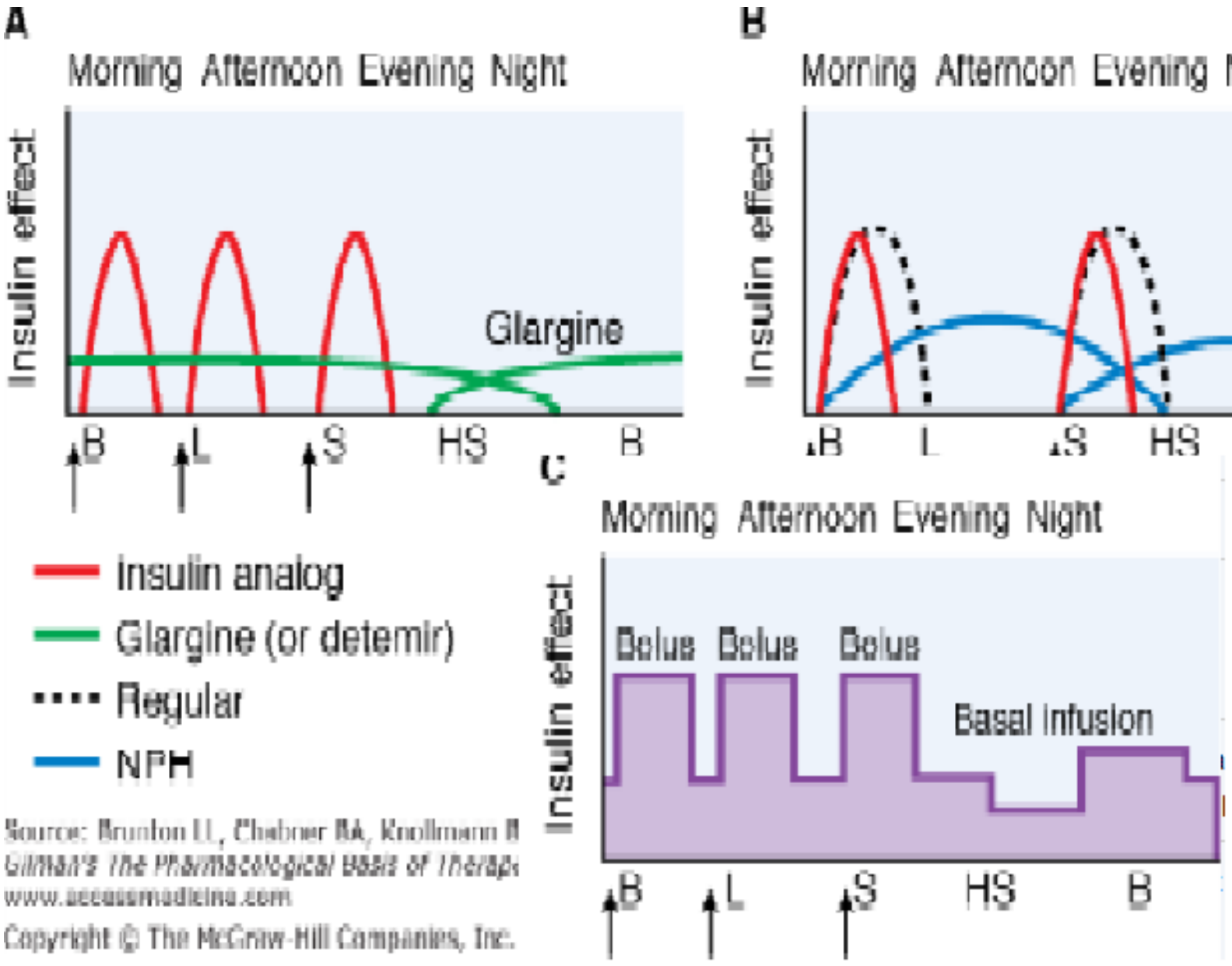


Premixed Regimen



Profile of Insulin Glargine vs NPH





Source: Brunton LL, Chabner BA, Knollmann B
Goodman & Gilman's The Pharmacological Basis of Therapeutics
www.accessmedicine.com

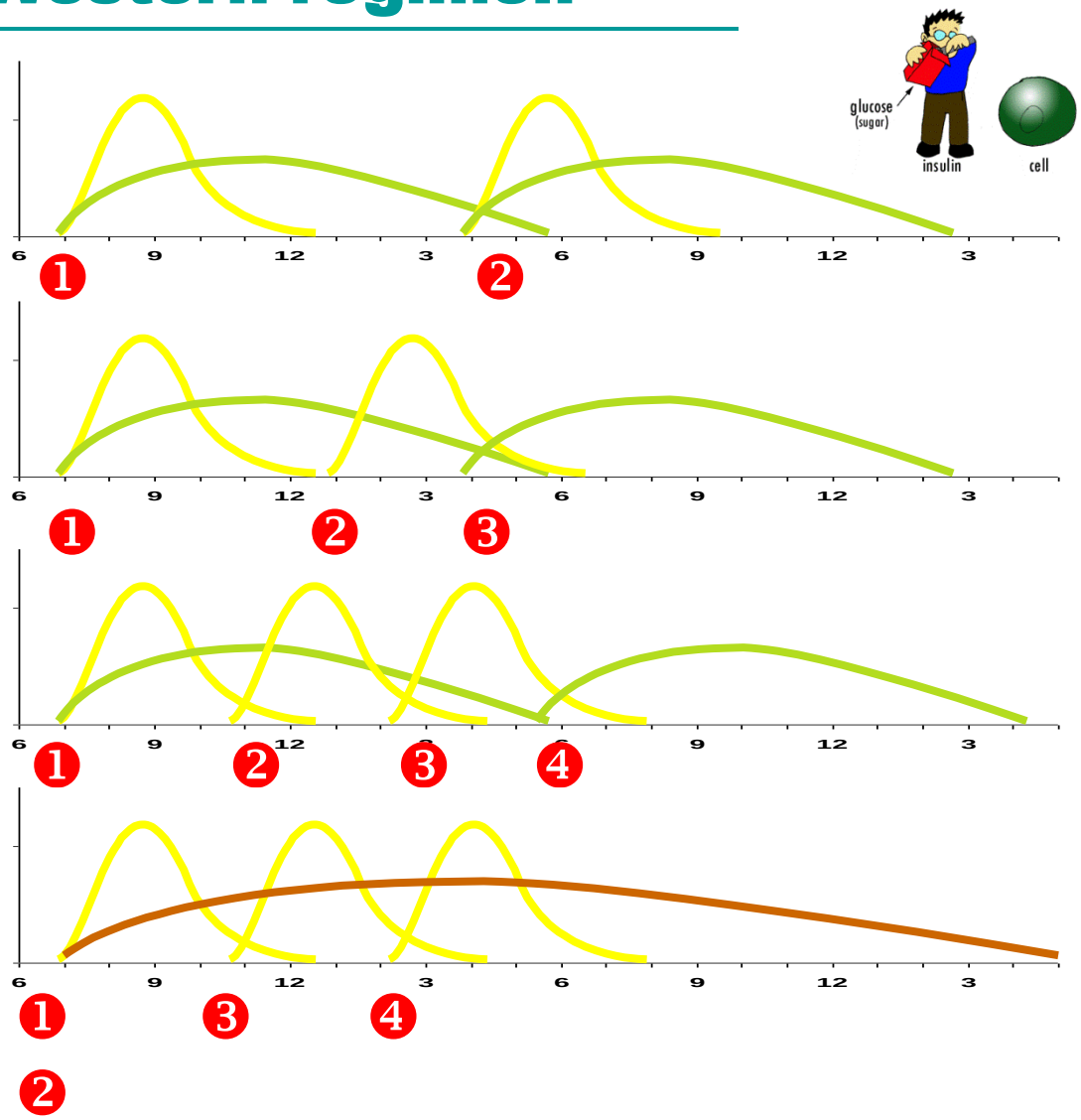
Western regimen

Two doses:
The usual dosing commonly used.
Initial insulin therapy

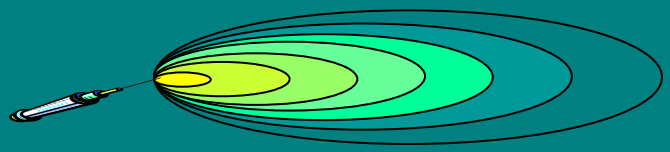
Three doses:
Used for active patients.
Patients taking two main meals.

Four doses:
Brittle diabetic patient.
Pregnant mothers specially type 1.

Four doses:
Brittle diabetic patient.
Pregnant mothers specially type 1.
Motivated patients.



INSULIN INJECTION



Multiple Insulin Injection Therapy

Western regimen

Two doses:
The usual dosing commonly used.
Initial insulin therapy

Three doses:
Used for active patients.
Patients taking two main meals.

Four doses:
Brittle diabetic patient.
Pregnant mothers specially type 1.

Four doses:
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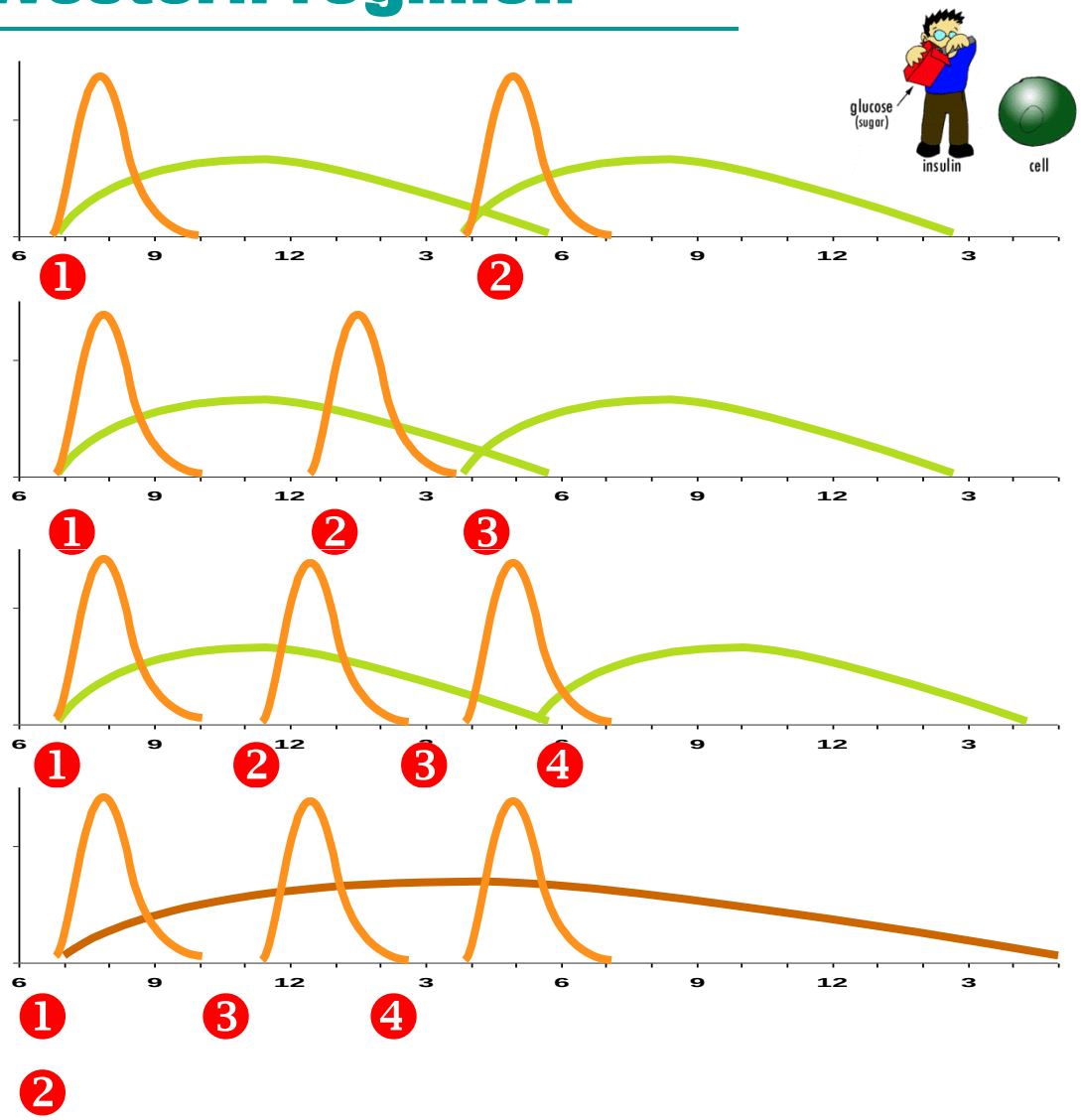
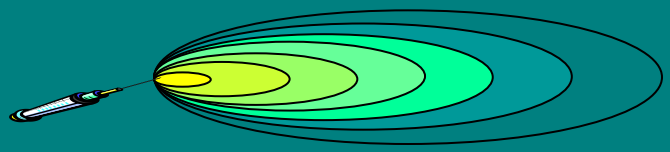
Motivated patients.



INSULIN INJECTION



Multiple Insulin Injection Therapy

Insulin

- In hyperglycemic emergency, regular insulin (unmodified) in injected intravenously.

- Adverse effects of insulin:

  the symptoms of hypoglycemia is the most serious and common to overdose of insulin.

  Weight gain

  other adverse effects include lipodystrophy, a lump or small dent in the skin that forms when a person keeps performing injections in the same spot). (less common with human insulin), and allergic reaction.

  diabetics with renal insufficiency must have their doses of insulin adjusted.

Amylin

Amylin is a hormone secreted by β-cell together with insulin

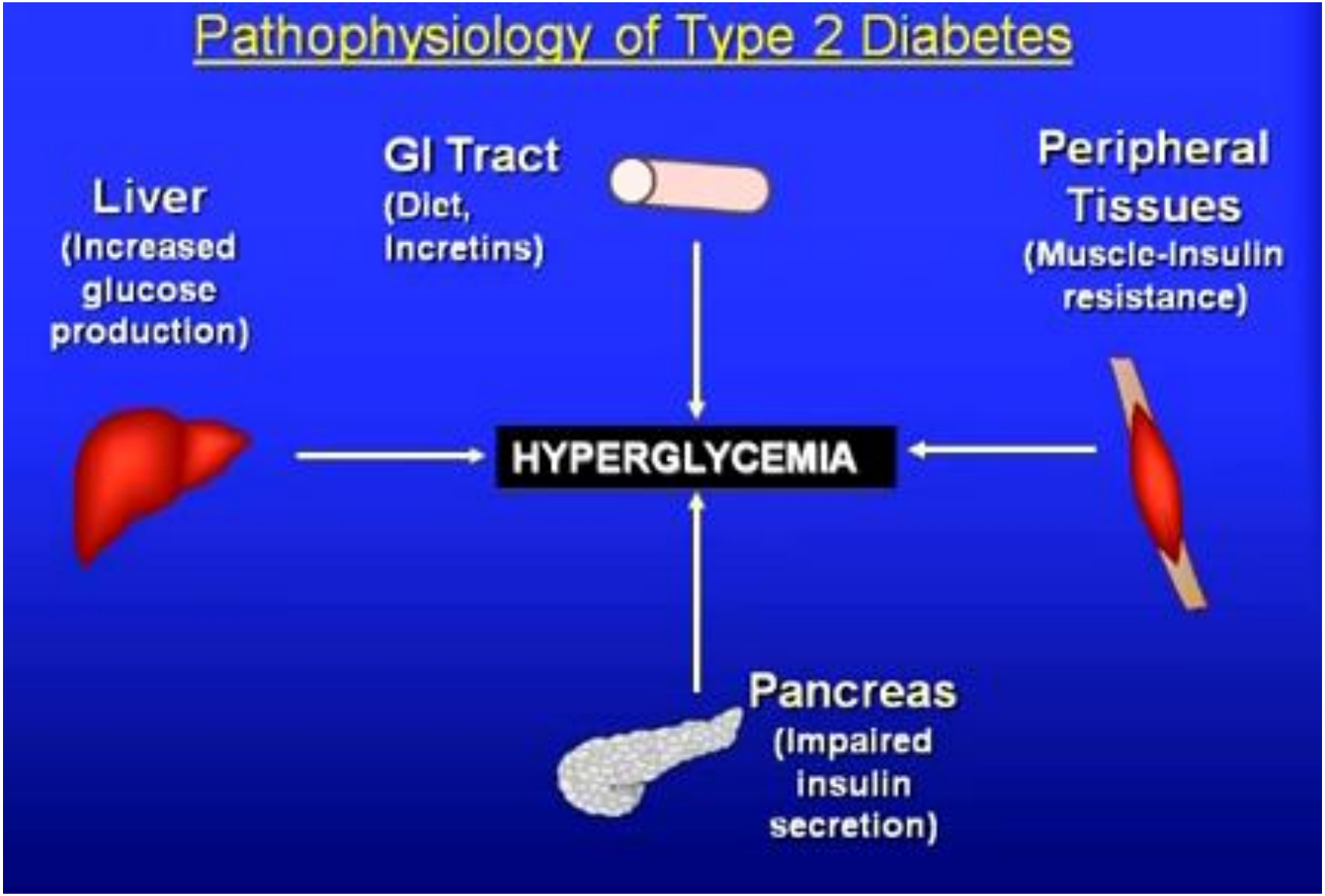
Amylin helps In the absorption of Glucose by:

slowing gastric emptying
Promoting satiety
and inhibiting inappropriate secretion of glucagon

Pramlintide is an Amylin analogue
Aproved for type 1 and 2

Oral hypoglycemic agents

- Are useful in treatment of type 2 diabetes patient that cannot manage their glucose level by diet only.
- Patients with long-standing disease may require a combination of hypoglycemic drugs with or without insulin to control their hyperglycemia.
- The insulin is added because of the progressive decline in beta-cells that occur due to the disease or aging.
- Oral hypoglycemic agents should not be given to patients with type 1 diabetes.


Pathophysiology of Type 2 Diabetes
Liver
(Increased glucose production)
GI Tract
(Diet, Incretins)
Peripheral Tissues
(Muscle-Insulin resistance)
HYPERGLYCEMIA
Pancreas
(Impaired insulin secretion)

Sulfonylureas

Glimepiride	(Amaryl)	1, 2, 4 mg	tablets
Glipizide	(Glucotrol, Glucotrol XL)	(2.5), 5, 10 mg (XL)	tablets
Glyburide	(DiaBeta)	1.25, 2.5, 5 mg	tablets

Indications

Adjuncts to diet and exercise to lower blood glucose in patients w/ type II diabetes mellitus

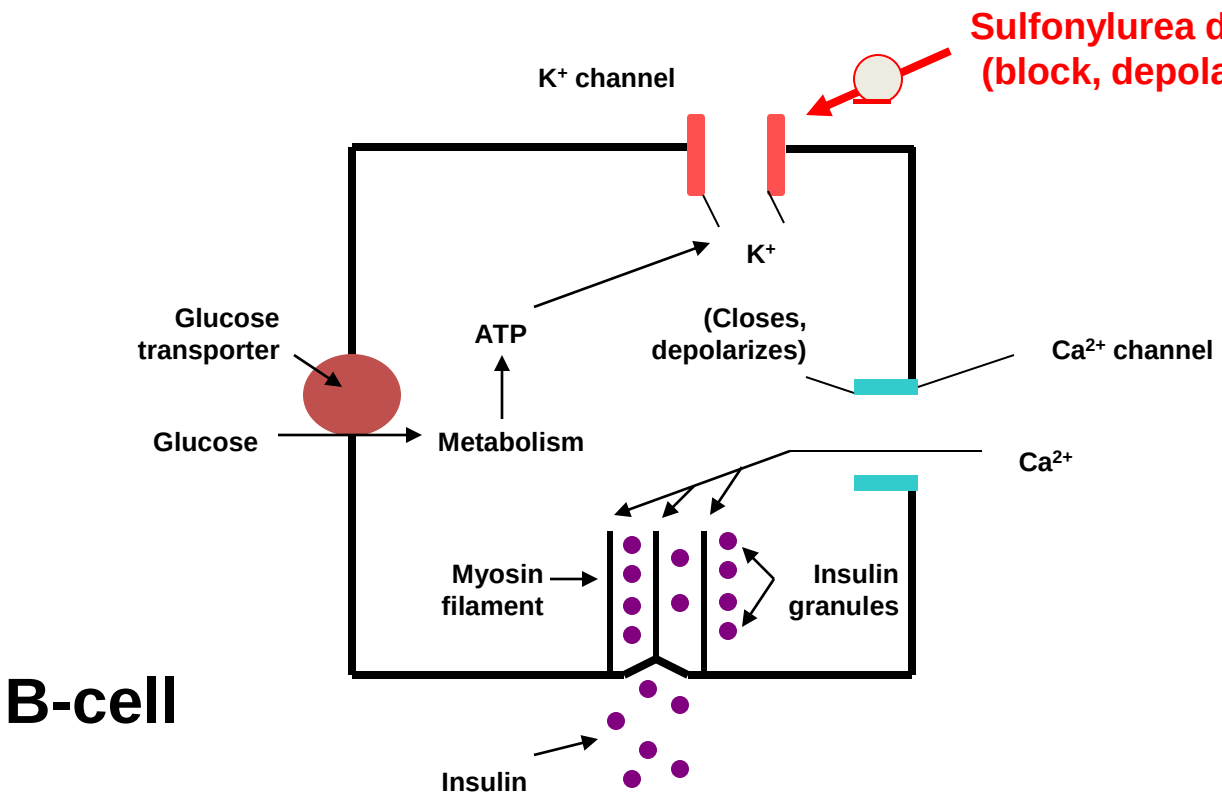
MOA

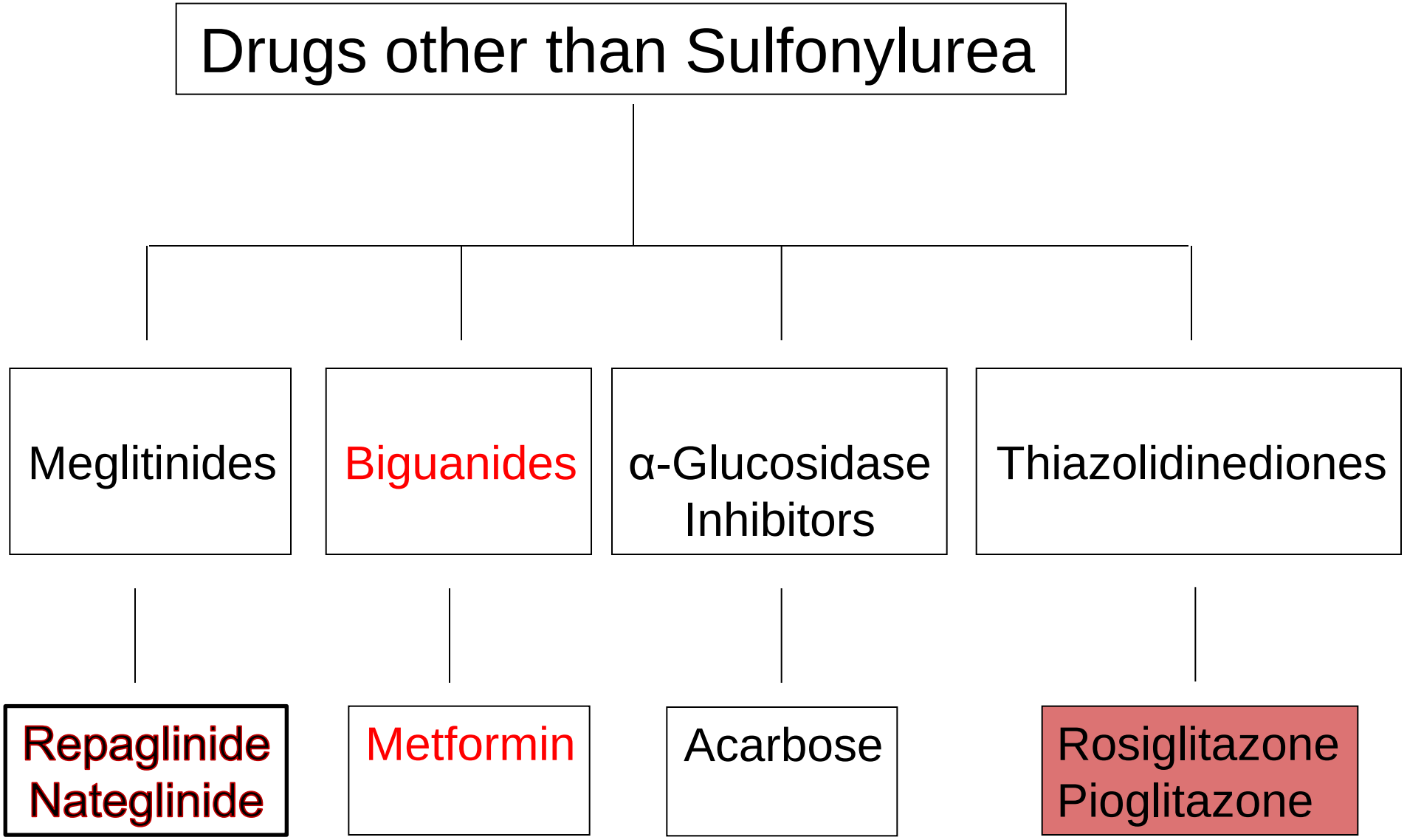
Stimulating insulin release from beta-cells of pancreatic islets

Sulfonylureas

- These agents bind to an ATP-dependent K+ channel on the cell membrane of pancreatic beta cells.
- this binding promote insulin secretion from beta-cells of the pancreas, resulting in a reduction in the glucose serum level
- Their adverse effects include **weight gain**, hyperinsulinemea, and hypoglycemia.
- They are contraindicated in patient with hepatic and renal insufficiency.

Sulfonylureas




Drugs other than Sulfonylurea
Meglitinides
Biguanides
α-Glucosidase Inhibitors
Thiazolidinediones
Repaglinide
Nateglinide
Metformin
Acarbose
Rosiglitazone
Pioglitazone

Meglitinides

Insulin secretogogues

It restore initial insulin release in response to a meal.

This restoration of more normal insulin release may suppress glucagon release early in the meal resulting in less hepatic release of glucose.

It has minimal effect on overnight or fasting glucose level.

Biguanides

Stimulation of glycolysis in tissues

Reduction of hepatic and renal gluconeogenesis

Slowing glucose absorption from the intestine with increase glucose to lactate conversion by enterocytes.

Reduction of plasma glucagon levels

Metformin

- Like Sulfonylureas, Metformin requires insulin for its action, but differ from Sulfonylureas in that it does not promote insulin secretion. (The risk of hypoglycemia is far less than Sulfonylureas agents).

- Importantly, Metformin has a property of modestly reduce the hyperlipidemia and is the only hypoglycemic agent proven to decrease cardiovascular mortality.

Metformin

- Metformin is the drug of choice in newly diagnosed type 2 diabetes.
- The side effect are largely gastrointestinal. Metallic taste in the mouth
- Contraindicated in patient with hepatic and renal diseases, cardiac or respiratory insufficiency, severe infections, and **pregnancy**.
- Long term use may interfere with vitamin B12 absorption.
- Lactic acidosis (rare – 01/ 30,000-exclusive in renal & hepatic failure)

Advantages of Metformin over SUs

Does not cause hypoglycemia

Does not result in wt gain

(Ideal for obese pts)

Metformin & CKD

On the basis of quantitative and qualitative syntheses involving 17 observational studies, metformin use is associated with reduced all-cause mortality in patients with CKD, CHF, or CLD with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.

Annals of Internal Medicine 3 January 2017

Metformine

Compared with sulfonylurea users, metformine users had a 10% lower incidence of cancer
This 10% reduction was highly statistically significant.

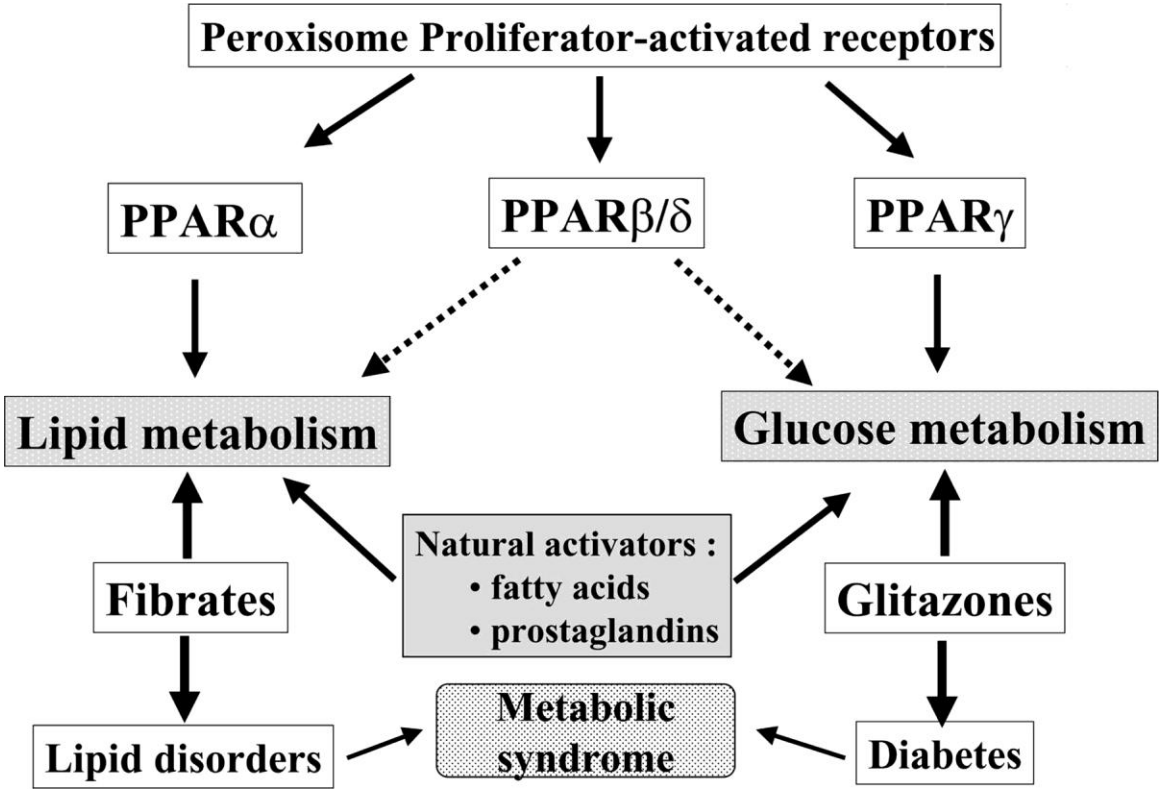
Metformine-associated lower risks were noted for cancers of the esophagus, stomach, colon, liver, pancreas, lung, breast, and prostate.

Diabetes Care 2012 Jan; 35:119.

Glitazones

- Although insulin is required for its action, they do not promote its release from the beta-cells. Thus, hyperinsulinemia does not result.
- They act by binding to a group of receptor molecules inside the cell nucleus, resulting in a decrease in the insulin resistance.
- This group has two members: Pioglitazone, and Rosiglitazone.
- Resiglitazone can be used in combination with other hypoglycemic agents but not with insulin, because edema occur with higher frequency.

PPAR


Peroxisome Proliferator-activated receptors
PPARα
PPARβ/δ
PPARγ
Lipid metabolism
Glucose metabolism
Natural activators :
• fatty acids
• prostaglandins
Fibrates
Glitazones
Lipid disorders
Metabolic syndrome
Diabetes

Glitazones

- The main side effect is fluid retention, leading to edema, weight gain, and potentially aggravating heart failure. Therefore, contraindicated in patients with decreased ventricular function.

- Because an old member of this group (Troglitazone) was withdrawn from the market due to an increased incidence of drug-induced hepatitis. It is now common practice that liver enzymes are monitored during the first year of treatment with the newer Glitazones.

Special Alert February 2011

Addition of Risk Evaluation and Mitigation Strategy to rosiglitazone. The medication is restricted to those patients already on rosiglitazone, for fails pioglitazone or cannot be managed by other oral antidiabetic medications.

Alpha-Glucosdase inhibitors

- **Acarbase and Miglitol**, are the members. they are taken in the beginning of the meals.
- Act by delayed the digestion of carbohydrates, thereby decreasing the glucose absorption.
- Both agents exert their effect by reversibly inhibiting membrane-bound alpha-Glucosdase in the intestine brush boarder.
- These agents have No effect on insulin release or action on the targeted tissue, and so do not produce hypoglycemia.

Alpha-Glucosdase inhibitors

- The major side effect is flatulence, diarrhea, and abdominal cramps

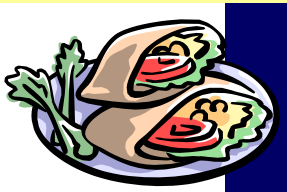
- Patient with inflammation bowel disorder, colonic ulceration, and intestinal obstruction should not use them (contraindicated).

GLP-1 localisation

- **Cleaved from proglucagon in intestinal L-cells (and neurons in hindbrain/hypothalamus)**
- **Secreted in response to meal ingestion**
- **Cleared via the kidneys**

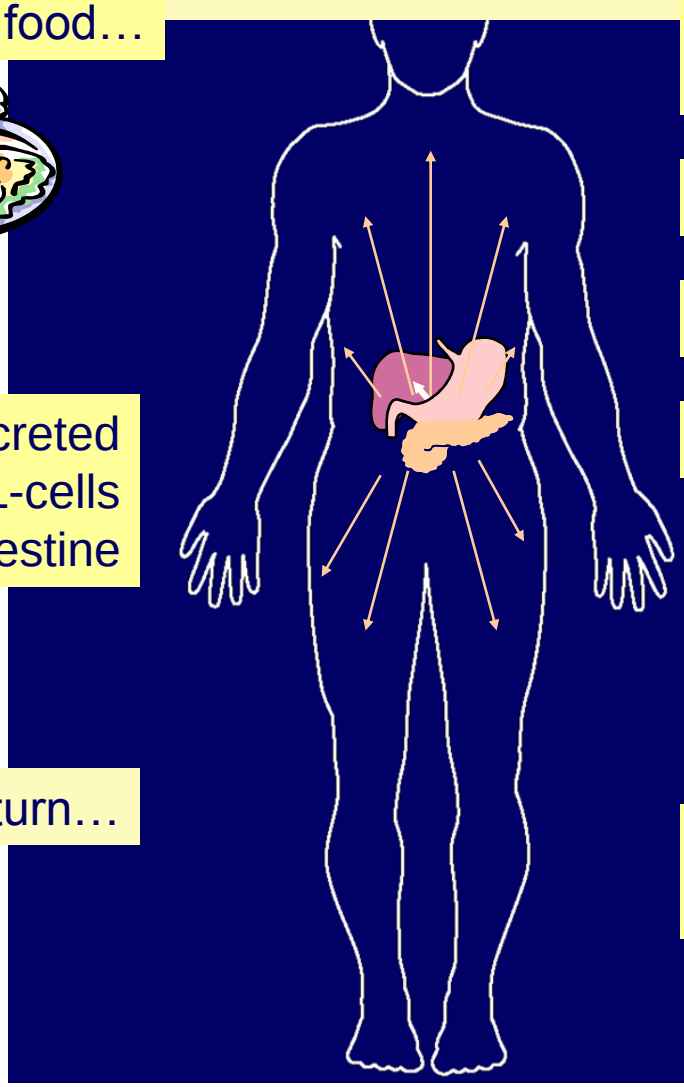
GLP-1 Modes of Action in Humans

Upon ingestion of food…



GLP-1 is secreted from the L-cells in the intestine

This in turn…



- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Reduces food intake
- Increases beta-cell mass and maintains beta-cell efficiency

Dipeptyl- peptidase inhibitors

Sitagliptin

Vildagliptin

Saxagliptin

Septagliptin

Allogliptin

Dipeptyl- peptidase inhibitors

- Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1(fixes 2 broken organs)
  - Glucagon suppression results in ↓ **liver** glucose production
  - Enhances appropriate insulin and amylin secretion from the **pancreas**
  - Can be used thru duration provided insulin is present
    - Promising durability
- Lowers **postprandial** glucose
  - Decrease A1c by 0.5% to 0.7% (~15-20 mg/dL; most postprandial)
- Most common side effects
  - Stuffy, runny nose
  - Headache
  - Upper respiratory tract infection

Cornell S, et al. Postgrad Med. 2012;124(4):84-94.

GLP-1 receptors agonist

Exenatide

Liraglutide

(recombinant DNA in *Saccharomyces cerevisiae)*

Semaglutide (phase 3)

Albiglutide (biological FDA approval April 2014)

Lexisenatide (EMA approved. FDA approved Sept 2014)

Dulaglutide (FDA approved Sept 2014)

- GLP-1 agonists "fix" 4 dysfunctional organs in T2DM
  - Glucagon suppression
    - Results in ↓ **liver** glucose production
  - Enhances appropriate insulin and amylin secretion from the **pancreas**
    - Results in **brain** satiety
  - Regulates the **GI tract** to slow gastric emptying time
  - Can be used thru duration provided insulin is present
    - Promising durability
- Short-acting agonists lowers **postprandial** glucose
  - Decreases A1c by 0.8% to 1.5% (~20-45 mg/dL; most postprandial)
- Long acting agonists lowers **fasting and postprandial** glucose
  - Decreases A1c by 0.8% to 1.8% (~20-50 mg/dL)
- Most common side effects
  - Weight loss
  - Stomach upset
  - Caution in patients at risk for pancreatitis

Cornell S, et al. Postgrad Med. 2012;124(4):84-94.

SGLT-2

Sodium Glucose Transport proteins

Re-absorption of 90% of glucose in the kidney

Blocking these transporters causes blood glucose To be eliminated in urine.

Dapagliflozin (FDA approved Jan. 2014)

Canagliflozin (FDA approved March 2013)

Remogliflozin (stopped)

Sergliflozin (stopped)

Empagliflozin (FDA approved August 2014)

Tofogliflozin (phase III)

SGLT-2

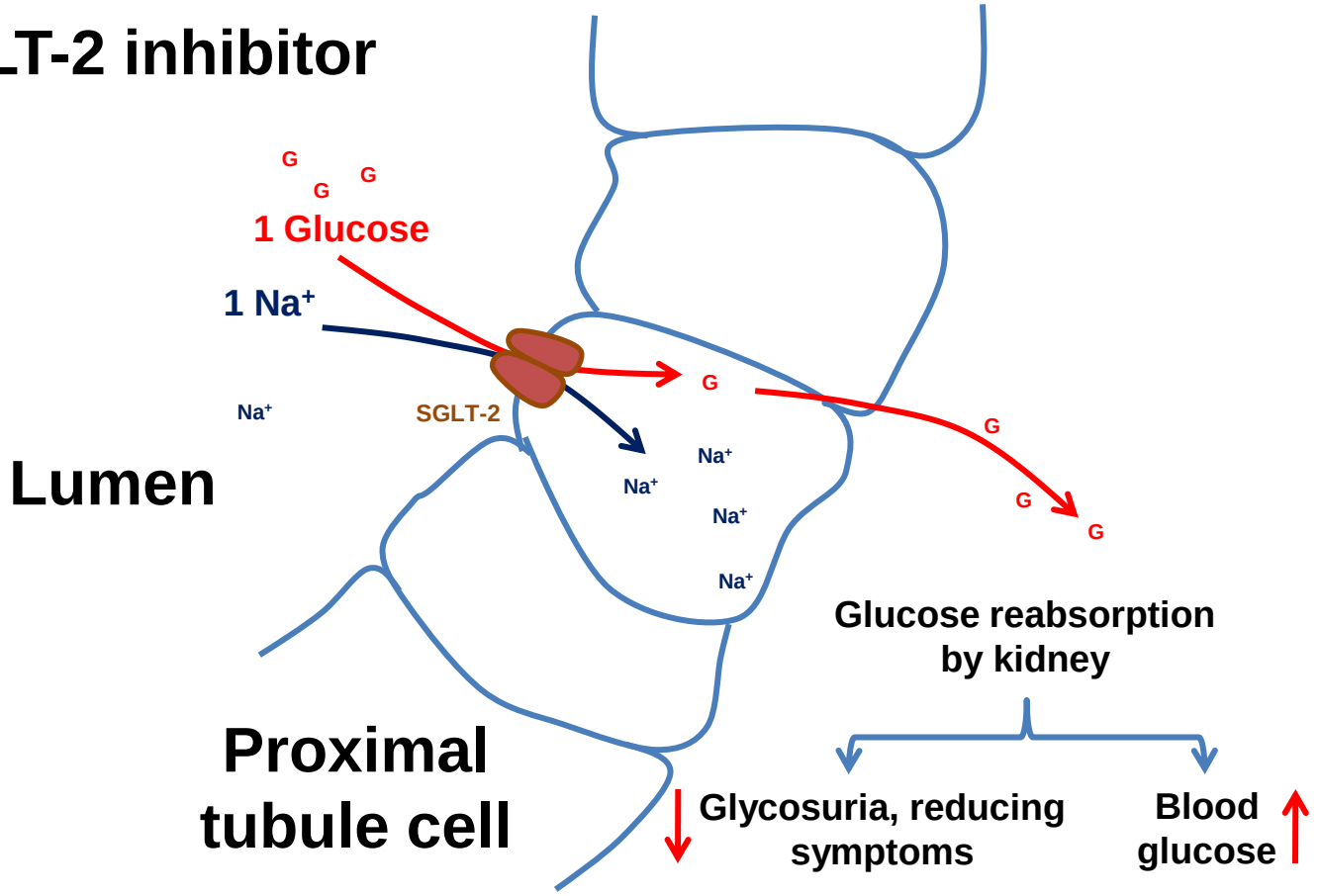
- ↓ Renal glucose reabsorption in the early proximal tubule of the kidney
  - ↓ **Body fat** - possibly due to ↑ water and fat urination (elimination)
- Lowers **fasting** glucose
  - Decreases A1C by 0.7% to 1% (~20-30 mg/dL)
- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - UTI
  - Frequent urination
  - Increased thirst
  - GI problems (when combined with metformin)

UTI = urinary tract infection.

List JF, et al. Diabetes Care. 2009;32:650-657. Wilding JP, et al. Diabetes Care. 2009;32:1656-1662.

SGLT-2

If no SGLT-2 inhibitor



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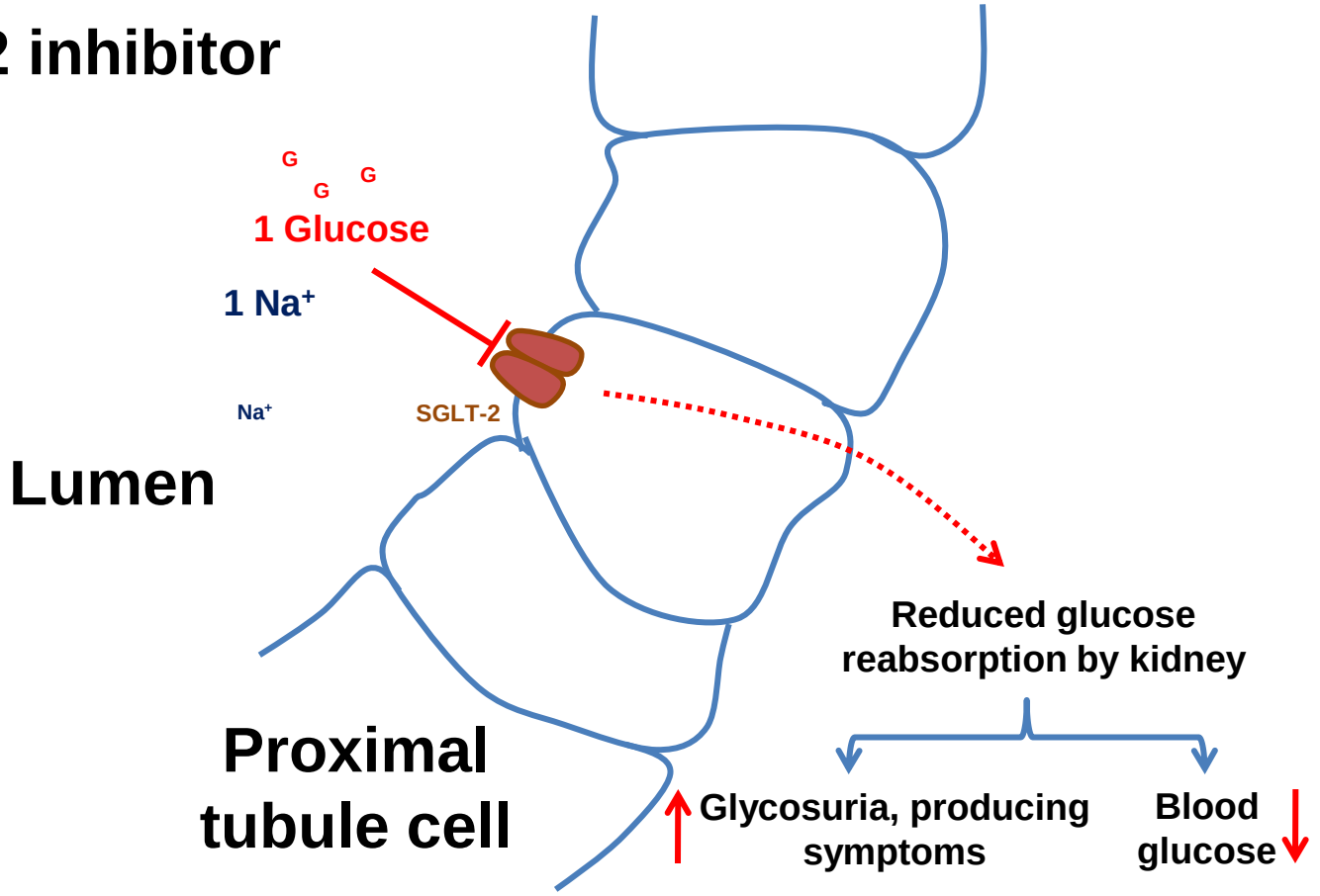
SGLT-2

If SGLT-2 inhibitor



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Gestational diabetes

Pregnancy is a diabetogenic state.

The hormones that lead to fetal growth and development do So by mobilizing the woman's nutritional resources, primarily glucose, and making them available to the fetus.

Human placental lactogen plays a pivotal role in triggering the changes that can lead to glucose intolerance.
It has strong anti-insulin and lipolytic effects.

Peripheral insulin sensitivity during the third trimester decreases to 50% of that seen in the first trimester, and basal hepatic glucose output is 30% higher despite higher insulin levels.

Gestational diabetes

Management

Diet and exercise, careful watching

Insulin is the drug of choice

Glyburide and metformine are prescribed

Glyburide does not cross the placenta.
Metformin crosses the placenta in small doses.