
DiABETES

Recent Guidelines

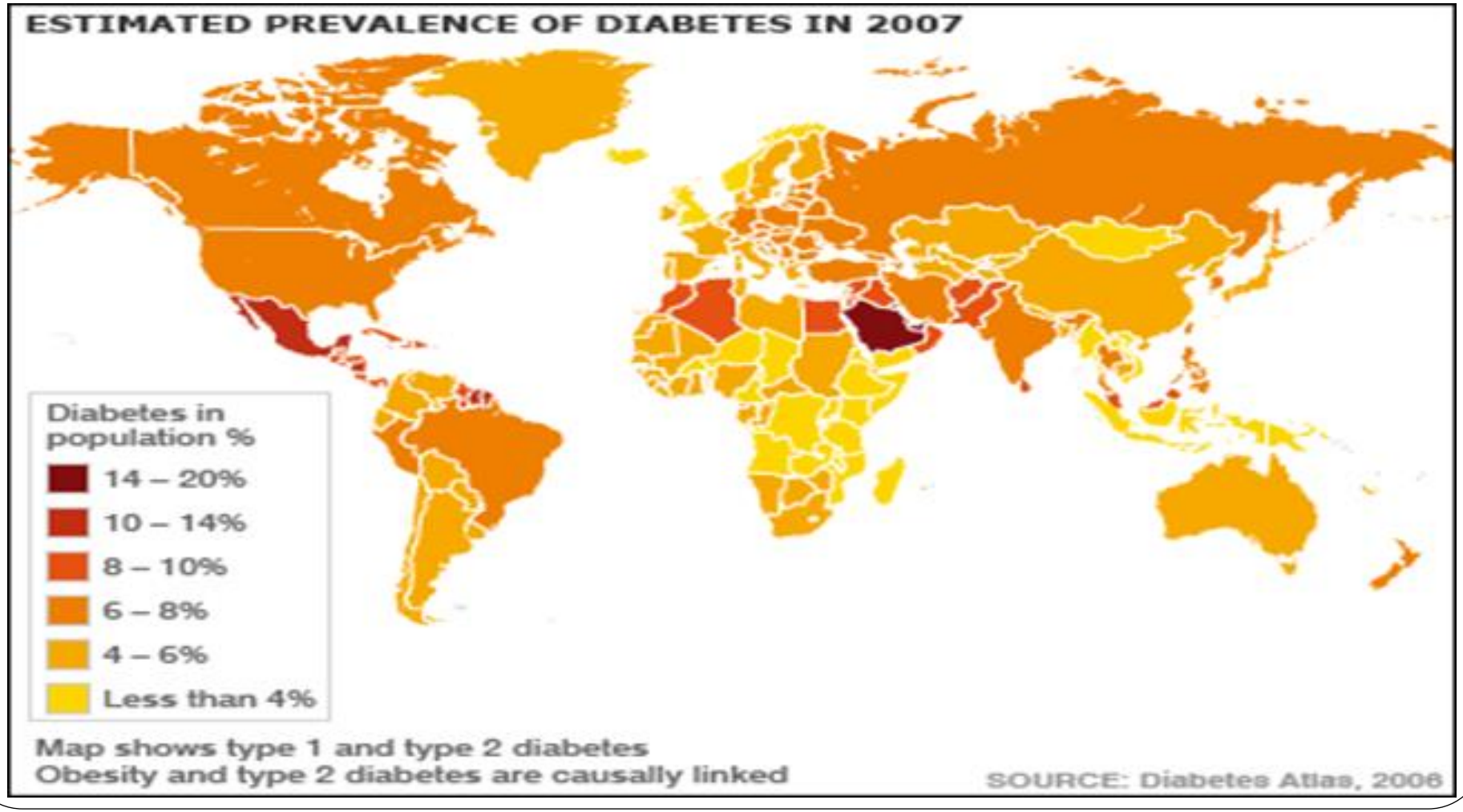
- **ADA T2DM 2015 Guidelines**
  - American Diabetes Association. Standards of medical care in diabetes – 2015. Diabetes Care. 2015;38(1):S17-S80.
- **ADA T1DM 2015 Guidelines**
  - American Diabetes Association. Type 1 Diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014;37(7):2034-2054.
- **AACE T2DM 2015 Guidelines**
  - Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a Diabetes Mellitus comprehensive care plan. Endocr Pract. 2015;21(1):1-62.
- **AACE T2DM 2015 Algorithm**
  - Garber AJ, et al. American Association of Clinical Endocrinologists comprehensive diabetes management algorithm 2013. Endocr Pract. 2015;21:438-447.

INTRODUCTION

- Diabetes comes from a Greek word meaning 'to pass or flow through' and mellitus means 'sweet'.
- DM is a group of metabolic disorders characterized by hyperglycemia. Diabetes is a metabolic disorder characterized by resistance to the action of insulin, insufficient insulin secretion, or both.
- It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders.
- The feet and eyes are at special risk and need special care and regular checks.
- Diabetes is controlled not curable
- Type 2 diabetes has a strong genetic predisposition.

INTRODUCTION

- About 1 person in 30 gets diabetes. It tends to increase as we get older because the pancreas, like other organs, tends to wear out.



CLASSIFICATION OF DIABETES

- The vast majority of diabetic patients are classified into one of three broad categories:
  - Type 1 diabetes
  - Type 2 diabetes
  - Gestational diabetes

- Type 1 diabetes:
  - Type 1 diabetes caused by an absolute deficiency of insulin.

- Type 2 diabetes:
  - Type 2 diabetes defined by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion.

- Gestational diabetes:
  - Women who develop diabetes because of the stress of pregnancy are classified as having gestational diabetes.

CLASSIFICATION OF DIABETES

- Finally, uncommon types of diabetes caused by infections,, endocrinopathies, pancreatic destruction, and known genetic defects (Named MODY from 1-7) are classified separately.

Drugs:

- Pentamidine
- Nicotinic acid
- Glucocorticoids
- Thyroid hormone
- Diazoxide
- β-Adrenergic agonists
- Thiazides
- Phenytoin
- γ-Interferon

Type 2 Diabetes

- Most individuals with type 2 diabetes exhibit abdominal obesity, metabolic syndrome causes insulin resistance. Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing macrovascular complications.

- **Five Components of the Metabolic Syndrome**
- **(Individuals with at Least 3 Components Meet the Criteria for Diagnosis)**

1-Abdominal obesity Waist circumference

- Men >102 cm (>40 in)
- Women >88 cm (>35 in)

2-Triglycerides ≥150 mg/dL (≥1.70 mmol/L)

3-High-density lipoprotein C

- Men <40 mg/dL (<1.03 mmol/L)
- Women <50 mg/dL (<1.29 mmol/L)

Blood pressure ≥130/≥85 mm Hg

Fasting glucose ≥110 mg/dL (≥6.1 mmol/L)

Gestational Diabetes Mellitus

- GDM is defined as glucose intolerance that is first recognized during pregnancy.
- Gestational diabetes complicates approximately 7% of all pregnancies.
- Clinical detection is important, as therapy will reduce perinatal morbidity and mortality.

Screening for Diabetes

- The American Diabetes Association (ADA) recommends screening for type 2 DM at any age in individuals who are:

1-overweight (BMI ≥25 kg/m2) and have at least one other risk factor for the development of type 2 DM.

2-Risk factorsinclude:

Age>45	prediabetes
physical inactivity	first-degree relative with diabetes
high-risk ethnicity/race	a history of GDM
Hypertension	high triglycerides
low HDL	polycystic ovary syndrome

history of cardiovascular disease.

Screening for diabetes

The recommended screening test is the fasting plasma glucose (FPG), HbA1c, or (OGTT).

Type 1 Diabetes Mellitus

The prevalence of type 1 DM is low. screening for type 1 DM in the asymptomatic general population is not recommended.

Screening for *β*-cell autoantibody status in high-risk family members may be appropriate.

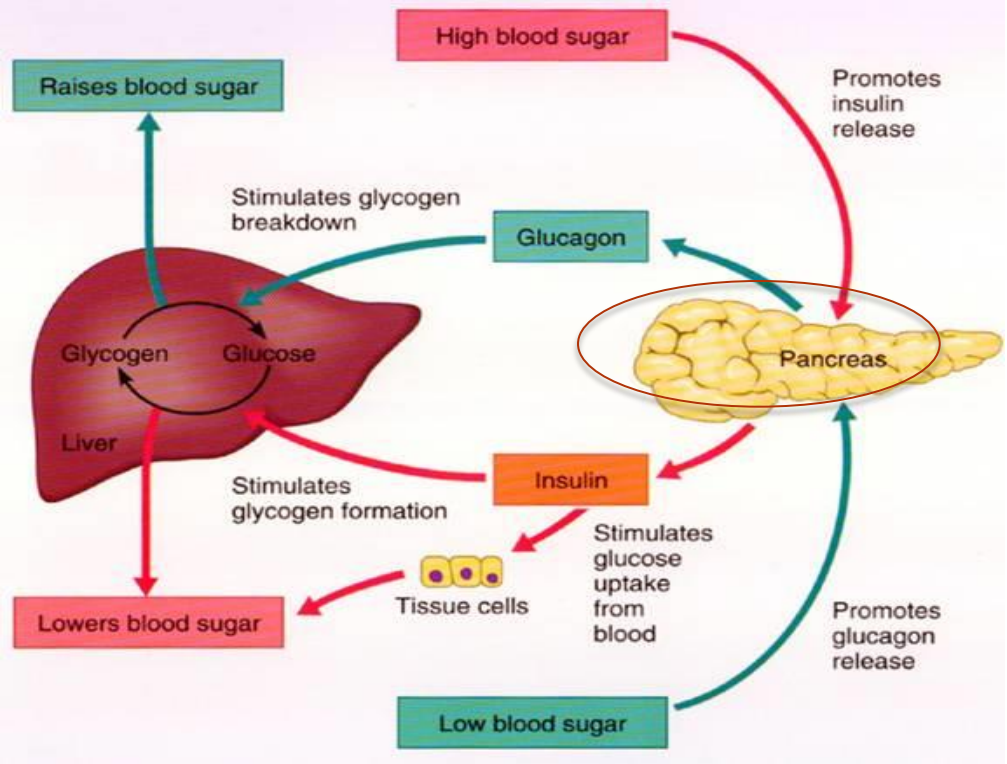
Normal Insulin Action

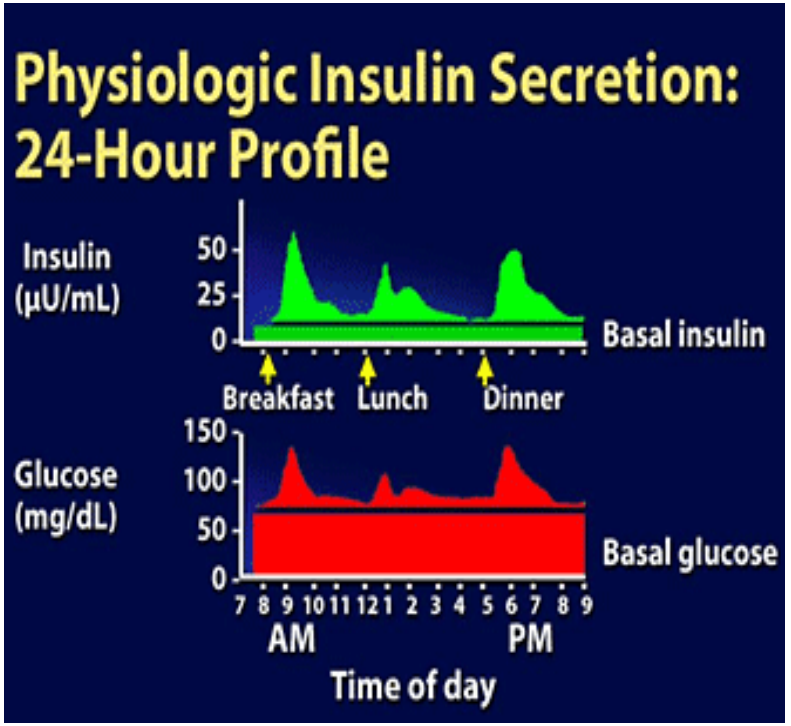
- In the fasting state 75% of total body glucose disposal takes place in non–insulin-dependent tissues: the brain and splanchnic tissues (liver and gastrointestinal [GI] tissues).
- The remaining 25% of glucose metabolism takes place in muscle, which is dependent on insulin.
- In the fasting state approximately 85% of glucose production is derived from the liver, and the remaining amount is produced by the kidney.
- Glucagon, produced by pancreatic α cells, is secreted in the fasting state to oppose the action of insulin and stimulate hepatic glucose production.

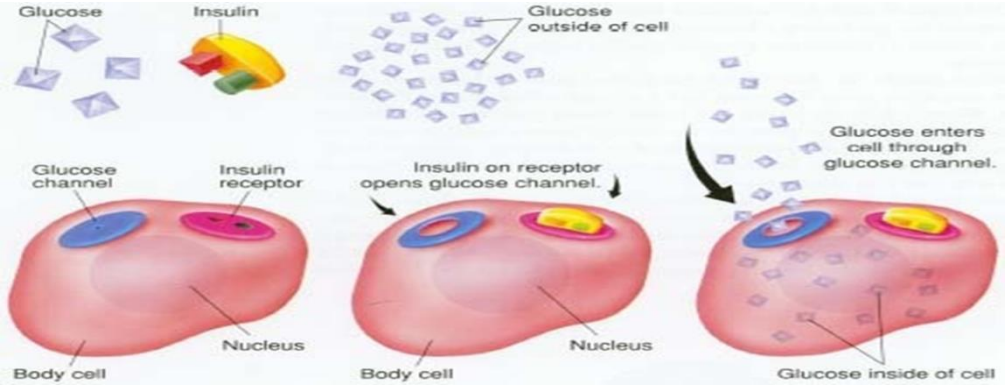
Normal Insulin Action

- In the fed state, carbohydrate ingestion increases the plasma glucose concentration and stimulates insulin release from the pancreatic β cells.
- The resultant hyperinsulinemia
  - Suppresses hepatic glucose production and
  - Stimulates glucose uptake by peripheral tissues.
  - Suppresses of free fatty acid release from fat cells
- The majority (80–85%) of glucose that is taken up by peripheral tissues is disposed of in muscle, with only a small amount (4–5%) being metabolized by adipocytes.
- The suppression of free fatty acids plays an important role in glucose homeostasis. Increased levels of free fatty acids inhibit the uptake of glucose by muscle.

Think Back: Insulin (the awesome man)







- Secreted in response to glucose
- Attempts to maintain euglycemia

Incretins

- In the type 2 diabetic patient, decreased postprandial insulin secretion is due to both impaired pancreatic *β*-cell function and a reduced stimulus for insulin secretion from gut hormones.

- This increased insulin secretion in response to an oral glucose stimulus is referred to as “the incretin effect” and suggests that gut-derived hormones when stimulated by glucose lead to an increase in pancreatic insulin secretion.

- It is now known that two hormones, Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are responsible for over 90% of the increased insulin secretion seen in response to an oral glucose load.

Incretins

- GLP-1 is secreted from the distal intestinal mucosa, in response to mixed meals. Since GLP-1 levels rise within minutes of food ingestion, neural signals and possibly proximal GI tract receptors stimulate GLP-1 secretion. The action of GLP-1 is glucose dependent, and for GLP-1 to enhance insulin secretion, glucose concentrations must be higher than 90 mg/dL (5 mmol/L).

- In addition, GLP-1 suppresses glucagon secretion, slows gastric emptying, and reduces food intake by increasing satiety.

- Also, GIP is secreted by K cells in the intestine and may have a role with insulin secretion during near-normal glucose levels and may act as an insulin sensitizer in adipocytes. However, GIP has no effect on glucagon secretion, gastric motility, or satiety. The half-lives of GLP-1 and GIP are short (<10 minutes).

- Both hormones are rapidly inactivated by removal of two N-terminal amino acids by the enzyme dipeptidyl peptidase-4 (DPP-4).

Criteria for the diagnosis of DM

- The diagnosis of diabetes requires the identification of a glycemic cut point, which discriminates normal persons from diabetic patients.

- The ADA recommends using the fasting glucose test as the principal tool for the diagnosis of DM in nonpregnant adults.

- The fasting and postprandial glucose levels do not measure the same physiologic processes and do not identify the same individuals as having diabetes.

- The fasting glucose reflects hepatic glucose production, which depends on insulin secretory capacity of the pancreas.

- The postprandial glucose reflects uptake of glucose in peripheral tissues (muscle and fat) and depends on insulin sensitivity of these tissues.

Criteria for the diagnosis of DM

Symptoms of diabetes plus casual[b] plasma glucose concentration ≥200 mg/dL (11.1 mmol/L)

or

Fasting[c] plasma glucose ≥126 mg/dL (7.0 mmol/L)

or

2-hour postload glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT[d]

Fasting plasma glucose (FPG)	**2-Hour postload plasma glucose (oral glucose tolerance test)**
Normal: FPG <100 mg/dL (5.6 mmol/L)	Normal: Postload glucose <140 mg/dL (7.8 mmol/L)
Prediabetes :Impaired fasting glucose (IFG) 100–125 mg/dL (5.6–6.9 mmol/L)	Prediabets: Impaired glucose tolerance (IGT): 2-hour postload glucose 140–199 mg/dL (7.8–11.1 mmol/L)
Diabetes mellitus: FPG ≥126 mg/dL (7.0 mmol/L)	Diabetes mellitus: 2-hour postload glucose ≥200 mg/dL (11.1 mmol/L)

Pathogeneses of Type 1 Diabetes

- This form of diabetes results from autoimmune destruction of the β cells of the pancreas.
- Markers of immune destruction of the β cell (islet cell antibodies and antibodies to insulin) are present at the time of diagnosis in 90% of individuals.
- The autoimmune process is mediated by macrophages and T lymphocytes with circulating auto-antibodies to various β-cell antigens. The most commonly detected antibody associated with type 1 DM is the islet cell antibody.
- Also, unknown or idiopathic processes can contribute.
- this form of diabetes mainly occurs in children and adolescents< 40 years

Pathogenesis of type 2 diabetes

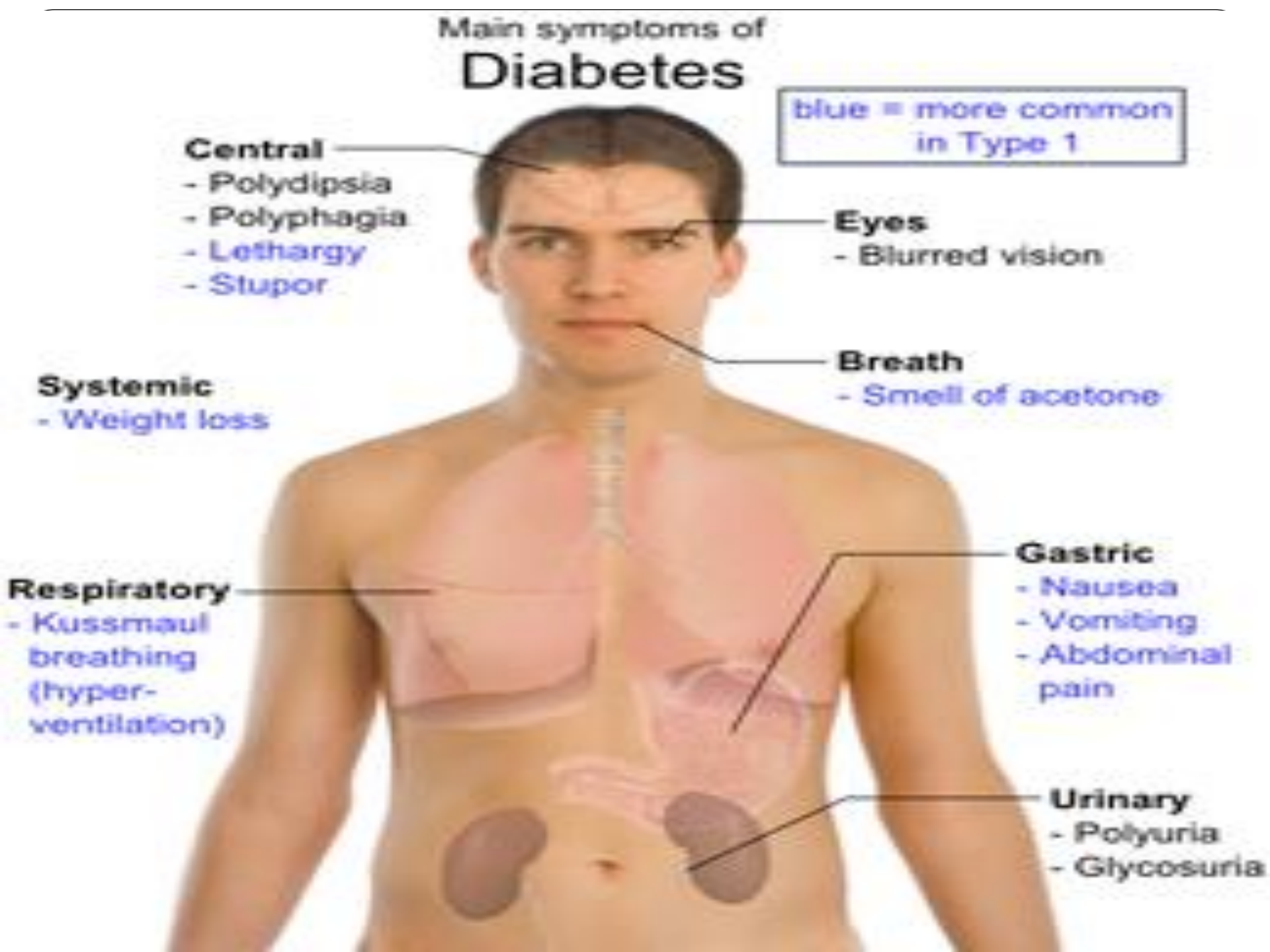
- Impaired insulin secretion is a uniform finding in type 2 diabetic patients due to β-cell dysfunction.
- In type 2 DM, the FPG concentration increases from 80 to 140 mg/dL, the fasting plasma insulin concentration increases progressively, peaking at a value that is 2- to 2.5- fold greater than in normal.
- When the FPG concentration exceeds 140 mg/dL, the β cell is unable to maintain its elevated rate of insulin secretion, and the fasting insulin concentration declines precipitously.
- This decrease in fasting insulin leads to an increase in hepatic glucose production, which results in an elevated FPG concentration.

Pathogenesis of type 2 diabetes

- In the type 2 diabetic patient, decreased postprandial insulin secretion is caused by impaired pancreatic β-cell function.
- Abdominal fat is resistant to the antilipolytic effects of insulin, resulting in the release of excessive amount of free fatty acid, which in turn lead to insulin resistance in the liver and muscle.
- The effect is an increase in gluconeogenesis in the liver and inhibition of insulin mediated glucose uptake in the muscles.
- These both result in increased levels of circulating glucose.

CLINICAL PRESENTATION

- Individuals with type 1 DM are often thin and are prone to develop diabetic ketoacidosis.
- About 20-40% percent of patients with type 1 DM present with diabetic ketoacidosis after several days of polyuria, polydipsia, polyphagia, and weight loss.
- Patients with type 2 DM often present without symptoms, even though complications tell us that they may have had type 2 DM for several years.
- Often these patients are diagnosed secondary to unrelated blood testing.
- Lethargy, polyuria, nocturia, and polydipsia can be seen at diagnosis in type 2 diabetes.

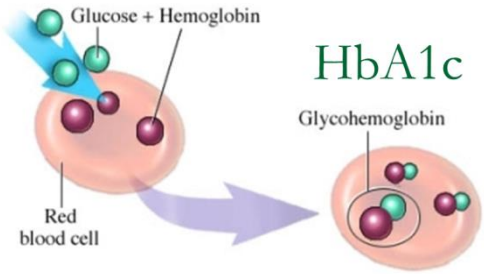

Main symptoms of
Diabetes
blue = more common in Type 1
Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor
Eyes
- Blurred vision
Breath
- Smell of acetone
Systemic
- Weight loss
Respiratory
- Kussmaul breathing (hyper-ventilation)
Gastric
- Nausea
- Vomiting
- Abdominal pain
Urinary
- Polyuria
- Glycosuria

Characteristic	Type 1 DM	Type 2 DM
Age	<30 years[b]	>30 years[b]
Onset	Abrupt	Gradual
Body habitus	Lean	Obese or history of obesity
Insulin resistance	Absent	Present
Autoantibodies	Often present	Rarely present
Symptoms	Symptomatic[c]	Often asymptomatic
Ketones at diagnosis	Present	Absent[d]
Need for insulin therapy	Immediate	Years after diagnosis
Acute complications	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Microvascular complications at diagnosis	No	Common
Macrovascular complications at or before diagnosis	Rare	Common

Treatment

DESIRED OUTCOME

- reduce the risk for microvascular and macrovascular disease complications
- ameliorate symptoms
- reduce mortality, and to improve quality of life
- Maintain FBG<126 and HbA1c target of <7%



GLYCEMIC GOAL SETTING AND THE HEMOGLOBIN A1c

- Glycemic control is paramount in reducing microvascular complications in both type 1 DM and type 2 DM.
- HbA1c measurements are the gold standard for following long-term glycemic control.
- A HbA1c target of <7% is appropriate and lower values should be targeted if significant hypoglycemia and/or weight gain can be avoided.

HbA_{1c} Levels and Blood Glucose Equivalents	
HbA_{1c} Level (%)	Average Blood Glucose (mg/dL)
14	360
13	333
12	300
11	270
10	240
9	210
8	180
7	150
6	120
5	80

NONPHARMACOLOGIC THERAPY

Diet

- Medical nutrition therapy is recommended for all persons with DM.
- For individuals with type 1 DM, a meal plan that is moderate in carbohydrates and low in saturated fat (<7% of total calories), with a focus on balanced meals is recommended.
- In addition, patients with type 2 DM often require caloric restriction to promote weight loss.
- As most patients with type 2 DM are overweight or obese, bedtime and between-meal snacks are not needed.

NONPHARMACOLOGIC THERAPY

Diet

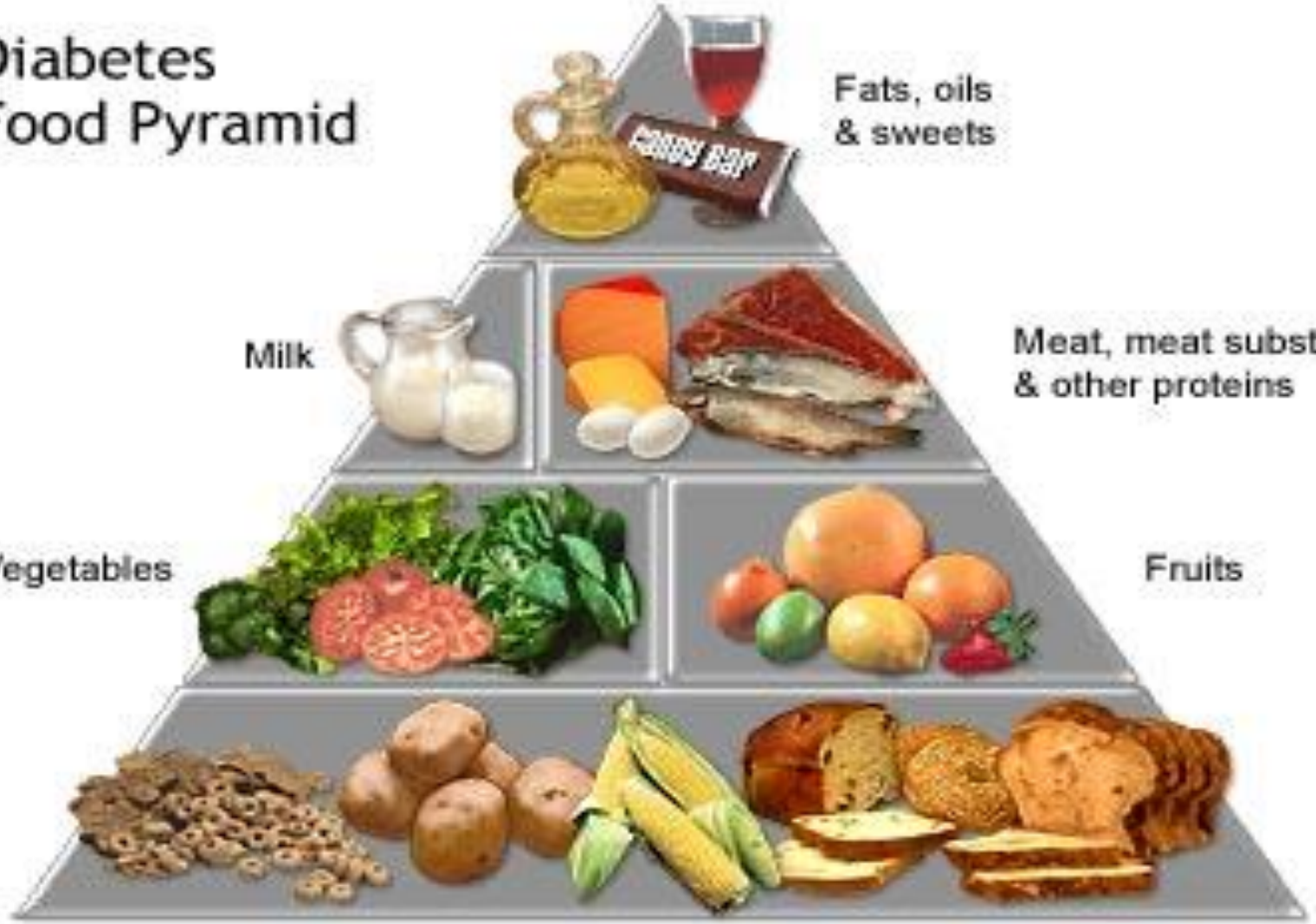
- eating good food regularly (not skimping)
- spacing the meals throughout the day (three main meals)
- cutting down fat to a minimum
- avoiding sugar and refined carbohydrates (e.g. jam, honey, chocolates, sweets, pastries, cakes, soft drinks)
- eating a balance of more natural carbohydrates (starchy foods) such as wholemeal bread, potatoes and cereals
- eating a good variety of fruit and vegetables

Diet check list

This chart will help you determine which foods are high in sugar or fat. It suggests alternatives. You may want to look over the chart with your doctor, so that he or she can see what changes you will be making to your diet.

Foods to avoid or limit	*Suitable alternatives*
High in sugar	
sugar, honey	tablet or liquid artificial sweetener
spreads: jam, marmalade, syrups, Nutella	low joule jam/marmalade, Promite, Vegemite, meat/fish paste
sweet drinks: cordial, soft drink, flavoured mineral water, tonic water, fruit juice drinks, ordinary flavoured milk, milkshakes	low joule cordial/soft drink, plain mineral/soda water, pure fruit juice (limit to 1 small glass a day), coffee, tea herbal teas
sweet wine/sherry, port, liqueurs, ordinary beer	dry wine or spirit or low alcohol beer (1 to 2 drinks a day)
confectionery: lollies, cough lollies, chocolate (ordinary/diabetic/carob), muesli/health bars	low joule pastilles
sweet biscuits (e.g. cream, chocolate, shortbread), cakes, doughnuts, iced buns, sweet pastries	crispbreads, Cruskits, wholemeal crackers, wheatmeal or coffee biscuits, scones, 'no added sugar' fruit loaf
sweet desserts: ordinary jelly, fruit in sugar syrup, fruit pies, cheesecakes, puddings, ordinary flavoured yoghurt or ice-cream, ice-cream toppings	low joule jelly, fresh or tinned/stewed fruit without added sugar, custard or junket made with liquid sweetener plain or diet-lite 'no added sugar' yoghurt, plain ice-cream (1 scoop occasionally), low joule ice-cream toppin
sweet cereals: some mueslis, Nutrigrain, Cocopops, Honeysmacks, Sugar Frosties	most other cereals, e.g. porridge, Weetbix, All-Bran, Ready Wheats
High in fat	
mayonnaise, oily dressings, cream sauces, fatty gravies, sour cream	low joule dressings, vinegar, lemon juice, low joule Gravox, plain yoghurt
fat on meat, chicken skin, fatty meats (sausages, bacon, salami)	lean cuts of meat with skin and fat removed
deep-fried foods, pies/pasties	foods cooked without fat, or with a minimal amount of vegetable oil
snack foods: nuts, crisps, corn chips	crisp, raw vegetables, fruit, plain popcorn
large amounts of margarine, butter, oil, cream, peanut butter, dripping, lard,	limit to 3-6 teaspoons a day, preferably polyunsaturated margarine or oil

Diabetes Food Pyramid



Activity

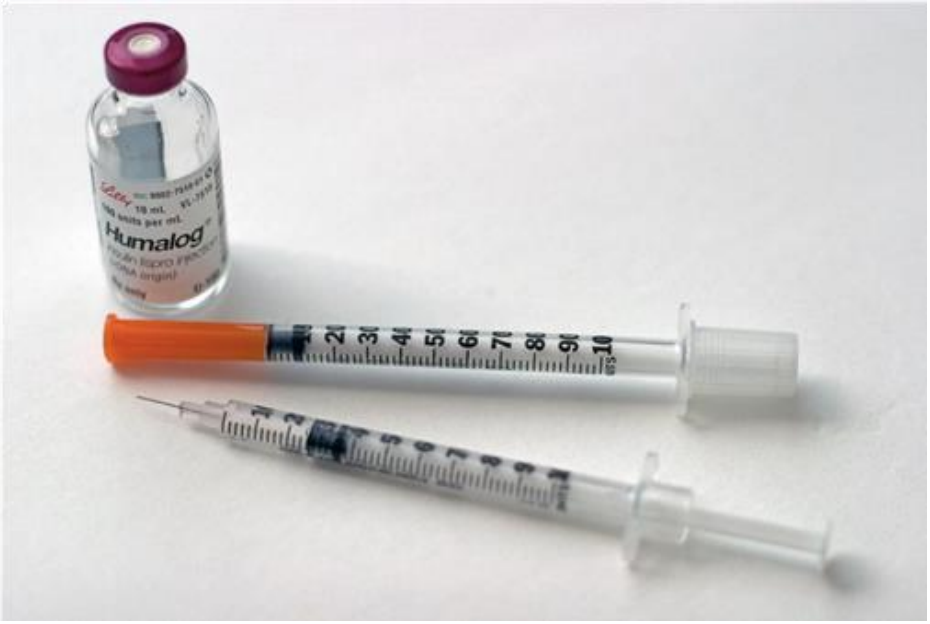
- Regular exercise, in any form, can help reduce the risk of developing diabetes. Activity can also reduce the risk of developing complications of diabetes such as heart disease, stroke, kidney failure, blindness, and leg ulcers.

- As little as 20 minutes of walking three times a week has a proven beneficial effect.

- If the patient has complications of diabetes (eye, kidney, or nerve problems), they may be limited both in type of exercise and amount of exercise they can safely do without worsening their condition.

- Consult with your health care provider before starting any exercise program.

INSULIN THERAPY
IN
TYPE 1 DM



INSULIN THERAPY

- All patients with type 1 DM require treatment with insulin in order to survive.
- Exogenous insulin is used to mimic the normal physiological pattern of insulin secretion as closely as possible, for each individual patient.
- However, a balance is needed between tight glycemic control and hypoglycemia risk.
- If the risk of hypoglycemia is high, then it may be necessary to aim for less glycemic control.
- Insulin is the most effective option we have at controlling diabetes type 1: Replace the absolute defiecincy in insulin secretion, no ceiling for A1c reduction, Highly adjustable and individualizable, Reduces microvascular complications

Barriers to insulin

- **Patients**
  - Fear of needles
  - Fear of side effects (weight gain, hypglycemia)
  - Change in lifestyle
  - Embarrassment

- **Health Care Professionals**
  - Time consuming
  - Risk of hypoglycemia
  - Lack of staffing/education

INSULIN THERAPY

- There is a wide variety of insulin preparations which differ in:
  - Species of origin , Onset of action , Time of peak effect and Duration

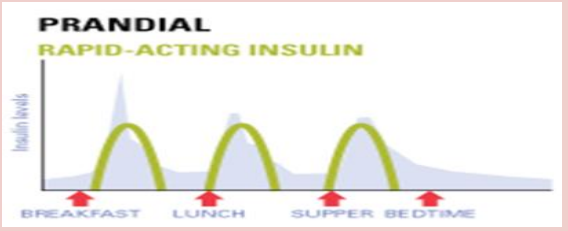
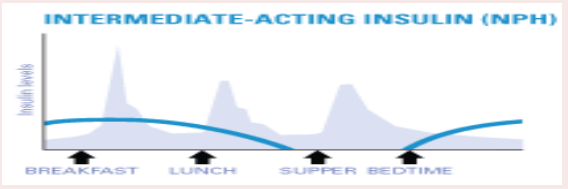
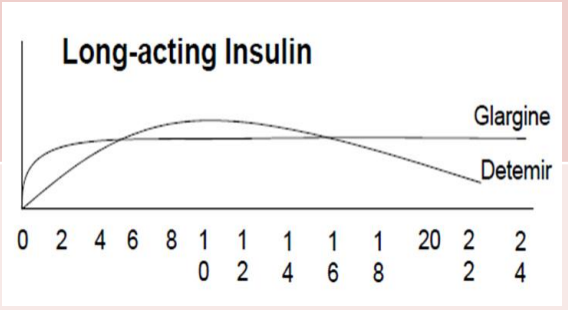
Insulin formulations:

- Soluble insulin:
  - Human actrapid
  - Novorapid
- Biphasic insulin:
  - Human mixtard 30/70
- Isophane insulin:
  - Human insulatard
  - Humulin
- Insulin zinc suspension:
  - Human monotard
  - Human bovine lente
- Protamine zinc
  - Hypurin Bovine PZI
- Long acting analogues:
  - Lantus
  - levemir

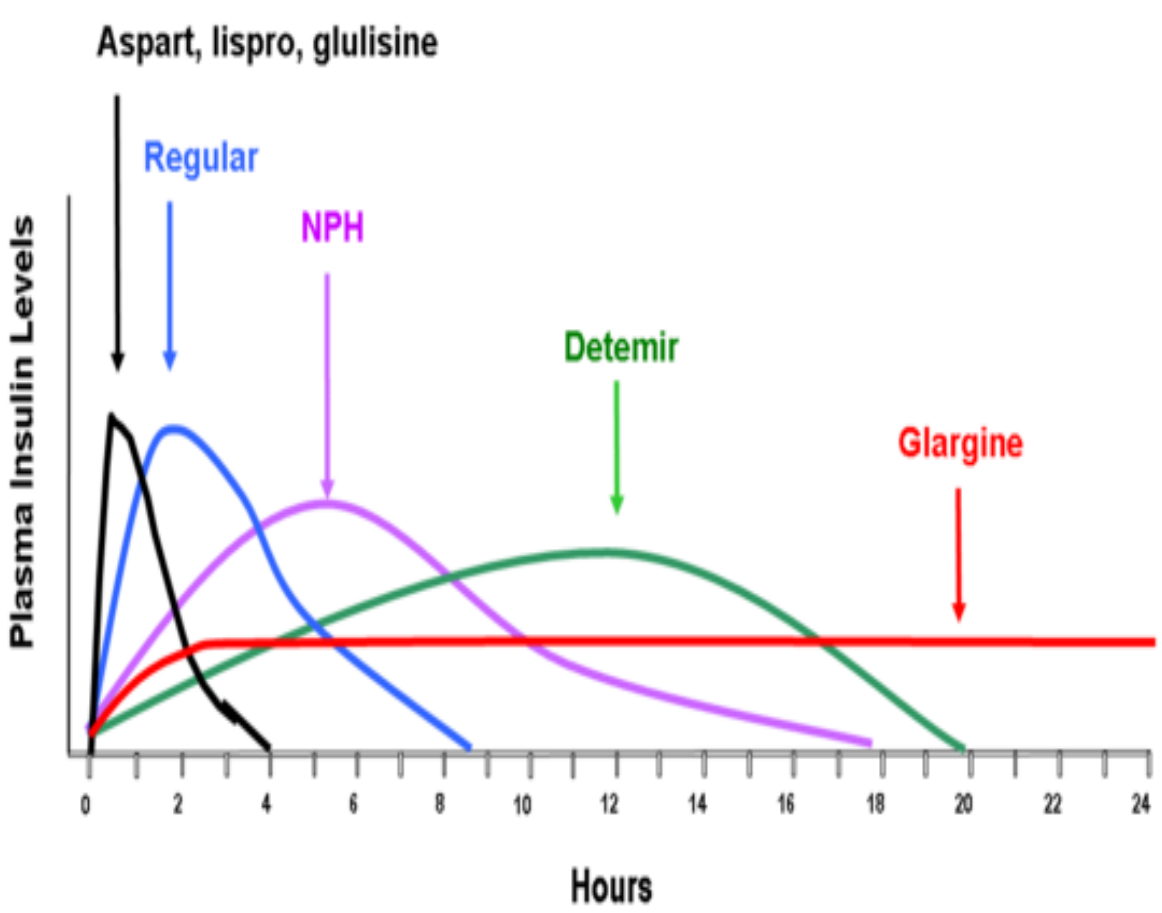
TYPES OF INSULIN

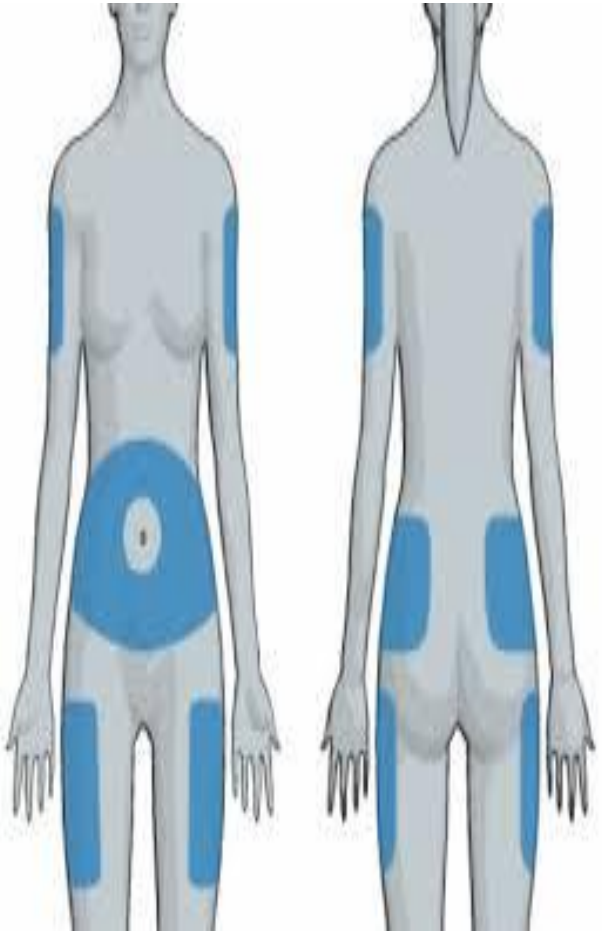
- There are several different types of insulin. These types are classified according to how quickly they begin working and how long the insulin lasts
  - **Rapid-acting (actrapid)**
  - **Short-acting (eg, insulin regular (Novolin R, Humulin R))**
  - **Intermediate-acting (eg, insulin NPH (Novolin N, Humulin N))**
  - **Long-acting (eg, insulin glargine [Lantus®], insulin detemir [Levemir®])**
  - **Premixed (Mixtard 70/30)**

- Standard formulations- U 100
- Concentrated formulations – U 500, U 300

Category	Insulin Name	Onset	Peak	Duration	
Rapid acting	Aspart/ Lispro/ Glulisine	5-15 minutes	0.5-2 hours	4-5 hours	
Short acting	Regular	30-60 minutes	2-4 hours	5-8 hours	
Regular U-500	U-500	30-60 min	2-4 hours	12-24 hours	
Intermediate acting	NPH	30-60 min	4-12 hours	10-16 hours	
Long acting	Detemir	2-4 hours	6-8 hours	20-23 hours	
	Glargine	1-2 hours	No peak	~24 hours	

Insulin Kinetics and injection sites

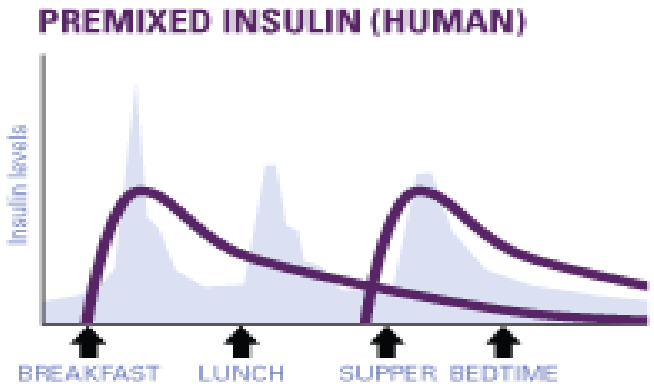




Pre-Mixed Insulin

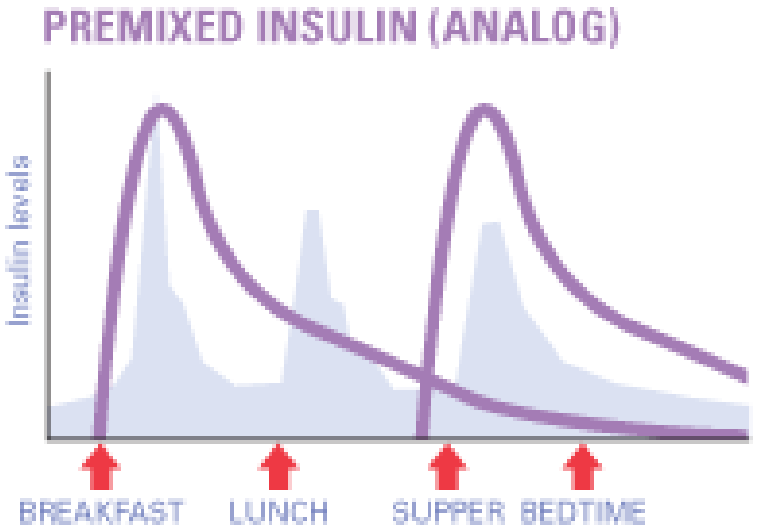
- Human
  - NPH and regular insulin (Humulin 70/30, Novolin 70/30, Humulin 50/50, Mixtard 70/30)
  - BID 30 min before meal

  - Notes
    - Typically dose twice daily with breakfast and dinner
    - Less flexibility than with individual insulin doses
    - Less injections, no mixing
    - Roll/mix before use
    - Available in pens and vials



New Pre-Mixed Insulin

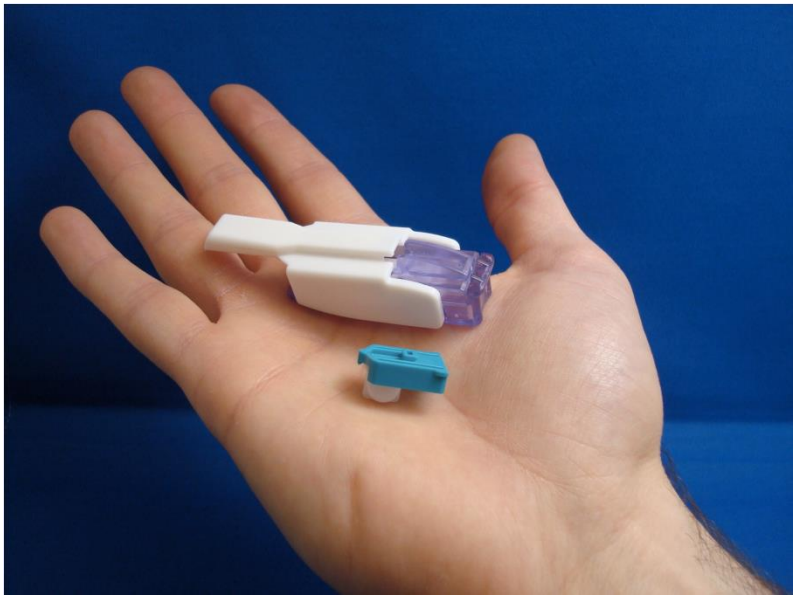
- Analog
  - Protamine lispro (long-acting) & lispro
    - Humalog 75/25
    - Humalog 50/50
  - Protamine aspart & aspart
    - Novolog Mix 70/30
  - Notes
    - Cloudy
    - Roll/mix before use



Key: 1st number = %NPH, 2nd number = %bolus

Inhaled Insulin

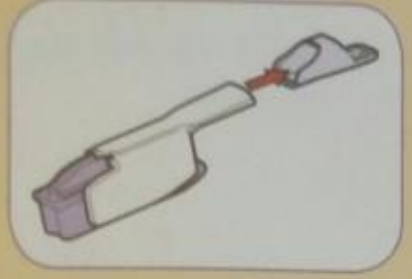
- Afrezza approved in 2014
- Exubera discontinued in 2007



- Dosed in mg instead of units (need conversion as shown)

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of **4 unit** (blue) cartridges needed		# of **8 unit** (green) cartridges needed
up to **4** units	**4** units	1		
5-8 units	**8** units			1
9-12 units	**12** units	1	+	1
13-16 units	**16** units			2
17-20 units	**20** units	1	+	2
21-24 units	**24** units			3

- Warnings:
  - Acute bronchospasm risk
  - Contraindicated
    - Asthma
    - COPD



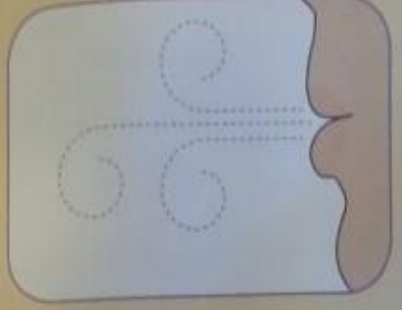
- Be sure you have REMOVED the mouthpiece cover.

- HOLD the inhaler level with your thumb on the **purple bottom** and your first two fingers on the **white top.**

REMEMBER: After loading a cartridge, to avoid spilling medication:

- DO NOT turn your inhaler upside down.
- DO NOT shake the inhaler.

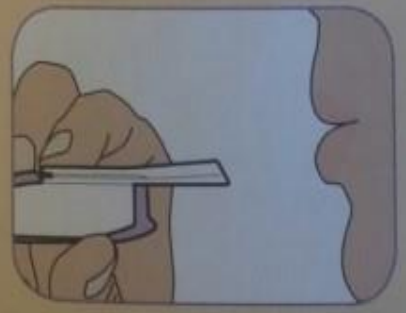
- DO NOT point the mouthpiece toward the floor.



- Make sure your mouth is empty. Breathe out while holding your inhaler away from your mouth.

- Place the mouthpiece in your mouth and close your lips around the mouthpiece to form a seal. Hold the inhaler with the mouthpiece tilted slightly.

- INHALE deeply through your inhaler.



- Remove the mouthpiece from your mouth. Briefly hold your breath as long as you comfortably can, then breathe normally.

What are we Trying to Control?

- **Fasting Plasma Glucose (FPG)**
  - Basal insulin
    - Intermediate-acting or Long-acting
    - Suppress glucose rises between meals and overnight
    - Nearly a constant level
    - Typically 50% of daily need

- **Post-prandial Plasma Glucose (PPG)**
  - Bolus or prandial
    - Rapid-acting or Short-acting
    - Limits hyperglycemia after meals
    - Immediate rise in insulin
    - Typically 50% of daily need
      - Divided between each meal of the day

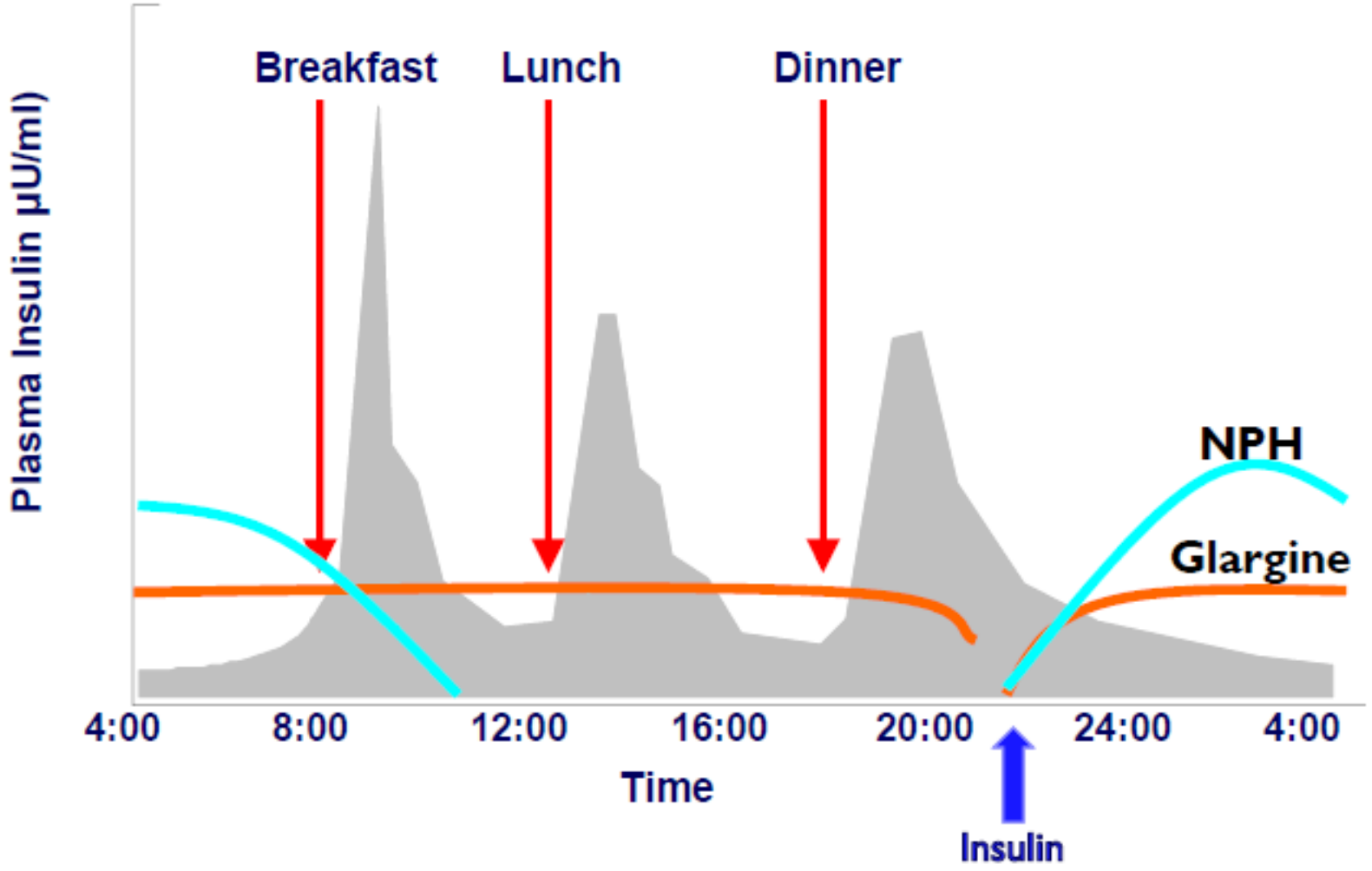
INSULIN REGIMEN

- Two regimens are used worldwide for the control of type 1 DM:
  - Mealtime plus basal regimens (basal-bolus regimen)
  - Twice-daily regimen

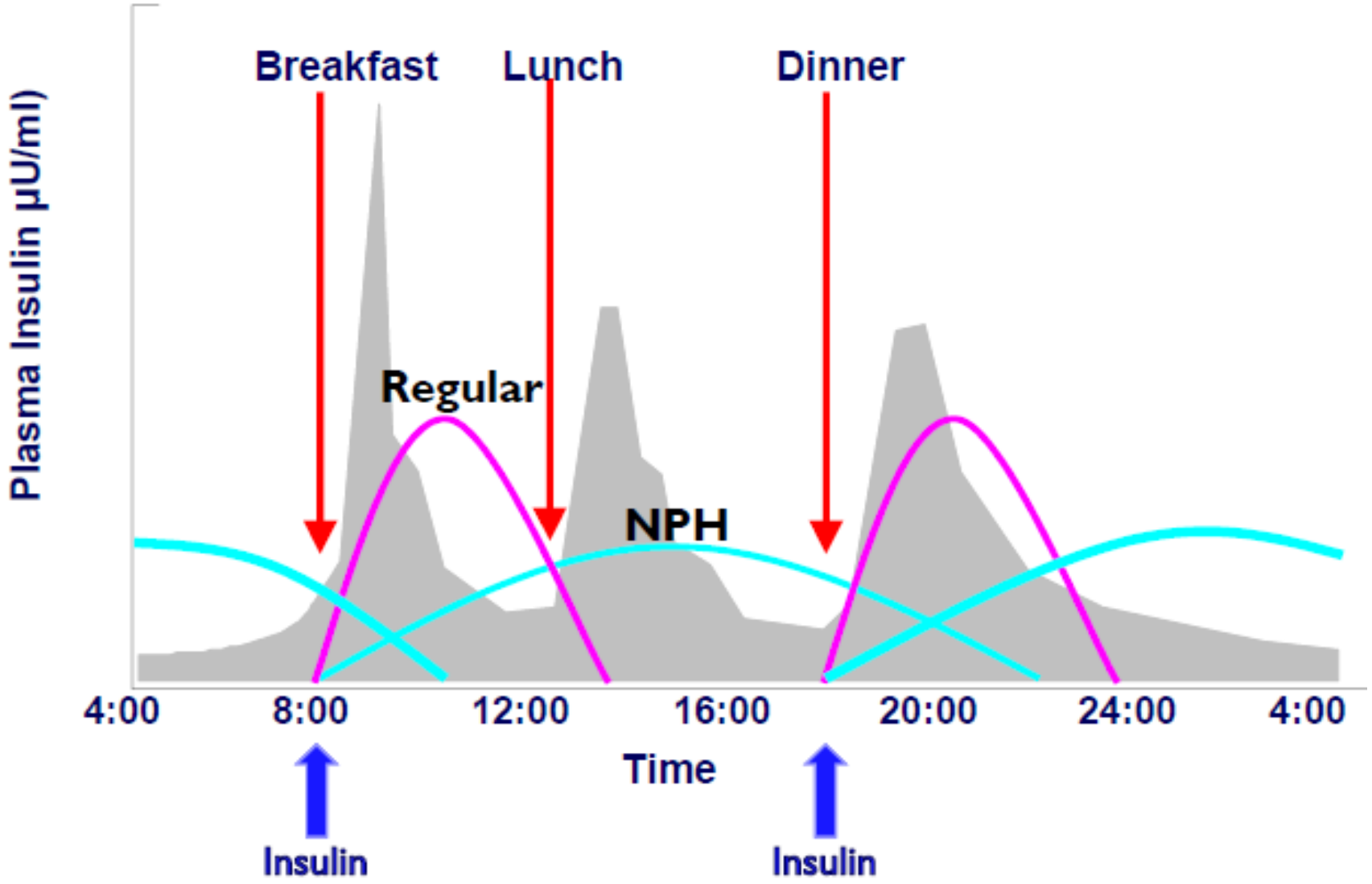
MEALTIME PLUS BASAL REGIMEN:

- It is also referred as basal-bolus regimen.
- This regimen requires
  - mealtime injections of insulin with a fast acting preparation
  - One or two injections of a basal (intermediate or long acting) insulin.
- This regimen offers the most flexibility of dosing and eating habits and often better glucose control.
- The disadvantage of this regimen is that it require multiple injections and requires regular blood glucose monitoring.

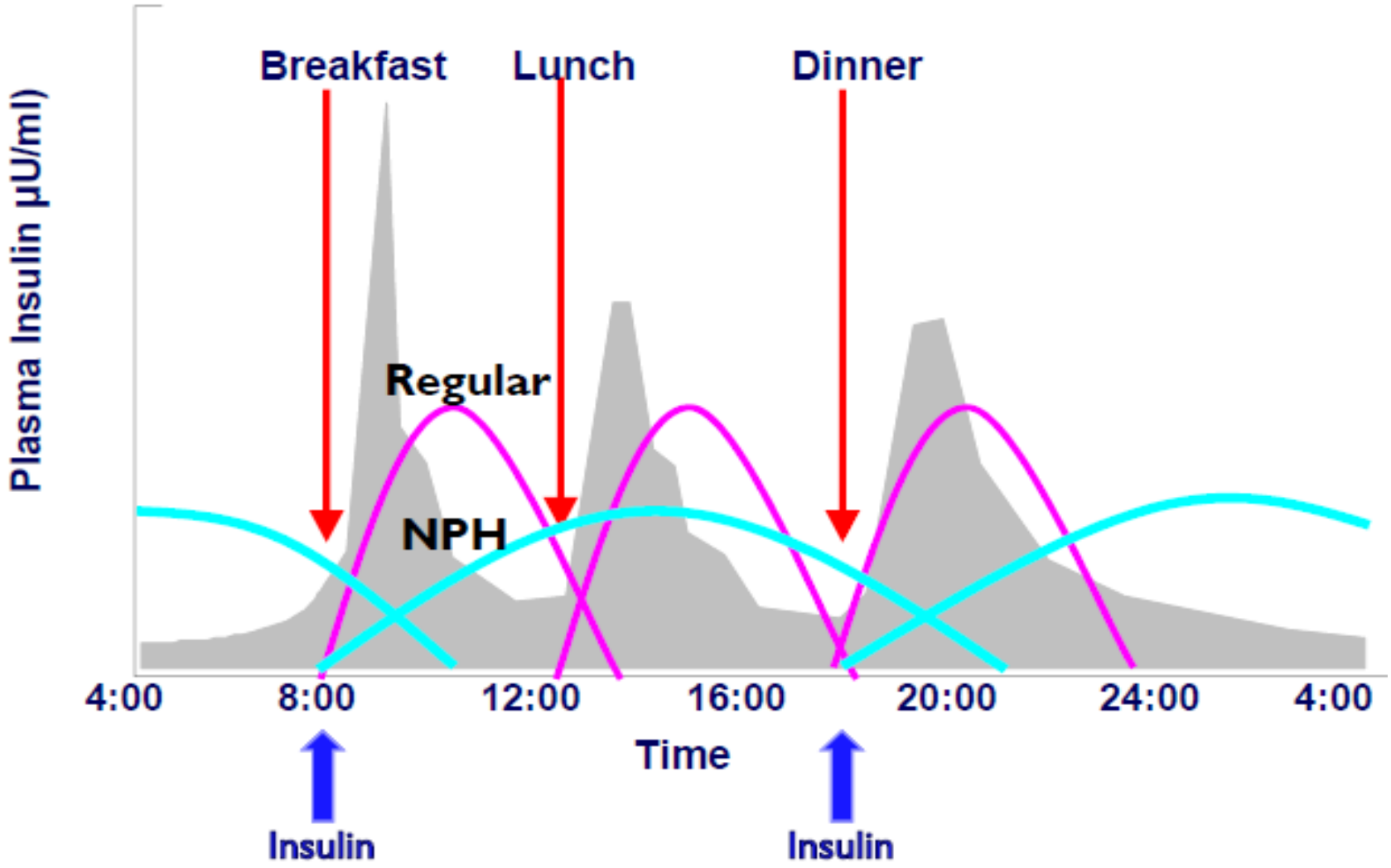
1 Injection Schedule (basal only) exception)



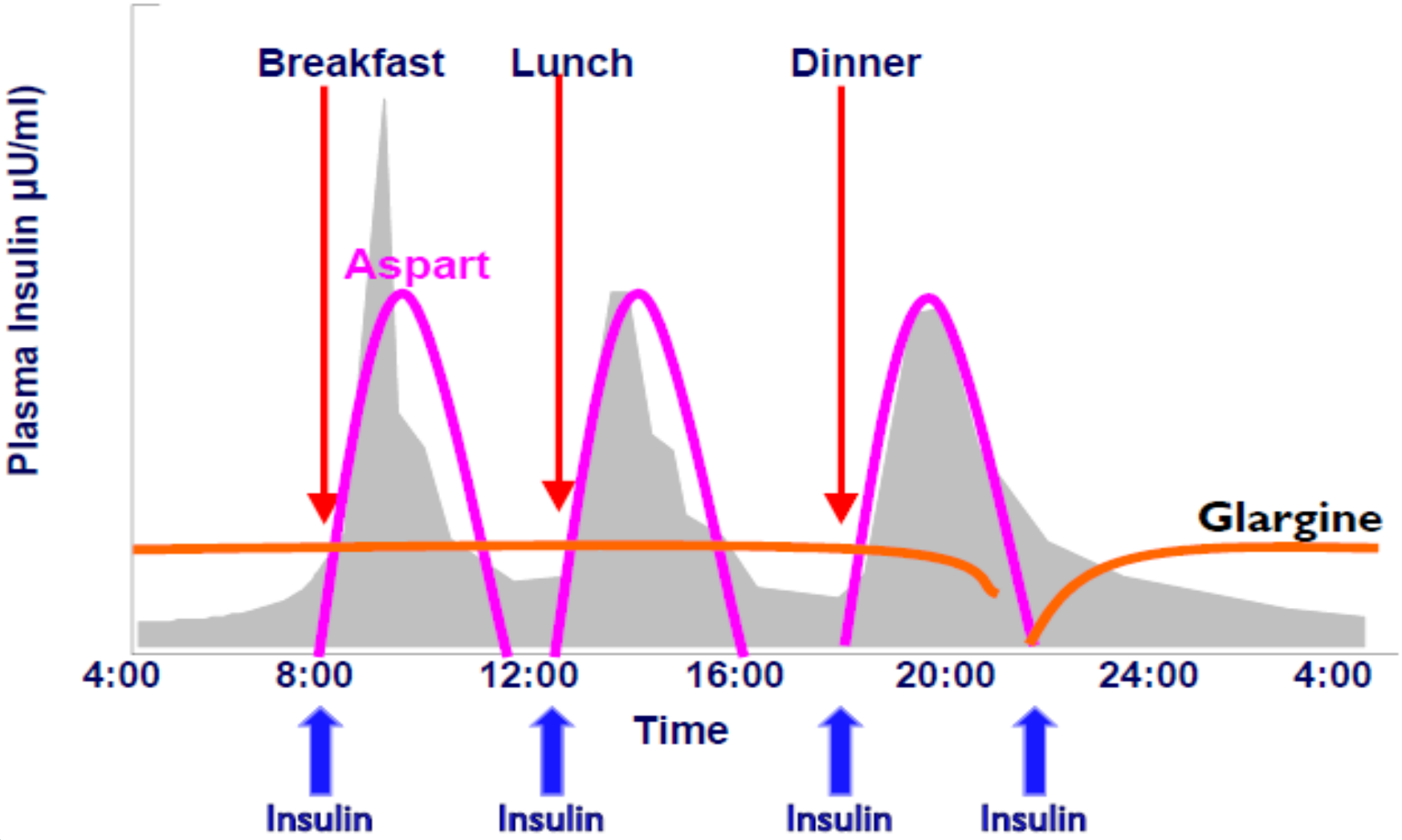
2 Injection Schedule (basal + prandial)



3 Injection Schedule (basal + prandial)

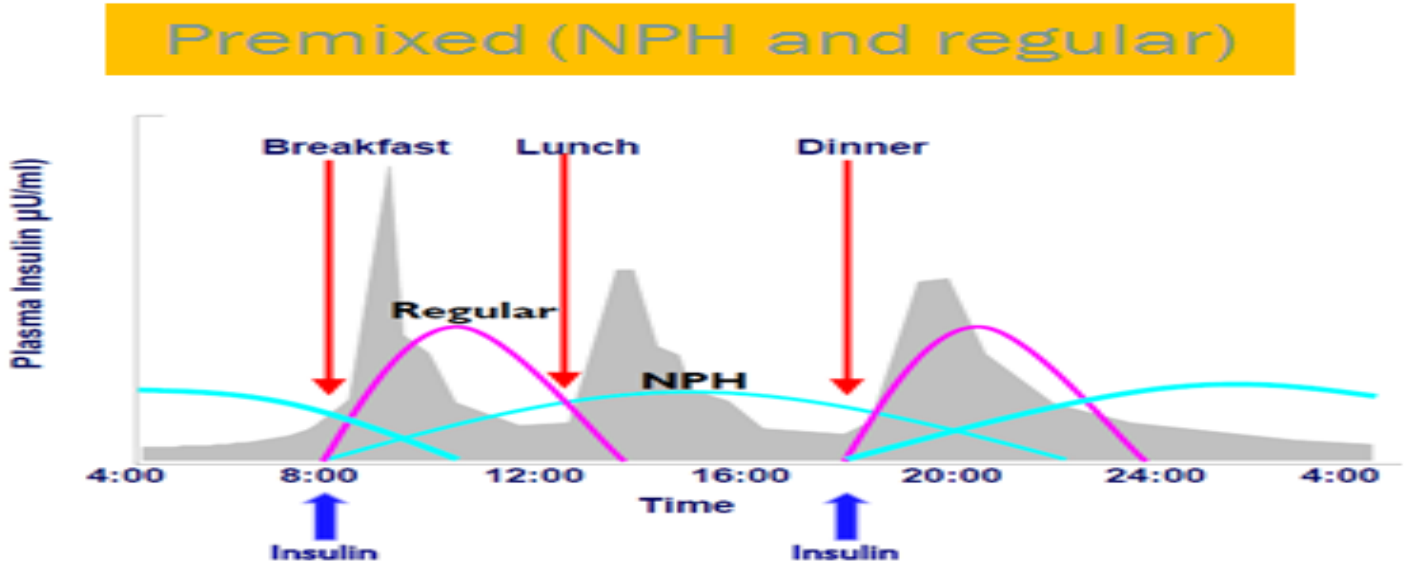


4 Injection Schedule (basal + prandial)

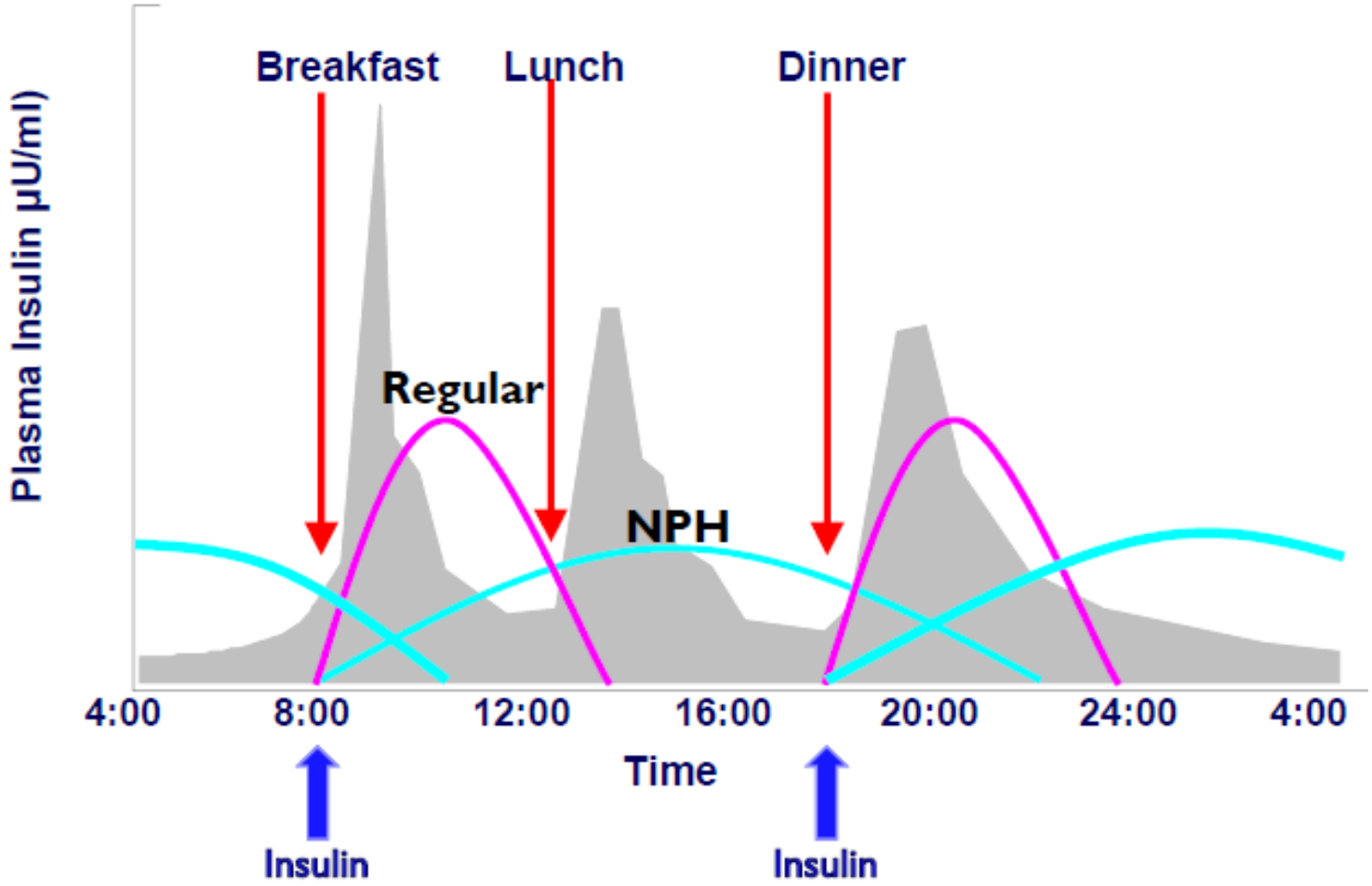


INSULIN REGIMEN

- Twice-daily regimen:
  - This regimen uses a premixed insulin, comprising a short (fast) acting insulin and an intermediate acting insulin.
  - The regular human insulin mixes should be given 30 minutes before breakfast and 30 minutes before evening meal.



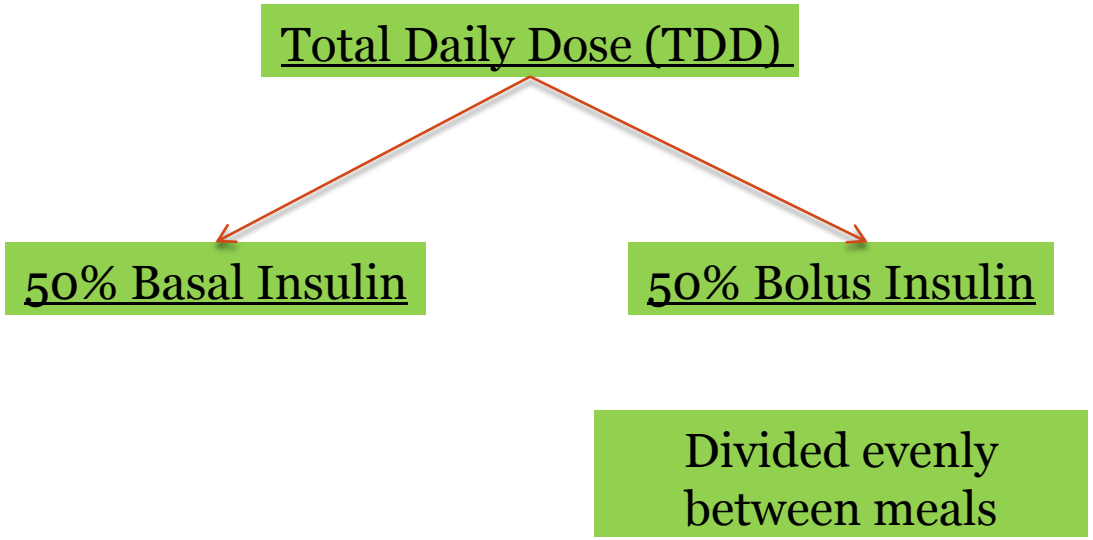
Premixed (NPH and regular)



Adjusting insulin dose

- The patient varies the amount of before meal rapid-acting insulin injected, depending on the preprandial BG level, the anticipated activity and anticipated carbohydrate intake. Many patients start with **a prescribed dose** of insulin before meals that they vary by use of an **"adjusted scale insulin" or "correction factor"** to normalize a high premeal plasma glucose reading.

- In type 1 DM, approximately 50% of total daily insulin replacement should be basal insulin, and the other 50% will be bolus insulin, divided into doses before meals.



Now you try

JT is a 12-year old male with newly diagnosed T1DM (BG=650 mg/dL, Wt=176 lb). He is going to start insulin therapy with insulin glargine and insulin aspart. Use 0.6 units/kg

- What is his estimated total daily dose?
- What is his estimated insulin glargine dose?
- What is his estimated insulin aspart dose?

Now You Try Answers

- **What is his estimated total daily dose?**
  Weight: 176 lb / 2.2 = 80 kg
  TDD: 80 kg (0.6 unit/kg/day) = 48 units

- **What is his estimated insulin glargine dose?**
  Basal dose: 50% of TDD
  Basal dose: 48 units x 0.5 = 24 units
  Insulin glargine 20 units once daily

- **What is his estimated insulin aspart dose?**
  Prandial dose: 50% of TDD, split between 3 meals
  Prandial dose: 48 x 0.5 = 24 units
  Individual prandial dose: 24 units / 3 meals = 8 units
  Insulin aspart 8 units TID 15 min before meals

Correction factor

- A “correction factor” can be calculated as a starting point to estimate the approximate plasma glucose–lowering effect of 1 unit of short-acting insulin in mg/dL.
- For regular insulin, one may use a factor of 1,500 divided by the total daily insulin dose in number of units that the patient currently uses.
- For rapid-acting insulin analogs, a factor of 1,700 is more often used when calculating the correction factor.
- For example, if a patient is currently taking 40 units of basal insulin and 12 units of rapid-acting insulin at each of three meals, the total daily insulin dose (TDD) equals 76 units.
- Using this calculation 1,700 divided by 76 equals 22; thus, each unit of rapid-acting insulin analog will lower the plasma glucose approximately 22 mg/dL.
- Review of follow-up BG data permits better individualization of the correction factor.

Carbohydrate counting (500 rule)

- Carbohydrate counting is a very effective tool for determining the amount of rapid-acting insulin that should be injected preprandially in people with type 1 DM.

- Instead of using a prescribed or preset dose of rapid-acting insulin before meals, patients can self-adjust their premeal dose based on the estimated grams of carbohydrates that will be consumed.

- One method of calculating how much carbohydrate (grams) 1 unit of rapid-acting insulin will cover is to use 500 divided by the total daily dose of insulin in number of units. Therefore, using the example above with a total daily insulin dose of 76 units, we would use 500 divided by 76, which estimates that 1 unit of rapid-acting insulin will cover approximately 7 g of carbohydrate.

- "Rule of 450" for short acting (regular) insulin

- Review of follow-up BG data before and 2 hours after meals will enable more precise determination of an individual's insulin-to-carbohydrate ratio.

Insulin Sensitivity Factor (ISF)

- "Rule of 1800" aka "Insulin Sensitivity Factor"
  - Estimates the drop in blood glucose (mg/dl) per 1 unit of rapid activity insulin

Use "Rule of 1500" for short acting (regular) insulin

- Can be used to calculate a correction dose of insulin

- Rule of 1800 equation
  - 1800 ÷ TDD

- Step 1: Determine the pt's total daily insulin requirement
  - JT's total daily insulin requirement = 48 units

- Step 2: Divide 1800 by total daily insulin requirement
  - 1800 ÷ 48 units = 37.5 units = 37 or 38 units

- Interpretation
  - 1 unit of aspart will reduce JT's blood glucose by roughly 37 mg/dL

- Application
  - He can use this to treat unusually high BGs (i.e. during times of illness etc.)

Determining a Correction Dose

1. Calculate the difference between current BG and goal BG
   - Example: current BG – goal BG = mg/dl reduction needed
     - 180 mg/dl – 90 mg/dl = 90 mg/dl
2. Correction dose = BG difference ÷ ISF
   - 90 mg/dl ÷ 37 mg/dl/unit = 2.4 ≈ 2 units
3. Add correction dose to regularly scheduled insulin dose and inject prior to the meal

- If JT calculated that he needs 8 units to cover his meal, and his pre-meal glucose was 180 he would inject 10 units total to hopefully get back to goal

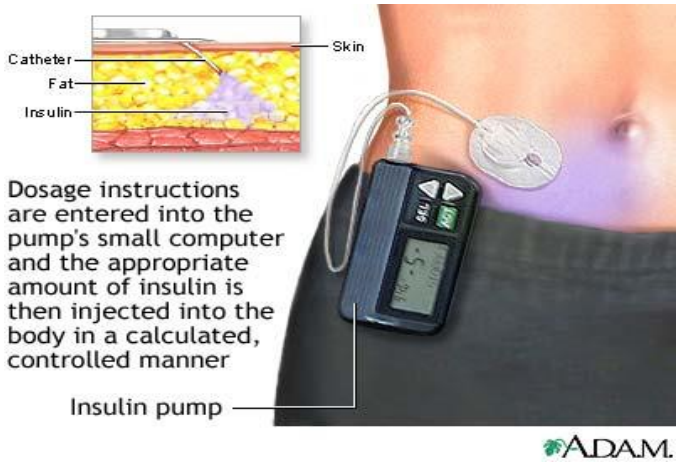
Erratic glucose fluctuations

- There are several common errors in the management of patients with type 1 DM that can cause :
- **Failure to take into account action of insulin**: The timing of meals and/or physical activity must be planned around the peaks of insulin action accordingly.
- **Choice of insulin injection sites**: There is variability of insulin absorption from site to site such that random selection of insulin injection sites may cause wide glucose swings.
- **Overinsulinization**.
- **Injection technique and BG monitoring**: When in doubt, always reevaluate the patient's technique for insulin dosing, insulin injection, and BG testing. Sometimes simple errors result in unpredictable glycemic control.

Insulin Pumps

- Primarily used for T1DM, interest in T2DM
  - Studies have found similar efficacy between basal/bolus & the pump
- Typically use rapid-insulin over regular
  - 50% basal dose; 50% bolus dose
  - Bolus dose adjusted by patient based on SMBG monitoring
- Converting from multi-dose insulin to pump
  - If previously controlled then may reduce TDD by 20%
  - If previously uncontrolled then may use same TDD

V-Go Disposable Pump



Compatibility of Mixtures

Insulin	Compatible	Not Compatible
Aspart	NPH, Regular	Glargine, Detemir
Lispro	NPH, Regular	Glargine, Detemir
Glulisine	NPH, Regular	Glargine, Detemir
Regular	NPH	Glargine, Detemir

Always mix **clear** before **cloudy**

- Always draw rapid or regular insulin first
- Then draw NPH
- NPH will disrupt kinetics of reg. or rapid if gets in vial
- Mixture should be used within 5 minutes of mixing

Insulin Conversions & Max Injection

- Common insulin conversions
  - Rapid ↔ Regular
    - 1:1 ratio
  - Lantus ↔ Levemir
    - 1:1 ratio
  - NPH ↔ Levemir
    - 1:1 ratio
  - NPH once daily ↔ Lantus
    - 1:1 ratio; give once daily
  - NPH twice daily ↔ Lantus
    - 80% of daily NPH dose; give once daily

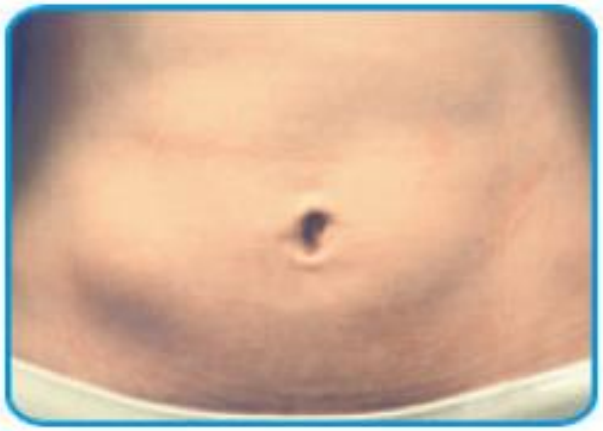
Converting From Mixed Insulin

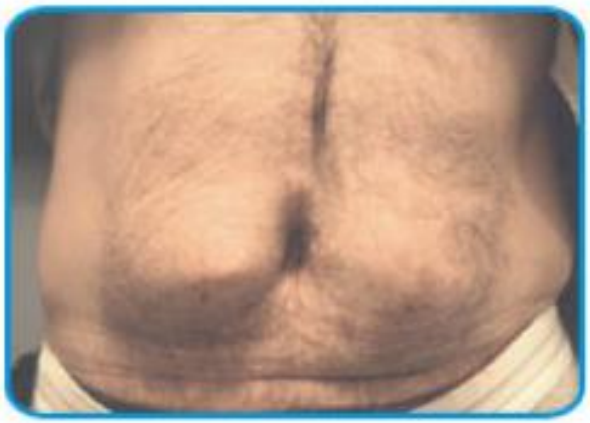
Example:

- Novolin 70/30 (insulin NPH/regular) 40 units qAM and 20 units qPM before meals ➔ insulin detemir and insulin lispro
  - TDD = 60 units
    - NPH dose = 60 (0.7) = 42 units
    - Regular insulin dose = 60 (0.3) = 18 units
  - NPH ↔ detemir (1:1)
    - 42 units NPH = 42 units insulin detemir
    - Inject 42 units insulin detemir once daily
  - Regular ↔ rapid (1:1)
    - 18 units regular = 18 units rapid
    - Rapid = TID dosing; 18/3 = 6
    - Inject 6 units insulin lispro TID 15 min before meals

Insulin Adverse Effects

- Hypoglycemia
  - Most serious adverse effect
  - Patients must be educated about hypoglycemic symptoms
- Weight gain
  - Now utilizing nutrients
- Injection site pain
- Lipohypertrophy (avoided by site rotation)





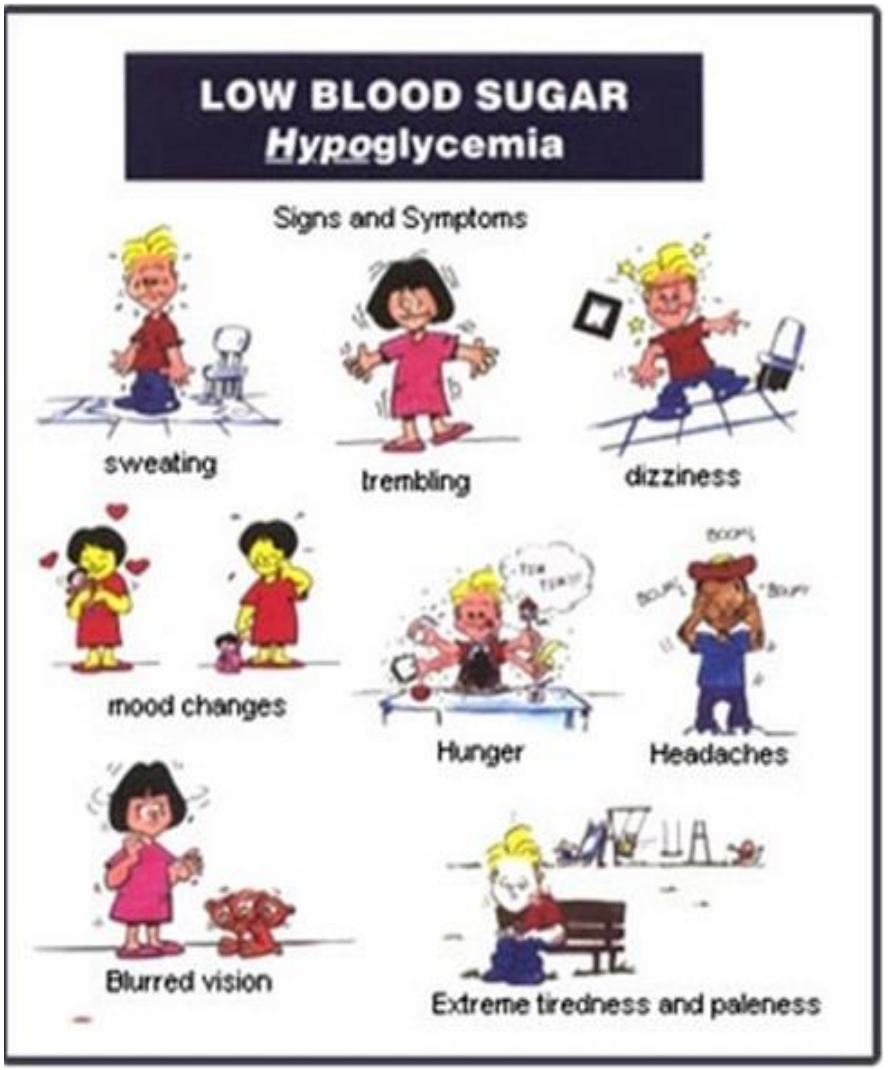
DIABETIC EMERGENCIES

- **HYPOGLYCEMIA:**
  - It occurs both with insulin treatment and oral agents, especially the longer acting sulphonylureas (chlorpropamide and glibenclamide).
  - Hypoglycemia in DM is defined as a blood sugar level of 70mg/dl
  - Sweating, trembling, tachycardia, drowsiness, confusion, loss of concentration headache and coma are the symptoms.
  - If occur take glucose tablet of carbohydrate juice. if unconcious Iv dextrose or Glucagon vial1 to 2 milligrams of glucagon in an intramuscular injection
  - Prevnention of the causetive factor for hypoglycemia like heavy activity, no eating

DIABETIC EMERGENCIES

- If the patient is not aware of hypoglycemia, blood glucose levels may drop further causing neuroglycopenic syndrome, in which the brain is starved of glucose may lead to death.

- Often the patient is confused and may not be able to control the hypoglycemia without assistance.



Diabetic Ketoacidosis

- Diabetic ketoacidosis is true diabetic emergencies.
- The absence of insulin in type 1 DM causes increased free fatty acid concentration in the blood and glucose is produced by the liver by gluconeogenesis.
- Ketone bodies (acetone, acetoacetate ester and hydroxybutyrate) are formed in an increased amount and released in the blood.
- Furthermore, osmotic diuresis is increased due to hyperglycemia, low plasma volume, loss of potassium occur.

Diabetic Ketoacidosis

- Vomiting, dehydration, deep gasping breathing (kussmaul respiration), confusion and occasionally coma are typical symptoms

- Impaired consciousness and coma developed in 10% of patients.

Diagnosis :

Added to hyperglycemia, ketones in the blood or on urinalysis and acidosis are demonstrated.

- **Treatment :**

1-Fluid replacement:

  - Fluid volume expansion (initially with 0.9% NaCl) to correct dehydration (specially if with shock or decrease of conciousness). rapid infusion of saline (1 liter for adults, 10 ml/kg in repeated doses for children) is recommended to restore circulating volume

Diabetic Ketoacidosis

2-Insulin:

a bolus (initial large dose) of insulin of 0.1 unit of insulin per kilogram of body weight. This can be administered immediately after the potassium level is known to be higher than 3.3 mmol/l; if the level is any lower, administering insulin could lead to a dangerously low potassium level (see below).

It is possible to use rapid acting insulin analogs injections under the skin for mild or moderate cases

In general, insulin is given at 0.1 unit/kg per hour to reduce the blood sugars and suppress ketone production.

3-Hypokalemia prevention:

measurement of the potassium levels and addition of potassium to the intravenous fluids once levels fall below 5.3 mmol/l. If potassium levels fall below 3.3 mmol/l, insulin administration may need to be interrupted to allow correction of the hypokalemia

LONG TERM DIABETIC COMPLICATIONS

- **1-MACROVASCULAR DISEASES**
- CARDIOVASCULAR DISEASE:
  - The most common cause of death in type 2 DM is CVD (estimated 80% death)
  - Most of the patients with type 2 DM are affected by MI.
  - Cerebrovascular disease is also more commonly associated with diabetes.
- HYPERTENSION:
  - HTN is twice as common in diabetics compared to the normal population.
  - It affects 80% of type 2 diabetic patients.

MICROVASCULAR DISEASES

- RETINOPATHY:
  - Diabetic retinopathy is a leading cause of blindness in people under the age of 60.
  - After 20 years from the onset of DM over 90% of people with type 1 and over 60% of people with type 2 will have diabetic retinopathy.
  - Tight glycemic control and tight blood pressure control reduce the risk of developing retinopathy.

MICROVASCULAR DISEASES

- NEPHROPATHY:
  - Nephropathy affects most of the type 1 and type 2 diabetic patients.
  - The presence of nephropathy is indicated by Microalbuminuria.
  - Proteinuria signifies the more severe renal damage.
  - Tight control of both glycemic levels and blood pressure reduces the risk of nephropathy.

MICROVASCULAR DISEASES

- DIABETIC FOOT:
  - Infected diabetic foot ulcers are the leading cause of amputations.
  - There are three kinds of foot ulcers: Neuropathic, ischaemic and Neuroischaemic.
  - Neuropathic ulcers occur when peripheral peripheral neuropathy causes loss of pain sensation.
  - Ischaemic ulcers result from peripheral vascular disease and poor blood supply causing reduction in available nutrients and oxygen required for healing.

Why are doctors so concerned about your feet?

- A foot problem can be very difficult to heal once it has set in.
- Diabetics are also prone to infection because the feet are almost 'out of sight and out of mind' and problems can develop without your being aware of them.

What type of problems occur?

- Pressure sores can develop on the soles of your feet from things such as corns, calluses or nails in your shoes.
- Minor injuries such as cuts and splinters can become a major problem through poor healing.
- Problems with toenails such as *paronychia* (infection around the nail) and ingrowing nails can get out of control.
- Prevention of these problems is the best way.

What should the patient do?

1. Check your feet *daily*. Report any sores, infection or unusual signs. Make sure you check between the toes.
2. Wash your feet daily:
    1. Use lukewarm water (beware of scalds).
    2. Dry thoroughly, especially between the toes.
    3. Soften dry skin, especially around the heels, with lanoline.
3. Attend to your toenails regularly:
    1. Clip them straight across.
    2. Do not cut them deep into corners or too short across.
4. Wear clean cotton or wool socks daily; avoid socks with elastic tops.
5. Exercise your feet each day to help the circulation in them.

How to avoid injury

- Wear good-fitting, comfortable leather shoes.
- The shoes must not be too tight or too loose.
- Do not walk barefoot, especially out of doors.
- Do not cut your own toenails if you have difficulty reaching them or have poor eyesight.
- Avoid home treatments and corn pads that contain acid.
- Be careful when you walk around the garden and in the home.
- Do not use hot-water bottles or heating pads on your feet.
- Take extra care when sitting in front of an open fire or heater.

MANAGEMENT OF TYPE 2 DM

- Diet, exercise, oral medication, and insulin are the cornerstones of type 2 diabetes treatment.

Treatment Guidelines:

- Considerations: Agent Related
- Considerations: patient Related

Considerations: Agent Related

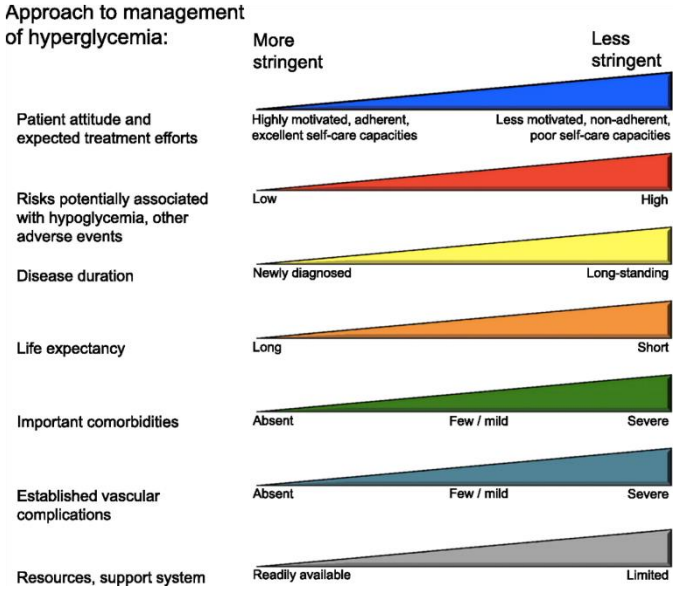
- Degree of A1c-lowering needed to reach goal
- Reduction of complications
  - Microvascular
  - Macrovascular
- Side effect profile
- Route of administration
- Cost
- Target blood glucose
  - Fasting
  - Postprandial
  - Both?

- **S**afety
- **T**olerability
- **E**fficacy
- **P**rice
- **S**implicity

Considerations: Patient Related

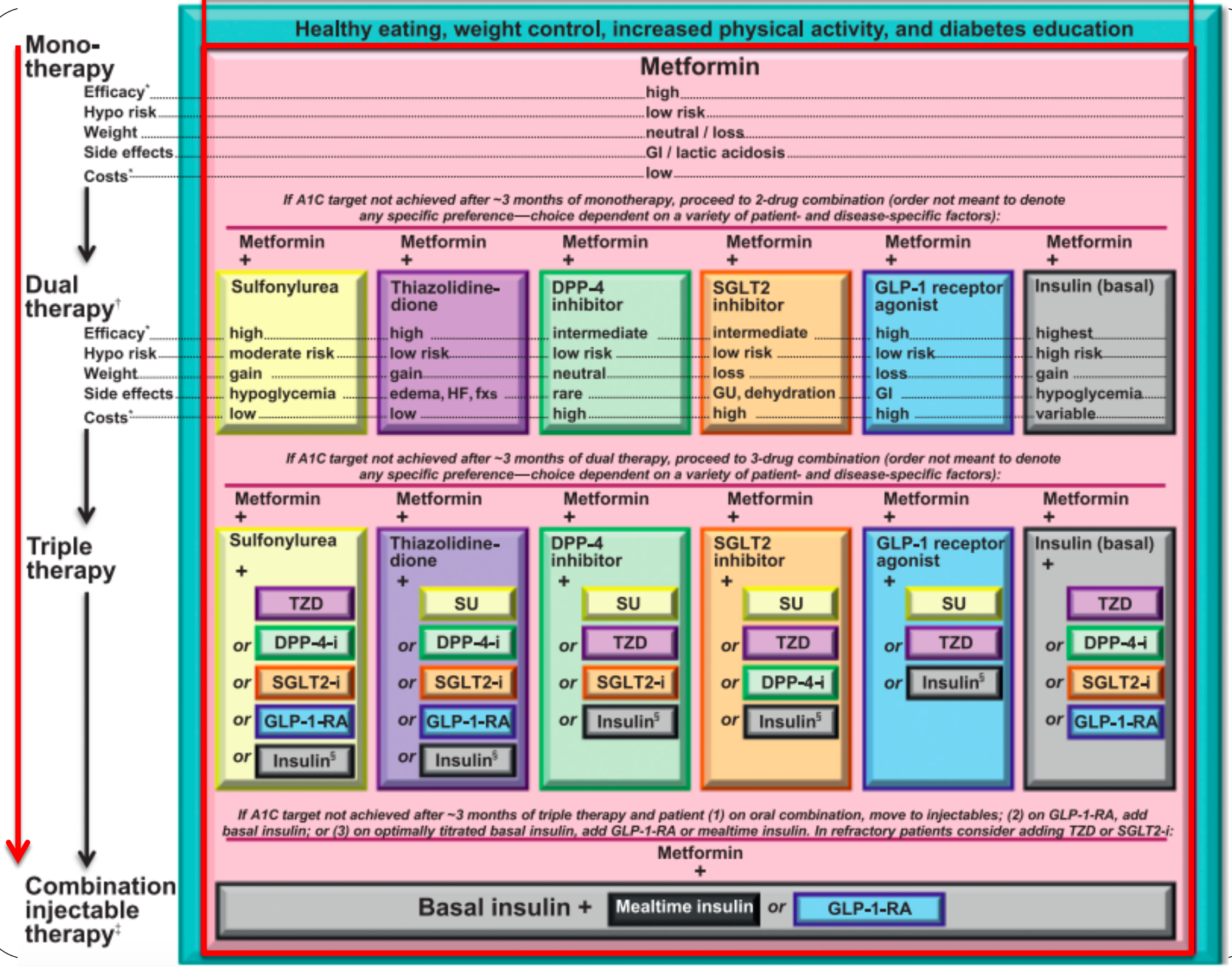
Take a patient-centered approach!

- Age
- Social history
- Renal function
- Liver function
- Allergies/intolerances
- Comorbidities
  - Microvascular complications
  - Macrovascular complications
- Goals
- Level of understanding/willingness to participate



Antihyperglycemic Medications

- Insulin Sensitizers
  - Biguanides
  - Thiazolidinediones
- Insulin Secretagogues
  - Sulfonylureas
  - Meglitinides
- Incretin-based therapy
  - GLP1 agonists
  - DPP-4 Inhibitors
- Glucose absorption inhibitors
  - SGLT2 inhibitor
- Other agents
  - Alpha-glucosidase inhibitor
  - Amylin agonist
  - Bile acid sequestrant
  - Dopamine agonist
- Insulin
  - Review tomorrow


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin
high
low risk
neutral / loss
GI / lactic acidosis
low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin + Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Metformin

- Biguanides (metformin) stimulates the tissue uptake of glucose, particularly in muscles and reduces the GI absorption of carbohydrate.
- It also decreases the production of glucose by the liver (gluconeogenesis and glycogenolysis)
- The action of metformin does not involve the stimulation of pancreatic insulin secretion and therefore it is beneficial agent when beta cell function has declined.
- It's another advantage is it doesn't cause hypoglycemia and weight gain.
- Metformin has a short duration of action with a half-life of between 1.3 and 4.5 hours.

BIGUANIDES

- A suggested regimen is to start with 500 mg twice daily for 1 week, increasing the dose at weekly intervals until the desired glycemic is achieved.
- The maximum licensed dose is 3g per day but doses of more than 2g per day may cause intolerance.
- Level of impact
  - A1c: 1.5-2% reduction
  - **FPG: ↓ 60-80 mg/dl**
  - Weight loss (2-5 kg)
  - Lipid improvement: ↓ LDL ~8%, ↓ TG ~16%, ↑ ~2% HDL
  - Reduction in micro- and macrovascular complications
  - Reduced all-cause mortality in obese patients
  - First-line optimal agent!!!!

  - Pre-diabetes
  - Children ≥ 10 years old

Biguanide: Metformin

- Adverse Effects
  - Primarily gastrointestinal (more with IR formulation)
    - Diarrhea most common (53%)
    - N/V
    - Metallic taste
    - Interferes with B12 absorption
    - Lactic acidosis (BBW, rare, very fatal)
  - **Low hypoglycemia risk**

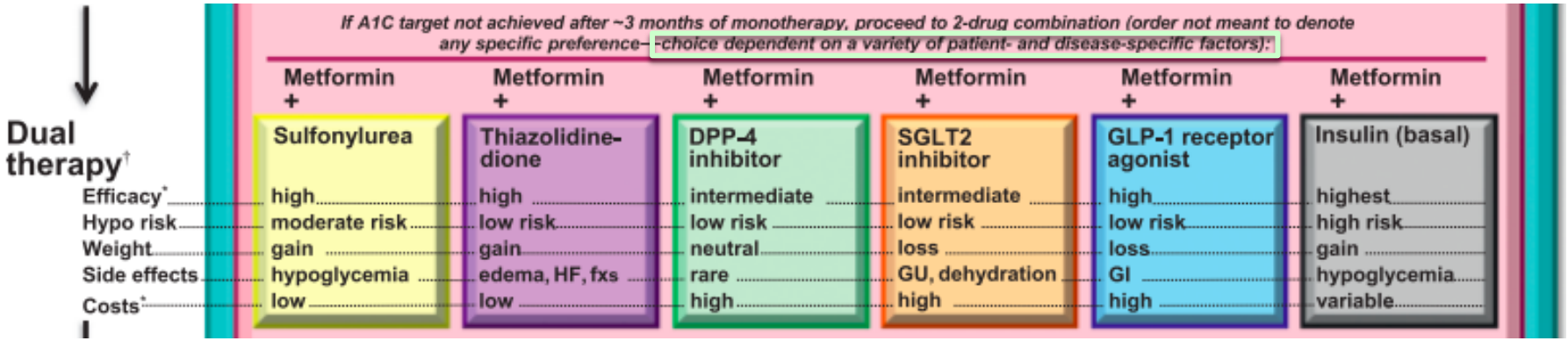
- Contraindications
  - SCr: $\geq$ 1.5 males, $\geq$ 1.4 females
  - History of lactic acidosis

Metformin & Renal Concerns

- ADA has proposed recommendations based on GFR versus SCr
  - GFR ≥60 ml/min: No contraindication
  - GFR ≥45 - <60 ml/min: Continue use, monitor every 3-6 months
  - GFR ≥30 - <45 ml/min: 50% dose reduction, monitor every 3 months
  - GFR < 30 ml/min: Do not use

- Metformin should still be avoided if risk for sudden renal deterioration

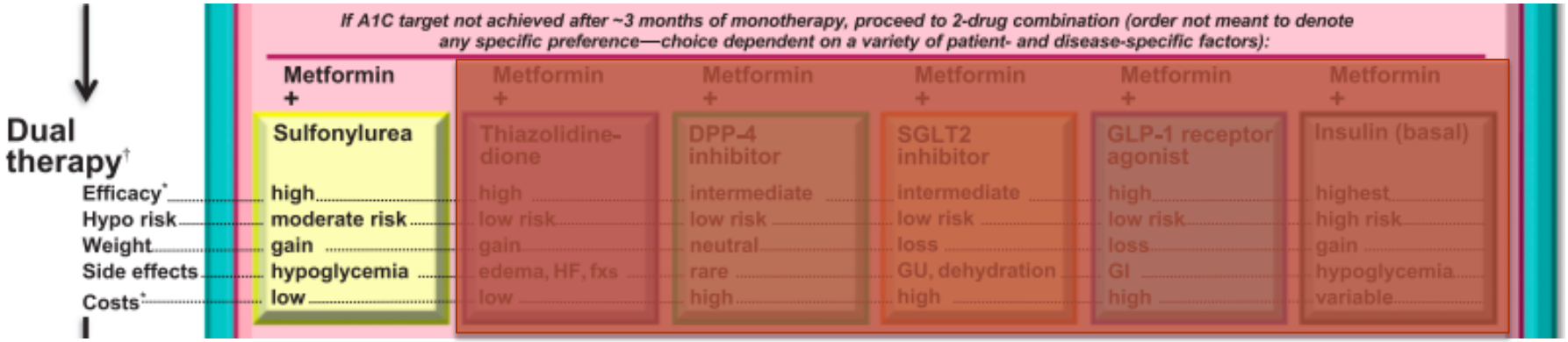
Dual therapy



-choice dependent on a variety of patient- and disease-specific factors):

The addition of a second agent will reduce the A1c by an average of 0.9-1.1%

Sulfonylureas



- 1st Generation
  - Tolbutamide (Orinase)
  - Chloropropamide (Diabinese)
  - Tolazemide (Tolinase)

Rarely Used

- 2nd Generation
  - Glimepiride (Amaryl)
  - Glipizide (Glucotrol)
  - Glyburide (Diabeta, Micronase)

Most Common

2nd gen: More potent, improved kinetics, decreased side effects

SULFONYLUREAS

- Sulphonylureas lower blood glucose level by increasing the β-cell sensitivity to glucose, allowing more insulin to be released from the beta cells.
- It also increases the tissue sensitivity to insulin.
- Treatment should be started with a low dose and be increased if necessary.
- The dose should be taken before meals 30 min rather than with food and after food.

SULFONYLUREAS

- Level of Impact
  - A1c reduction: 1.5-2%
  - **PPG: ↓ 90 mg/dl**; FPG: 50-70 mg/dl
  - Reduction of microvascular complications
  - Weight gain (1-3 kg)
- Indication: Type 2 Diabetes
  - Typically first choice for combination with metformin
  - Initial therapy/monotherapy if intolerant/contraindicated to metformin
- Second most commonly prescribed combination agent, 60-75% patient respond

SULFONYLUREAS

Adverse Effects

- Hypoglycemia
- Weight gain
- Rash/pruritus (sulfa allergy).
- Hemolytic anemia

Precautions

Severe renal/hepatic impairment
Severe acute illness (surgery, infection, trauma)

Concepts:

•Explain importance of NOT skipping meals, 1st daily dose taken with first meal and (depending on agent) 2nd daily dose taken with dinner.

•Explain that if first dose is missed the next dose should NOT be doubled!

MEGLITINIDES

- Meglitinides (Repaglinide and Nateglinide) are insulin releasing agents (secretagogues).
- The mode of action is same as sulphonylureas (considred short acting sulfonylureas)
- The recommended starting dose is 0.5 mg before or with each meal, increasing as necessary to a maximum single dose of 4mg and maximum daily dose of 16mg per day.
- They are beneficial in patients who experience problems with postprandial glucose elevation and as a single therapy in patients who eat at unpredictable times or tendency to miss meals.

MEGLITINIDES

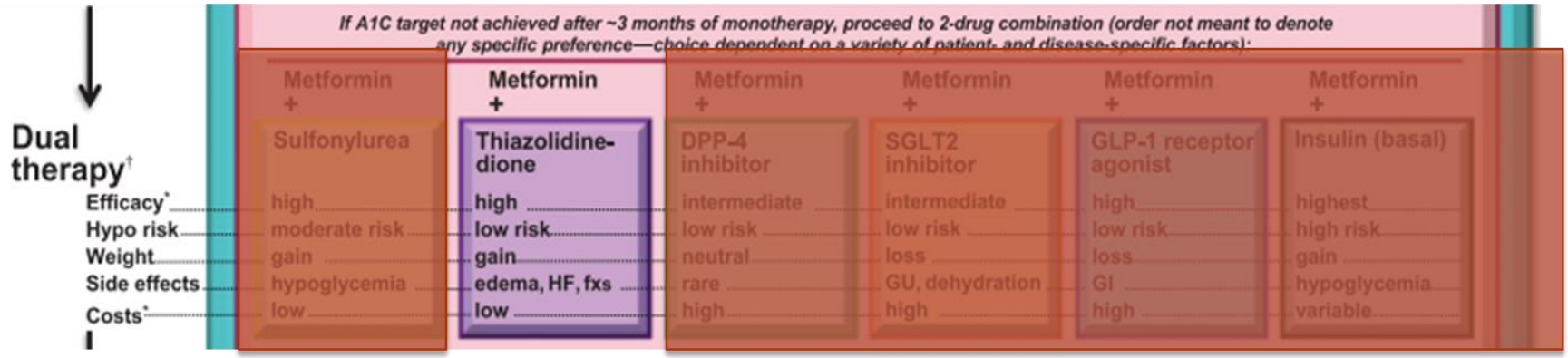
- Level of Impact
  - A1c Reduction: 0.7-1.5%
  - **Reduce PPG** more than FPG
  - Weight gain
  - **Useful for those with irregular eating schedules or who get postprandial hypoglycemia with sulfonylurea**
    - Fast onset ~45 mins, short duration ~ 3-4 hours
- Indication: Type 2 Diabetes
  - Combination with metformin, particularly if unable to take SUs
  - Monotherapy if metformin is ineffective.

MEGLITINIDES

- **Dosing**
  - **Nateglinide (Starlix©)**
    - Starting dose/max: 120 mg PO TID, 1-15 minutes before meals
      - More rapid and shorter duration
  - **Repaglinide (Prandin©)**
    - A1C <8%: 0.5 mg PO TID, 1-15 minutes before meals
    - A1C >8%: 1-2 mg PO TID, 1-15 minutes before meals
      - Max dose: 4 mg/dose up to 16 mg/day
    - More potent
    - May take extra dose if have extra meal
- **Adverse Effects**
  - Hypoglycemia (less than SU) and Weight gain
- Precautions
  - CYP450 modulators
  - Not effective if previously failed an SU and

THIAZOLIDINEDIONES

- They are otherwise called as glitazones.
- Two glitazones are currently available, pioglitazone and roziglitazone.
- These agents lower fasting and postprandial glucose levels and free fatty acid concentration.
- They enhance the insulin sensitivity and promote glucose uptake by the peripheral tissues.
- They suppress the gluconeogenesis in the liver.



Thiazolidinediones (TZD)

- Level of impact
  - A1c reduction: 1-1.5%
  - **FPG: ↓60-70 mg/dl,** modest ↓PPG
  - Lipid benefits
  - Low hypoglycemia risk
  - Reduction in microvascular complications
  - May preserve beta cell function

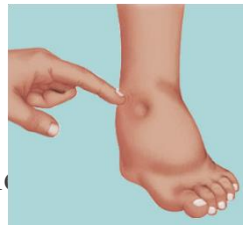
- Indication: Type 2 diabetes
  - Monotherapy if unable to tolerate/fail metformin or SU
  - Combinations

Thiazolidinediones (TZD)

- Adverse Effects
  - Edema➔weight gain
  - HF exacerbation
  - Increased LFTs
  - Hematologic effects
  - Bone fractures
    - Ca. and vit. D
- Bladder cancer (pioglit.)

Precautions

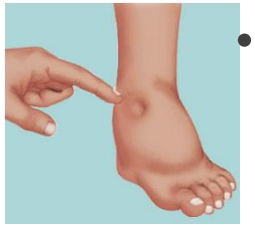
- CHF
- Hepatic impairm
- Anemic patients
- CYP 2C8 modulators



- Dosing
  - Pioglitazone (Actos©)
    - Starting dose: 15 mg PO once daily
    - Max dose: 45 mg / day
    - ↓TG & ↑HDL
  - Rosiglitazone (Avandia©)
    - Starting dose: 2-4 mg PO once daily
    - Max dose: 8 mg / day or 4 mg BID
    - ↑LDL
  - Delay to full onset of 8-12 weeks
  - wait the 8-12 weeks before considering dosage adjustments

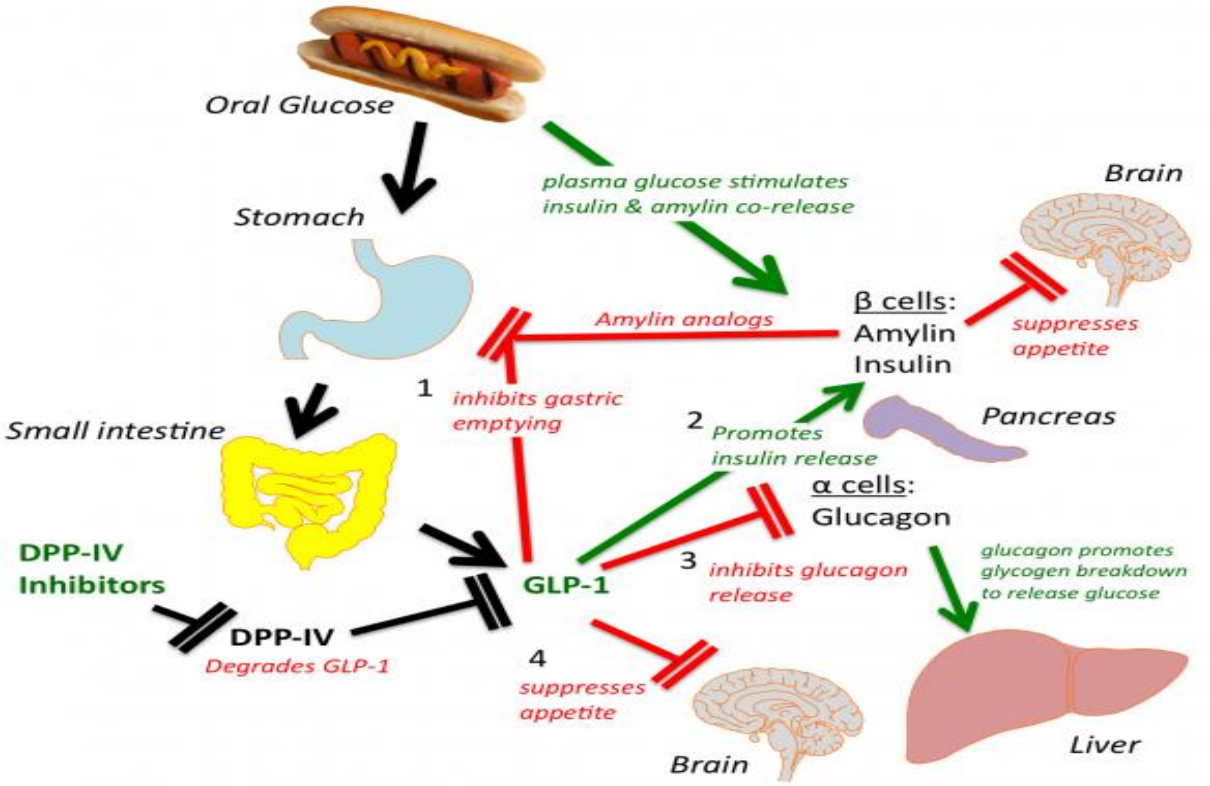
Thiazolidinediones (TZD)

- Adverse Effects
  - Edema➔weight gain
  - HF exacerbation
  - Increased LFTs
  - Hematologic effects
  - Bone fractures
    - Ca. and vit. D
  - Bladder cancer (pioglit.)



- Precautions
  - CHF
  - Hepatic impairment
  - Anemic patients
  - CYP 2C8 modulators

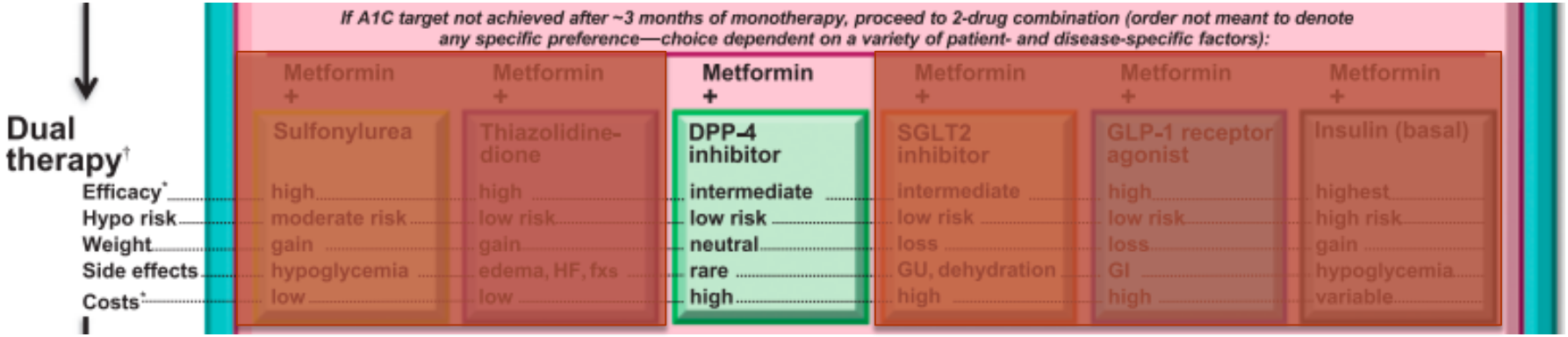
The Incretins



Approaches to addressing incretin deficiency

1. Inhibit inactivation (incretin enhancers)
2. Longer acting analogs (incretin mimetics)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors



Incretin-Based Therapy

"The gliptins"

Sitagliptin (Januvia)

Saxaglipitin (Onglyza)

Linagliptin (Tradjenta)

Aloglipitin (Nesina)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- MOA: inhibit the enzyme DPP-4 that degrades the incretin hormones GLP-1 and GIP → ↑insulin synthesis and release from β-cells and ↓glucagon secretion from α-cells.
  - Glucose dependent
- Level of impact
  - A1c reduction: 0.7-1% (some question efficacy)
  - FPG: ↓12-15 mg/dl, **PPG: ↓45 mg/dl**
  - Weight neutral
  - Low hypoglycemia risk
  - Can be used in renal & hepatic impairment with adjustments

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

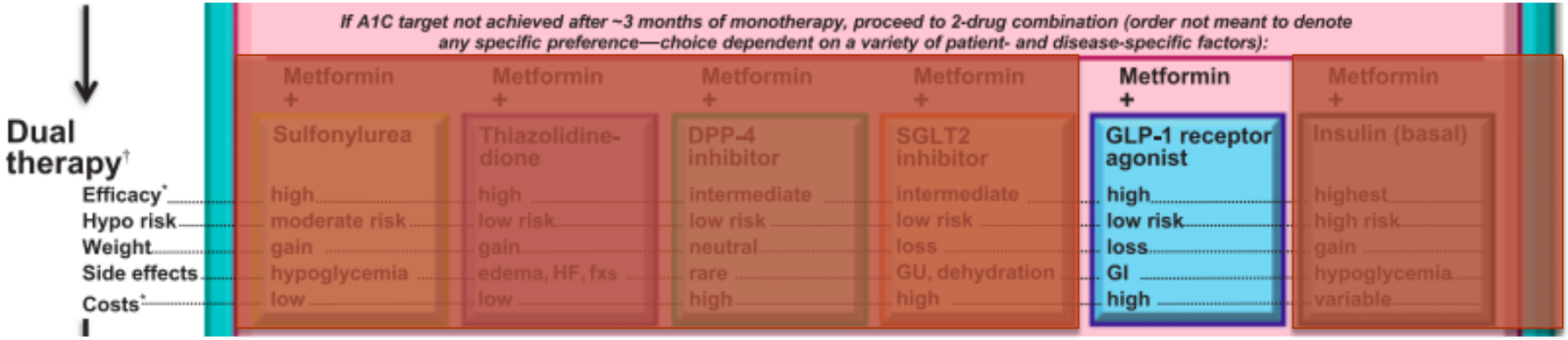
- Indication: Type 2 Diabetes
  - Combination with metformin or other agents
  - Monotherapy if intolerant to other agents

- Adverse Effects
  - Headache
  - Severe joint pain
  - Urinary tract infection
  - Upper resp. infection
  - Acute pancreatitis
  - Hypersensitivity.

- Contraindications
  - Hypersensitive to agent
  - DKA

- Precautions
  - History of pancreatitis
  - Renal impairment
  - CYP 3A4 modulators

Glucagon-Like Peptide (GLP-1) Receptor Agonists



Glucagon-Like Peptide (GLP-1) Receptor Agonists

- MOA: mimic GLP-1, hormone responsible for↑insulin secretion; ↓glucagon secretion, ↓gastric emptying; improves satiety ➔ ↓food intake
  - Glucose dependent insulin secretion
- Level of Impact
  - A1c reduction: 0.8-1.1%
  - FPG: ↓8-20 mg/dl, **PPG:↓60-70 mg/dl**
    - Both with longer agents
  - Weight loss (~3 kg)
  - Low hypoglycemia risk
  - Some BP reduction
  - May have some beta-cell preservation

Glucagon-Like Peptide (GLP-1) Receptor Agonists

- Indication: Type 2 Diabetes
  - Monotherapy or in combination with metformin and other agents
- Dosing
  - Exenatide (Byetta©): 1-60 min before 2 main meals
    - Starting dose: 5 mcg SC BID x 1 month
    - Max dose: 10 mcg BID
  - Exenatide (Bydureon©)
    - 2 mg SC q week
      - Start see effects around 2 weeks, max effect around 10 weeks
  - Liraglutide (Victoza©)
    - Starting dose: 0.6 mg SC qday x 1 week, increase by 0.6 mg weekly
    - Max dose: 1.8 mg SC q day

- New long-acting (once weekly agents)
  - albiglutide (Tanzeum)
  - dulaglutide (Trulicity)

- May need to reduce dose of insulin secretagogues if used in combo

Glucagon-Like Peptide (GLP-1) Receptor Agonists

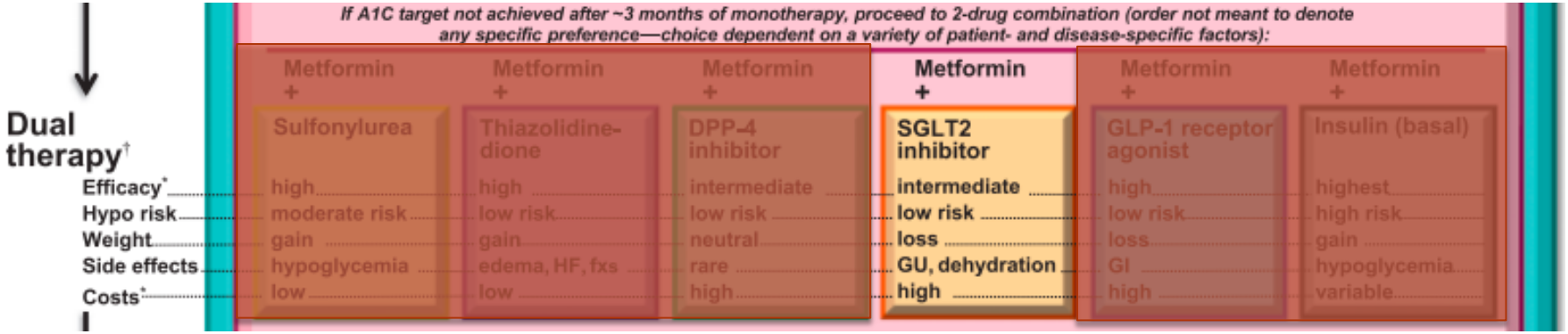
- **Adverse Effects**
  - GI discomfort (N/V/D)
  - Acute pancreatitis
  - Injection site reactions
  - Thyroid carcinoma

Contraindications

- History of thyroid cancer
- Severe renal impairment, CrCl: <30 ml/min (exenatide)
- End-stage renal disease
- Dialysis

- Precautions
  - History of pancreatitis
  - Gastroparesis
  - Impaired oral drug absorption (ABX, COC)
    - At least 1 hour prior
  - Warfarin use

Sodium Glucose Co-transporter 2 Inhibitors



The SGLT2's

Canagliflozin (Invokana)

Dapagliflozin (Forxiga)

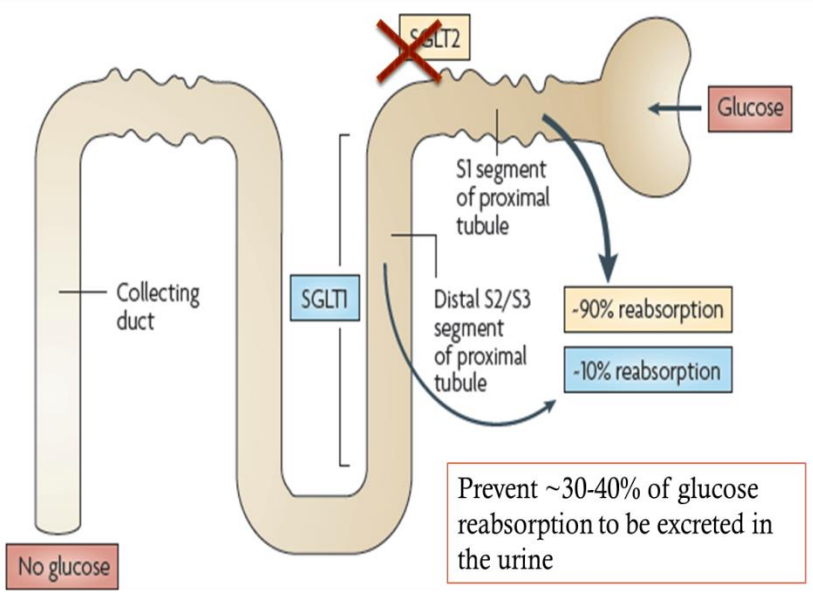
Empagliflozin (Jardiance)

SGLT2 Inhibitors

- MOA: ↑glucose excretion by inhibiting sodium glucose co-transporter 2 (SGLT-2) receptor in proximal convoluted tubule, lowering renal threshold for glucose
  - Not dependent on beta-cell function or insulin level
    - Insulin independent

- Level of impact
  - A1c reduction: 0.8-1%
  - FPG:↓10 mg/dl, PPG:↓50 mg/dl
  - Weight loss
  - Low hypoglycemia risk
  - May reduce blood pressure

- Indication: Type 2 Diabetes
  - Combination with metformin or other agents
  - Monotherapy if intolerant to other agents



Drug	Starting Dose	Max Dose	Renal Dosing
Canagliflozin (Invokana©)	100 mg	300 mg	Avoid if CrCl <45 ml/min
Dapagliflozin (Forxiga©)	5 mg	10 mg	Avoid if CrCl <60 ml/min
Empagliflozin (Jardiance©)	10 mg	25 mg	Avoid if CrCl <45 ml/min

- Adverse Effects
  - Genital mycotic infections
  - Urinary tract infections
  - Polyuria/Dehydration
    - Electrolyte concerns
  - Hypotension
  - Ketoacidosis
  - Bone fractures

- Contraindications
  - Severe renal impairment
  - End-stage renal disease
  - Dialysis

Other Agents

- Alpha-glucosidase Inhibitor
- Amylin agonist
- Bile Acid Sequestrants
- Dopamine agonists

These tend to be used less frequently due to modest efficacy, frequency of administration and/or adverse effects

α-GLUCOSIDASE INHIBITORS

- MOA: inhibit α-glucosidase enzymes to slow the rate of digestion of complex carbohydrates
  - Less glucose is absorbed as carbs are not converted to glucose
  - It may elevate the hepatic transaminase levels. If so, reduction in dose or withdrawal of therapy is considered.

- Level of Impact
  - A1c reduction: ~0.5%
  - Targets **PPG ↓40-50 mg/dl**
  - Little effect on FPG
  - Weight neutral

- Dosing
  - Acarbose (Precose) & Miglitol (Glyset)
    - Starting dose is 25 mg with first bite of each meal (TID)
    - Increase by 25 mg/meal every 4-8 weeks
    - Max doses: 50 mg/meal if <60 kg, 100 mg/meal if >60 kg

Alpha-glucosidase Inhibitors

- Adverse Effects
  - GI side effects
    - Flatulence, bloating
  - Hypoglycemia (in combo)

- Contraindications
  - Inflammatory bowel
  - Colonic ulceration
  - Intestinal obstruction
  - Cirrhosis (acarbose)

- Precautions
  - Hepatic impairment
  - Severe renal impairment
    - SCr >2 mg/dl
  - Concomitant administration of drugs

Amylin Agonist

- MOA: Activated amylin receptor↓glucagon production, slows gastric emptying, ↑satiety
  - Used in patients currently treated with insulin but failed to reach goal
  - Amylinomimetic
  - Does not promote insulin secretion which is different from incretins.
  -
- **Level of Impact**
  - A1c reduction: ~0.5%
  - **Targets PPG**
  - Weight loss
- **Dosing: Pramlintide (Symlin®)**
  - T1D: 15 mcg prior to meals, titrate 15 mcg q3day to 60 mcg
  - T2D: 60 mcg prior to meals, titrated up to 120 mcg after 3 days
    - Need to reduce prandial insulin dose by 30-50% when starting, or delay administration until blood glucose begins to rise (~3 hours)

Amylin Agonist

- Adverse Effects
  - Hypoglycemia when given in 3 hours of insulin intake (BBW)
  - N/V (>120 mcg dose)
  - Lack of appetite
  - Abdominal pain
- Contraindications
  - Gastroparesis
  - Hypoglycemia unawareness
- Precautions
  - Meds that require rapid absorption (ABX, COC)
  - Do not mix with insulin
  - A1c >9%

Bile Acid Sequestrants: Colesevelam (Welchol)

- MOA: Binds bile acids in intestine, increases bile acid production
  - Glucose reduction mechanism unclear
- Level of Impact
  - A1c Reduction: 0.3-0.4%
  - **FPG: ↓5-10 mg/dl**
  - LDL-C: ↓12-16%
  - ↑TG (~5%)
    - More SU's or insulin
  - Not routinely used in T2DM

- Dosing
  - 6-625mg tablets daily, or 3.75 g oral suspension
    - Should be given with meals to bind to bile released during meal

Dopamine Agonists: Bromocriptine

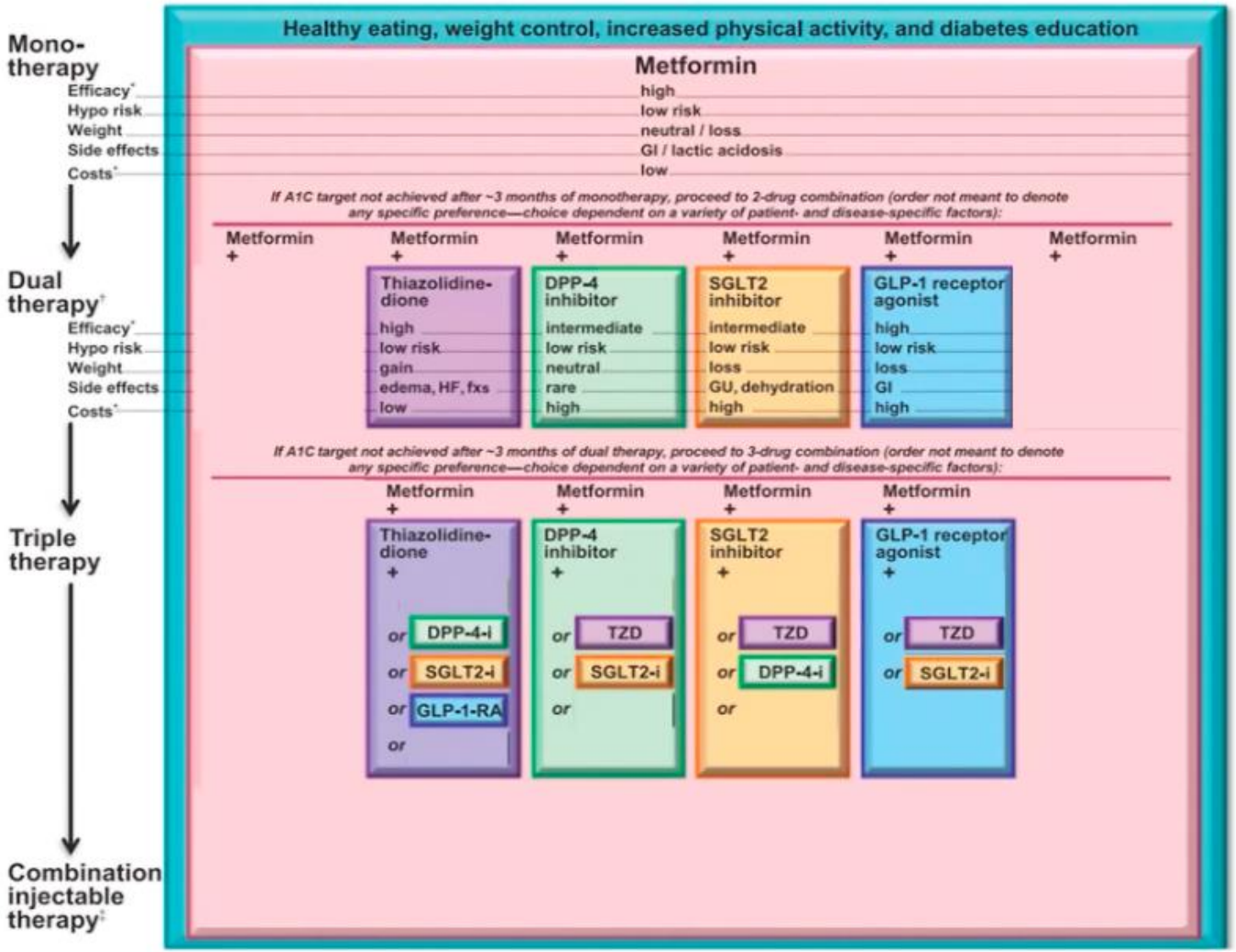
- MOA: Unknown
  - ↑insulin sensitivity ??
- Level of Impact
  - A1c reduction: 0.3-0.4%
- Dosing
  - 1.6-4.8 mg taken within 2 hours of waking with food
  - Supplied in 0.8 mg tablets
  - Other formulations available but not studied in DM

What are we striving for?

- Priority Number 1: Always trying to reach glycemic goal
  - Selecting the agent that is most likely going to get there
  - Reduce complications
  - Improve quality of life

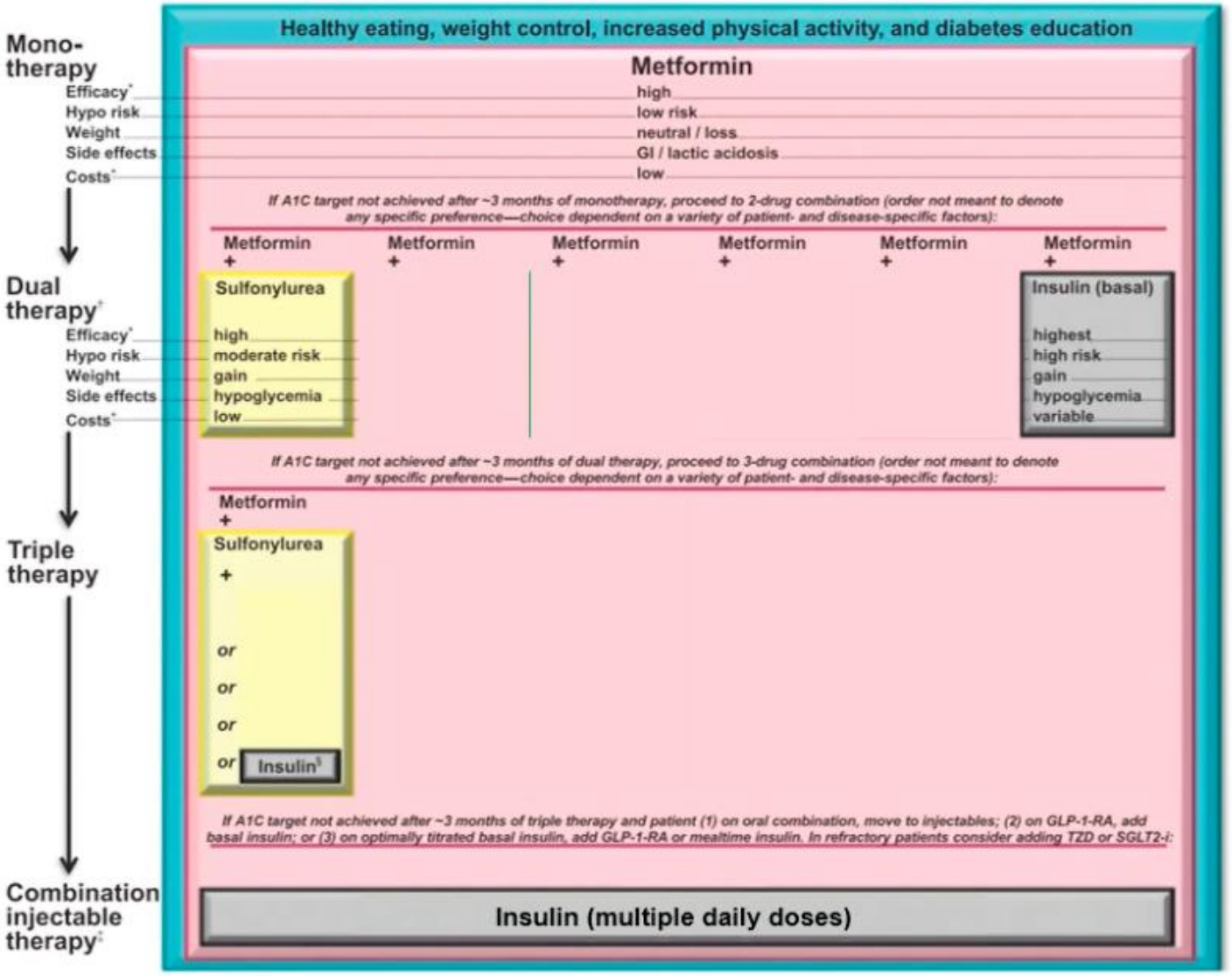
- Priority Number 2: Need to keep a patient centered approach
  - Age
  - Weight
  - Comorbid Condition

If Goal is to Avoid (elderly) Hypoglycemia



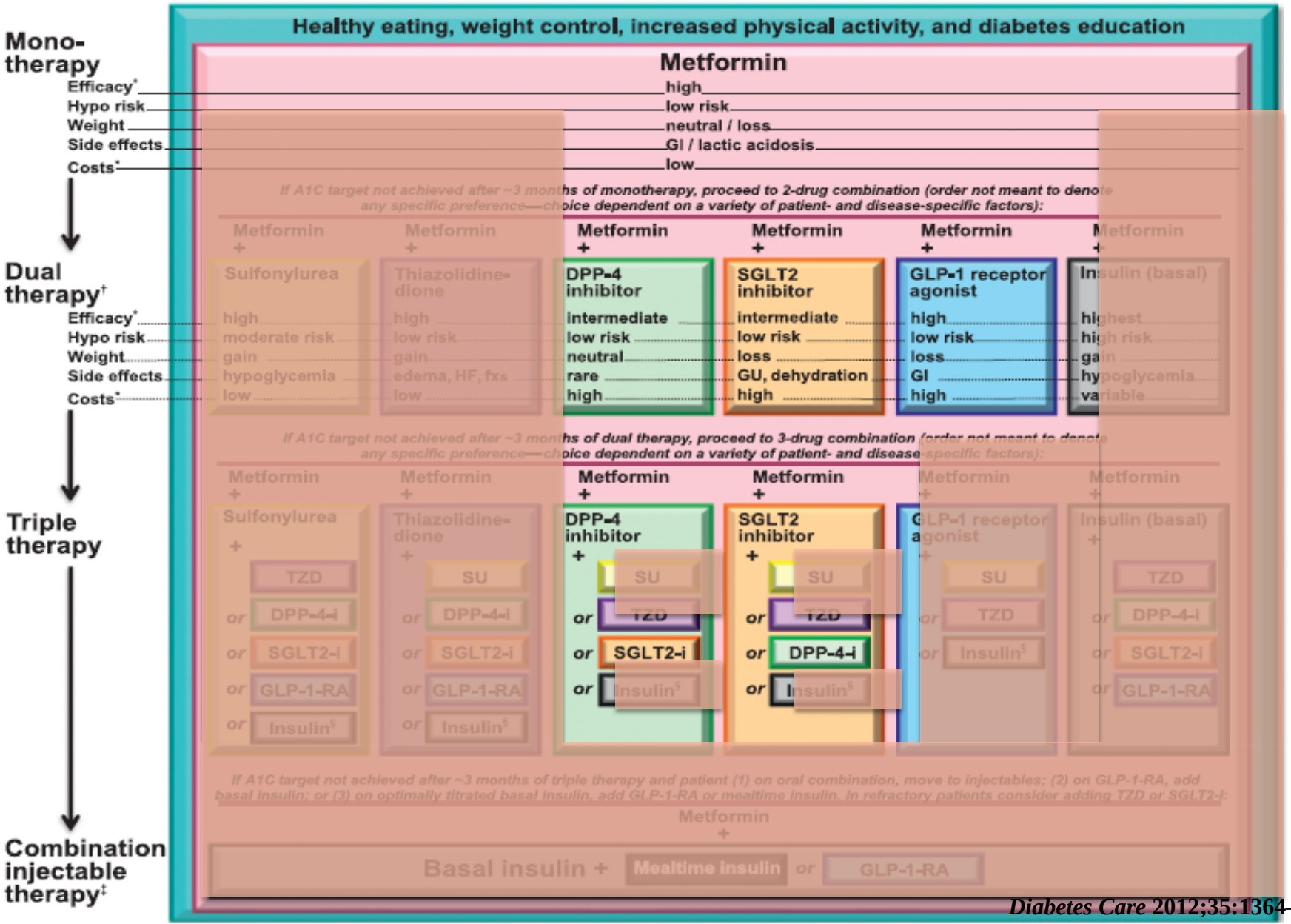
Diabetes Care 2012;35:1364–1379

If Goal is to Minimize Cost



Diabetes Care 2012;35:1364–1379

Agents to consider if weight is an issue



Diabetes Care 2012;35:1364–1379

Patient Factors: Comorbidities

- Coronary Disease ---------->
- Heart Failure ---------->
- Renal disease ---------->
- Liver dysfunction ---------->
- Hypoglycemia ---------->

Basis Concepts of T2DM Pharmacotherapy

- Glycemic targets & BG-lowering therapies must be individualized
- Diet, exercise, & education are the foundation of any T2DM treatment program
- Metformin is optimal 1st-line agent unless contraindicated
- After metformin, combination therapy with 1-2 oral or injectable agents is appropriate
- Ultimately, many patients will require insulin therapy to maintain BG control
  - Consider insulin therapy if A1c >10% and/or patient is markedly symptomatic
- All treatment decisions should be patient-centered
- Comprehensive CV risk reduction is essential

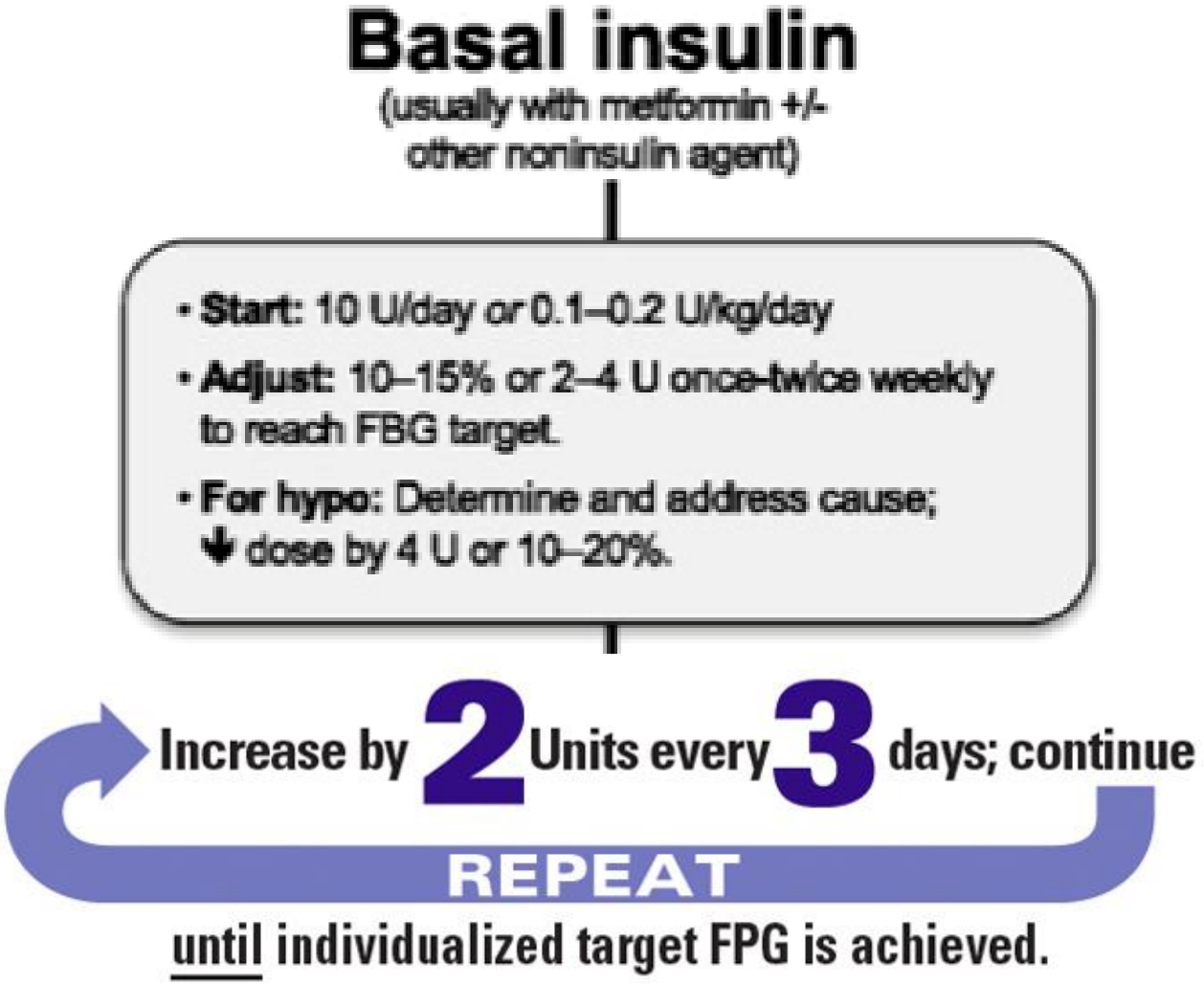
Insulin Dosing in type 2 DM

- Ultimately, many patients will require insulin therapy to maintain BG control in combination with oral drug therapy.
- Consider insulin therapy if A1c >10% and/or patient is markedly symptomatic
- The younger age of onset of type 2 DM and tight glycemic targets need insulin therapy.
- The overweight patients should be initiated on once daily basal insulin (usually at night) with metformin.
- The basal insulin is titrated to achieve a normal fasting glucose level.

Step 1: Start Insulin T2DM

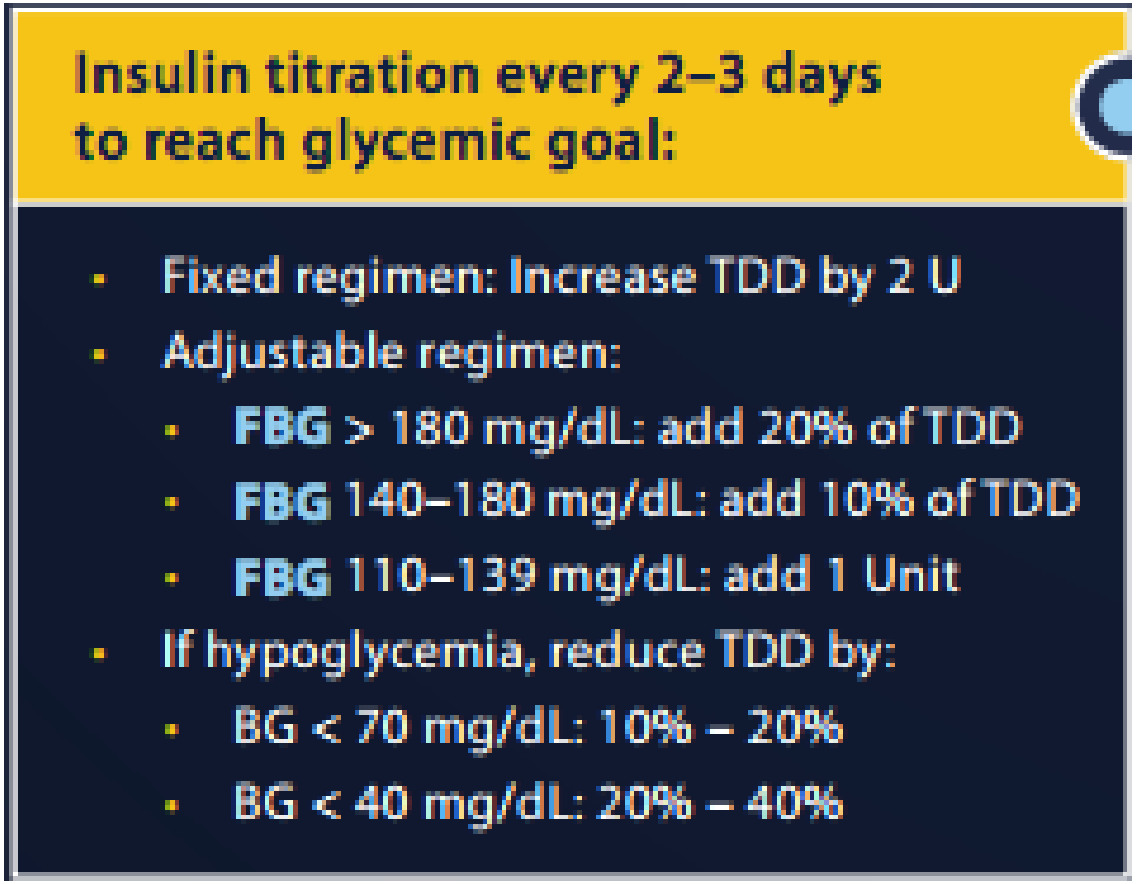
- Control FBGs first! – The 3 F's (Fix Fasting First)
  - Start the day off low, continue low
  - Helpful for easing into insulin therapy
- Which insulin will control FBG?
  - Glargine, detemir, NPH
- Oral agents are typically continued
  - Better glycemic control than with insulin alone
  - Lowers insulin dose requirement
  - Less weight gain with metformin in regimen

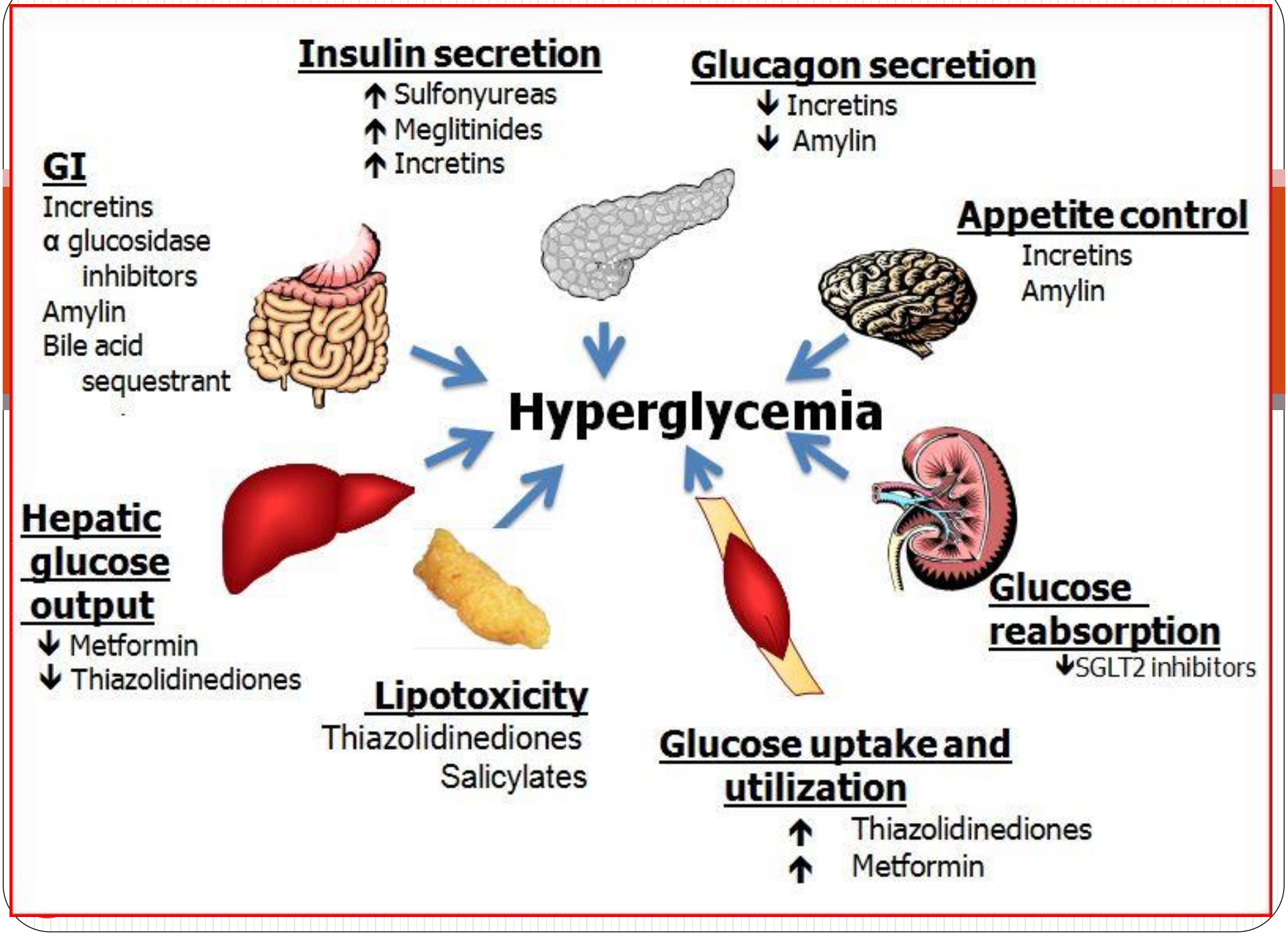
Initial Basal Dosing



Initial Basal Dosing

- AACE Flexible Adjustment Scale




Insulin secretion
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
Appetite control
Incretins
Amylin
Hyperglycemia
Hepatic glucose output
↓ Metformin
↓ Thiazolidinediones
Lipotoxicity
Thiazolidinediones
Salicylates
Glucose reabsorption
↓SGLT2 inhibitors
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin

When should you check the levels?

Routinely

For type II diabetes (usually controlled by diet and tablets, or by diet alone), 2-3 times each week at different times of the day is enough.

For type I diabetes (which requires insulin), more regular checking is required; that is, at least once a day, usually first thing before breakfast and then about 2 hours after a meal.

Your blood glucose levels are likely to be *low* before meals, and *high* 2 hours after meals.

Special circumstances (require checking)

- Stress, illness or too much food will push your blood glucose *up*.
- Exercise will pull the blood glucose *down*.

THANK YOU