Pharmacotherapy of Diabetes Mellitus

Debremarkos university

(2012 E.C)

Introduction

Definition

- Group of metabolic disorders characterized by **hyperglycemia** resulting from either or both of:
  - Insufficient insulin secretion
  - Resistance to the action of insulin
- Abnormalities in carbohydrate, fat, protein metabolism

Introduction…

- Results in chronic complications
  - Microvascular
    - Retinopathy, neuropathy, diabetic nephropathy
  - Macrovascular
    - Coronary artery disease, peripheral artery disease, stroke

Effects of Insulin on Various Tissues

Adipose Tissue

Increased glucose entry

Increased fatty acid synthesis

Increased glycerol phosphate synthesis

Activation of lipoprotein lipase

Inhibition of hormone-sensitive lipase

Increased K^+ uptake

Muscle

Increased glucose entry

Increased glycogen synthesis

Increased amino acid uptake

Increased protein synthesis in ribosomes

Decreased release of gluconeogenic amino acids

Increased ketone uptake

Increased K^+ uptake

Liver

Decreased ketogenesis

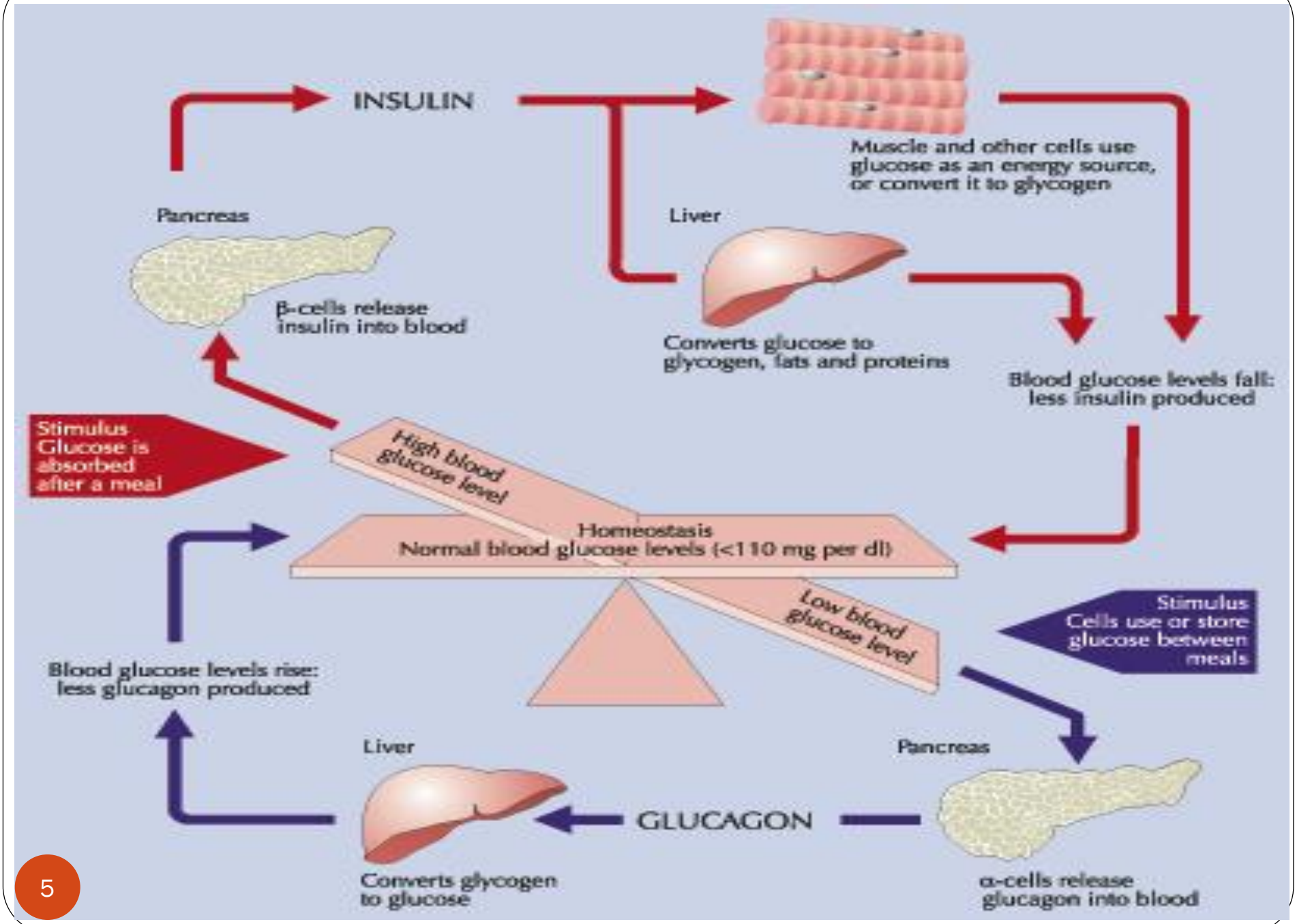
Increased protein synthesis

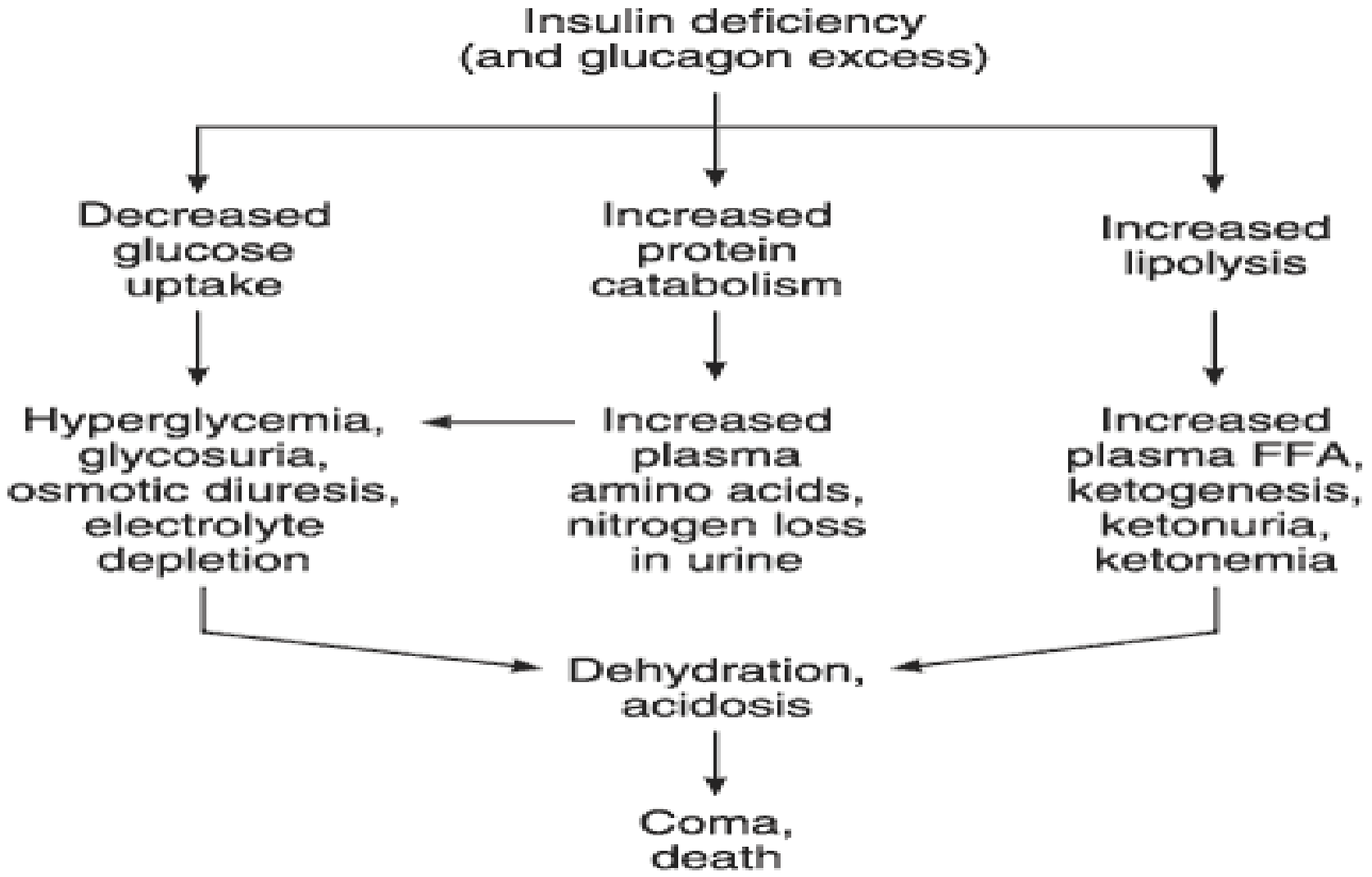
Increased lipid synthesis

Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis

General

Increased cell growth


INSULIN
Muscle and other cells use glucose as an energy source, or convert it to glycogen
Pancreas
β-cells release insulin into blood
Liver
Converts glucose to glycogen, fats and proteins
Blood glucose levels fall: less insulin produced
Stimulus Glucose is absorbed after a meal
High blood glucose level
Homeostasis
Normal blood glucose levels (<110 mg per dl)
Low blood glucose level
Stimulus Cells use or store glucose between meals
Blood glucose levels rise: less glucagon produced
Liver
GLUCAGON
Pancreas
Converts glycogen to glucose
α-cells release glucagon into blood



Source: Ganong WF: *Review of Medical Physiology*, 22nd Edition: http://www.accessmedicine.com

Effects of insulin deficiency. (Courtesy of RJ Havel.)

Epidemiology

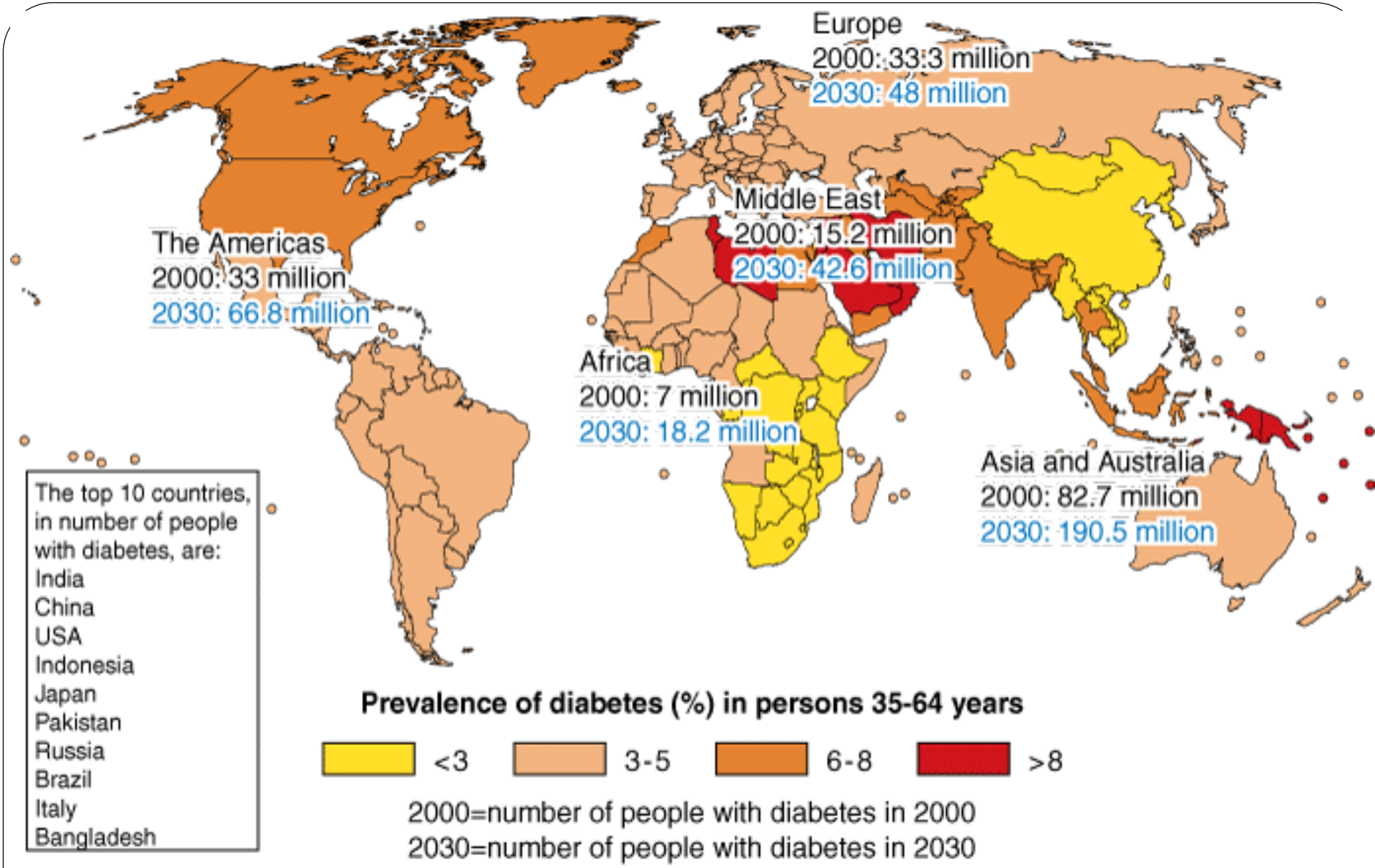
- Type 1 DM: 5% to 10% of all cases of DM
  - Develops in childhood or early adulthood
  - But new cases can occur at any age
- Type 2 DM: 90% of all cases of DM
  - Prevalence increases with age

Epidemiology…

- The development of diabetes is projected to reach pandemic proportions over the next10-20 years
- International Diabetes Federation (IDF)
  - By the year 2025: number of people affected 333 million
    - 90%: Type 2 diabetes
- The annual health costs caused by diabetes and its complications account for around 6-12% of all health-care expenditure

Epidemiology…

- DM
  - Leading cause of blindness in adults ages 20 to 74 years
  - Leading contributor to kidney failure
  - Accounts for ~71,000 lower-limb amputations annually
  - ~2/3 of deaths are caused by a CV event in DM patients



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Classification

- Majority of diabetics classified in categories of:
  - **Type 1 : absolute** deficiency of insulin
  - **Type 2 :** presence of insulin **resistance** with reduced insulin secretion
  - **Gestational diabetes**
  - Other specific types:
    - LADA, MODY, Secondary Diabetes Mellitus
      - Infections, drugs, pancreatic destruction, genetic defects

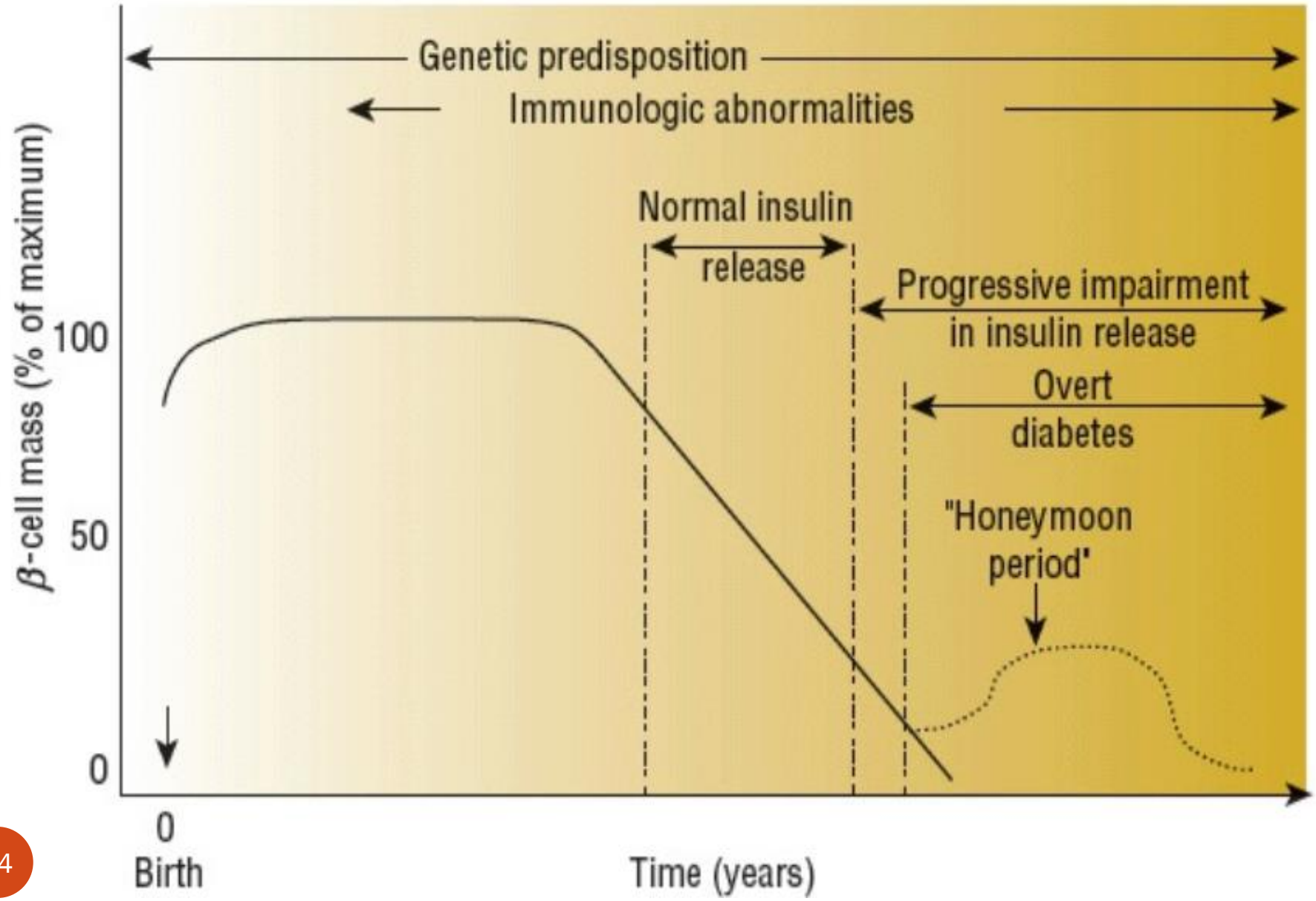
Type 1 DM

- **Autoimmune destruction of pancreatic β-cells**
  - Account for 5% to 10% of all diagnosed cases of diabetes.
  - Children & adolescents often have rapid β-cell destruction & present with ketoacidosis
  - May occur at any age
- **Risk factors: autoimmune**, genetic, and environmental factors

Type 1 DM Pathogenesis

1. Preclinical period
   - Immune markers present
   - β-cell destruction
2. Hyperglycemia
   - 80 to 90% of β-cells destroyed
3. Transient remission
   - honeymoon phase
4. Established disease

Type 1 DM Pathogenesis…



Type 2 DM

- Insulin **resistance**, with relative lack of insulin secretion
- **account for about 90% to 95% of all diagnosed cases of diabetes**
- Usually presents with cluster of abnormalities known as metabolic syndrome:
  - Abdominal obesity
  - Hypertension
  - Dyslipidemia
- Increased macrovascular complication risk

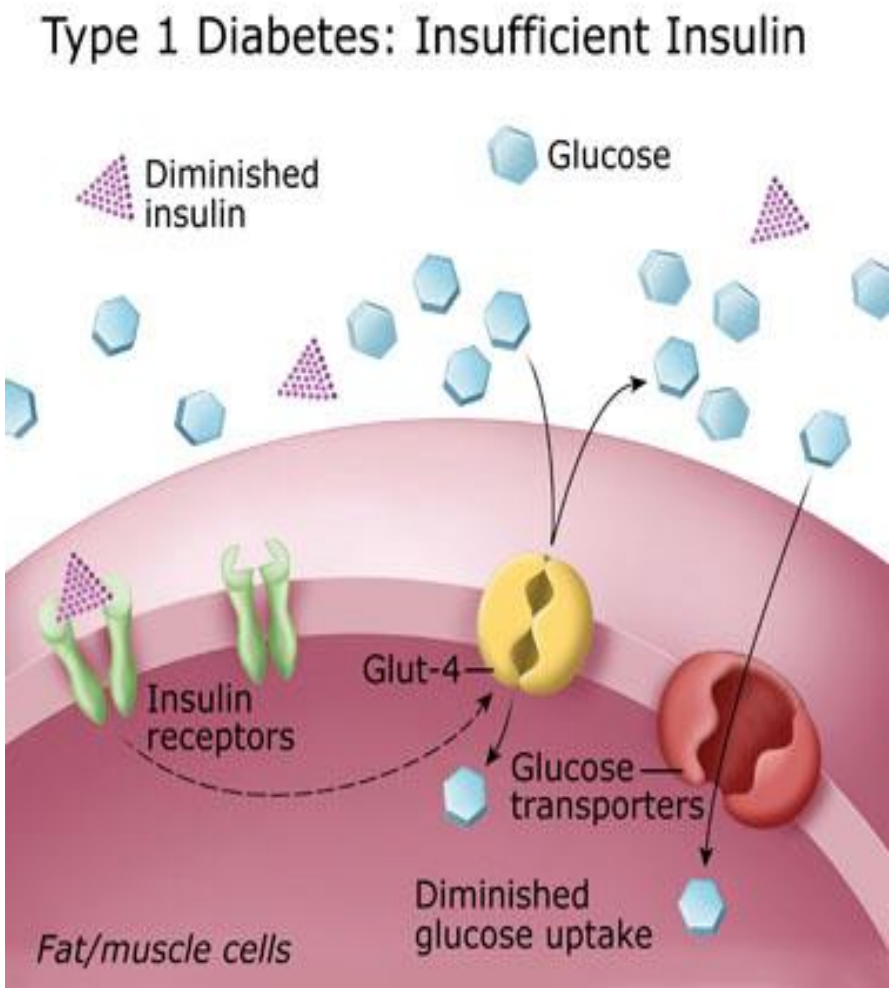
Metabolic Syndrome (≥ 3 for diagnosis)

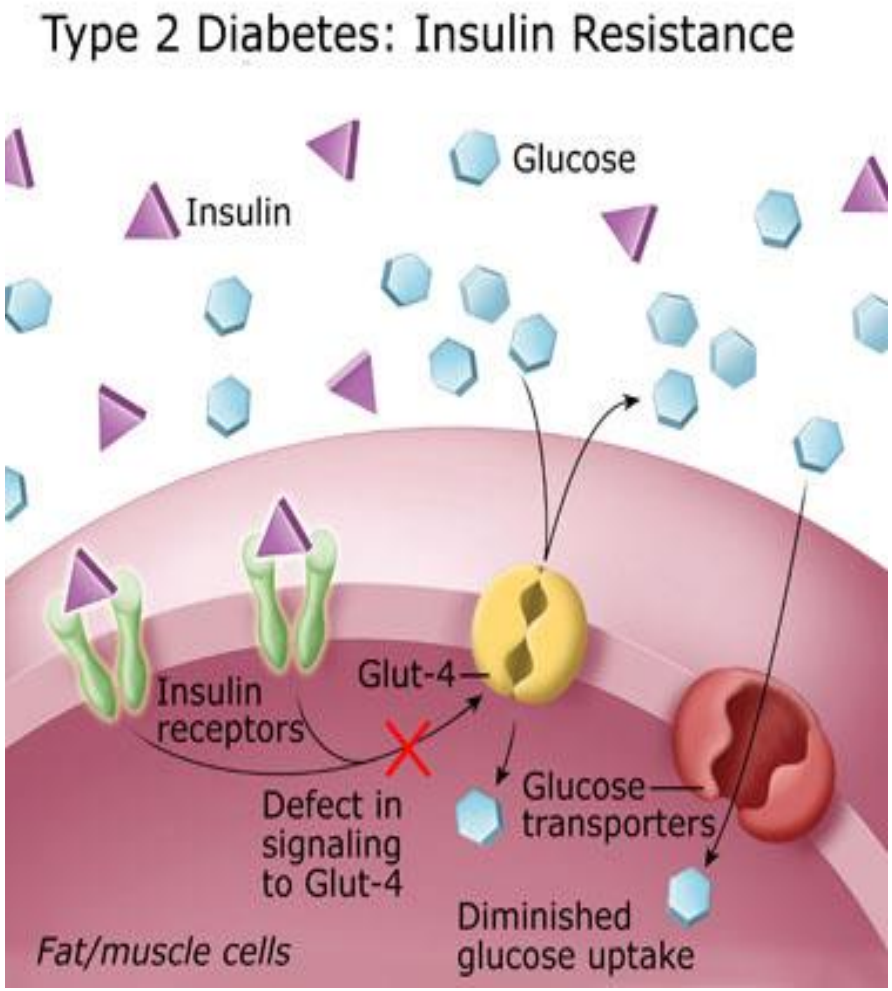
Risk Factor	Defining Level
Abdominal obesity	
Men (waist circumference)	> 102 cm (> 40 in.)
Women	> 88 cm (> 35 in.)
Triglycerides	> 1.7 mmol/L (> 150 mg/dL)
HDL cholesterol	
Men	< 1.0 mmol/L (< 40 mg/dL)
Women	< 1.3 mmol/L (< 50 mg/dL)
Blood Pressure	≥ 130/≥ 85 mmHg
Fasting glucose	> 6.1 mmol/L (> 110 mg/dL)

Risk Factors For Type 2 DM

- BMI ≥ 25
- Physical inactivity
- 1st degree relative with DM
- High risk ethnic group
- HTN: ≥ 140/90 mmHg or on therapy for HTN
- CV disease
- HDL < 40 mg/dL
- Triglycerides > 150 mg/dL
- Delivery of > 9 lb baby
- History of GDM
- Insulin resistance

DM Pathophysiology





Gestational diabetes

- A form of glucose intolerance diagnosed during pregnancy
- Common among obese women and women with a family history of diabetes
- Requires treatment
  - To normalize maternal blood glucose levels
  - To avoid complications in the infant
- After pregnancy, 5% to 10% of women with GDM develop type 2 DM

Other types of DM

- Can result from
  - specific genetic conditions
    - LADA, MODY
  - Surgery
  - Drugs
  - Infections and other illnesses
- Account for 1% to 5% of all diagnosed cases of diabetes

LADA

- A form of ***autoimmune*** (***type 1 diabetes***)
- Diagnosed in individuals who are older than the usual age of onset of type 1 diabetes
- Also called
  - Slow Onset Type 1 DM
- Often, patients with LADA are mistakenly thought to have ***type 2 diabetes***, based on their age at the time of diagnosis

LADA

- About 80% of adults diagnosed with LADA progress to insulin requirement within 6 years
- The potential value of identifying this group at high risk of progression to insulin dependence includes:
  - The avoidance of using metformin treatment
  - The early introduction of insulin therapy

MODY

- MODY – Maturity Onset Diabetes of the Young
- MODY is a monogenic form of diabetes with an autosomal dominant mode of inheritance:
  - Mutations in
    - Transcription factors or
      - Lead to insufficient insulin release from pancreatic ß-cells, causing MODY

MODY

- Originally, diagnosis of MODY was based on
  - Presence of non-ketotic hyperglycemia
  - Family history of diabetes
    - In adolescents or young adults
- However, genetic testing has shown that MODY can occur at any age and that a family history of diabetes is not always obvious
- Respond to sulfonylurea therapy

Secondary DM

Secondary causes of Diabetes mellitus include:

- Acromegaly
- Cushing syndrome
- Thyrotoxicosis
- Pheochromocytoma
- Chronic pancreatitis
- Cancer

Secondary DM

Drug induced hyperglycemia:

- **Atypical Antipsychotics:** Alter receptor binding characteristics, leading to increased insulin resistance
- **Beta-blockers:** Inhibit insulin secretion
- **Calcium Channel Blockers:** Inhibits secretion of insulin

- **Corticosteroids:** Cause insulin resistance and gluconeogensis
- **Phenothiazines:** Inhibit insulin secretion
- **Protease Inhibitors:** Inhibit the conversion of proinsulin to insulin

- **Thiazide Diuretics:** Inhibit insulin secretion due to hypokalemia.
  - They also cause increased insulin resistance due to increased free fatty acid mobilization

Screening

- **Type 1**
  - Not recommended
  - Low prevalence
  - Acute symptoms

Screening…

- **Type 2**
  - For adults
  - At any age in individuals who are overweight (BMI ≥25 kg/m2) and have at least one of the following risk factor
    - Physical inactivity
    - First-degree relative with diabetes
    - Women who have delivered a baby >9 lb (>4 kg)
    - A history of GDM
    - Hypertension
    - High triglycerides and low HDL
    - A history of cardiovascular disease

Screening…

- **Type 2…**
  - Fasting plasma glucose (FPG) recommended
  - Alternative: oral glucose tolerance test (OGTT)
  - HbA1c

Prediabetes

- Categories of **increased risk** for diabetes (prediabetes)
  - FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

    OR
  - 2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

    OR
  - A_1C 5.7–6.4% (39–46 mmol/mol)
- **Metformin** therapy is important for prevention or delay of type 2 diabetes

Clinical Presentation of Diabetes

Characteristic	Type 1 DM	Type 2 DM
Age	< 30 years	> 30 years
Onset	Abrupt	Gradual
Body habitus	Lean	Obese or history of obesity
Insulin resistance	Absent	Present
Autoantibodies	Often present	Rarely present
Symptoms	Symptomatic	Often asymptomatic
Ketones at diagnosis	Present	Absent
Need for insulin therapy	Immediate	Years after diagnosis
Acute complications	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state

Clinical Presentation…

- Clinical presentation can vary widely
- Type 1 can present acutely with symptoms of
  - Polyuria
  - Nocturia
  - Polydipisia
  - Polyphagia
  - Weight loss

Diagnosis

- **Criteria for the diagnosis of diabetes**

FPG ≥ 126 mg/dL (7.0 mmol/L)

OR

2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT

OR

A1C ≥ 6.5% (48 mmol/mol).

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a RPG ≥ 200 mg/dL (11.1 mmol/L)

Diagnosis…

- **FPG:** Fasting is defined as no caloric intake for at least 8 h
- **OGTT:** using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water

Categorizations of Abnormal Glucose Status

Fasting plasma glucose (FPG)

Impaired fasting glucose (IFG)

- 100–125 mg/dL (5.6–6.9 mmol/L)

Diabetes mellitus[a]

- FPG ≥126 mg/dL (7 mmol/L)

2-hour postload plasma glucose (oral glucose tolerance test)

Impaired glucose tolerance (IGT)

- 2-hour postload glucose 140–199 mg/dL (7.8–11 mmol/L)

Diabetes mellitus[a]

- 2-hour postload glucose ≥200 mg/dL (≥11.1 mmol/L)

HbA_{1c}

Increased risk of diabetes mellitus

- HbA_{1c} 5.7–6.4% (0.057–0.064; 39–46 mmol/mol Hb)

Diabetes mellitus[a]

- HbA_{1c} ≥6.5% (≥0.065; ≥48 mmol/mol Hb)

Treatment Goals

- Reduce risk for microvascular & macrovascular complications
- Ameliorate symptoms
- Reduce mortality
- Improve quality of life

Treatment Goals…

Glycemic Goals

Biochemical Index	ADA		ACE and AACE
Hemoglobin A_{1c}	<7% (<0.07; <53 mmol/mol/Hb)[a]		≤6.5% (≤0.065; ≤48 mmol/mol Hb)
Preprandial plasma glucose	70–130 mg/dL (3.9–7.2 mmol/L)		<110 mg/dL (<6.1 mmol/L)
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)		<140 mg/dL (<7.8 mmol/L)
ADA plasma glucose and HbA_{1c} goals for type 1 DM by age group[c]			
Values by age (years)	Plasma glucose goal		A_{1c}
	Before meals bedtime/overnight		
Toddlers and preschoolers (0–6)	100–180 (5.6–10 mmol/L)	110–200 (6.1–11.1 mmol/L)	7.5% to 8.5% (<0.085; <69 mmol/mol Hb)
School age (6–12)	90–180 (5–10 mmol/L)	100–180 (5.6–10 mmol/L)	<8% (<0.080; <64 mmol/mol Hb)
Adolescents and young adults (13–19)	90–130 (5–7.2 mmol/L)	90–150 (5–8.3 mmol/L)	<7.5% (<0.075; <58 mmol/mol Hb)

Non-pharmacologic Therapy

Dietary guidelines for people with diabetes:

- **Dietary fat :** *25-35% of total intake of calories*
  - *but saturated fat intake* < 7% of total energy
  - Cholesterol< 300 mg or less daily
- **Protein intake:** 10-15% total energy
  - Increase for children and during pregnancy
  - Protein should be derived from both animal and vegetable sources
- **Carbohydrates:** *50-60%*
  - Complex and high in fibre
- **Salt intake:** <2.3 g/day

Non-pharmacologic Therapy…

- **Exercise**
  - improves insulin resistance, glycemic control
  - reduces CV risk
  - helps with weight loss or maintenance
  - improves well-being
- Patients without contraindications
  - ≥ 150 min/week moderate-intensity aerobic exercise

Pharmacotherapy

- **Insulin**
  - Insulin secretagogues
    - Sulfonylureas
    - Meglitinides
  - Insulin sensitizers
    - Biguanides
    - Thiazolidinediones (TZDs)
- α–glucosidase inhibitors
- DPP-IV inhibitors
- Dopamine agonists
- Bile acid sequestrants
- Sodium-glucose cotransporter 2 inhibitors

Insulin

- Anabolic & anticatabolic hormone
- Necessary for carbohydrate, protein & fat metabolism
- Required for all type 1 DM patients
- Recommended for type 2 DM patients that do not achieve glycemic control with PO antidiabetic agents

Insulin…

- Originally derived from **bovine** & **procine** pancreas

- All human insulin now are made exclusively by recombinant DNA (rDNA) technology

  - Synthesized to overcome problems of human insulin
    - Onset of action
    - Duration of action
    - Absorption

Insulin…

- **Basal Insulin**
  - mimics **normal** pancreatic insulin secretion with constant levels
  - suppresses glucose production in the **fasting** & postabsorptive period

- **Bolus Insulin**
  - mimics spikes of physiologic secretion insulin **after eating**

Insulin Pharmacokinetics

Type of Insulin	Onset (hr.)	Peak (hr.)	Duration (hr.)	Maximum Duration (hr.)	Appearance
Rapid-acting					
Aspart	15–30 min	1–2	3–5	5–6	Clear
Lispro	15–30 min	1–2	3–4	4–6	Clear
Glulisine	15–30 min	1–2	3–4	5–6	Clear
Short-acting					
Regular	0.5–1.0	2–3	3–6	6–8	Clear
Intermediate-acting					
NPH	2–4	4–6	8–12	14–18	Cloudy
Long-acting					
Detemir	2 hours	6–9	14–24	24	Clear
Glargine	4–5	—	22–24	24	Clear

Rapid-Acting Insulin

- **Lispro, Aspart and Glulisine**
  - Recombinant insulin analogs
  - **Bolus** insulin
  - **Faster** absorption & **shorter** duration of action than regular insulin
  - Administer 5 to 15 minutes before meal
  - Superior postprandial glucose lowering compared to regular insulin

Short-Acting Insulin

- **Regular insulin**
  - **Bolus** insulin to control post-prandial spikes
  - Inject 30 to 60 min prior to meals due to onset of action
    - May cause postprandial hyperglycemia due to rapid increase in blood glucose after meals & delayed onset of action
    - Late hypoglycemia due to prolonged duration of action

Intermediate-Acting Insulin

- **NPH insulin** (Neutral Protamine Hagedorn)
  - Mimics **basal** insulin secretion
  - Administered **twice** daily

Long-Acting Insulin

- **Insulin glargine, insulin detemir**
  - Mimic **basal** insulin secretion
  - Slow action over 24 hours
  - Lower risk of hypoglycemia
  - Daily or BID dosing

Long-Acting Insulin…

- **Insulin glargine**
  - low solubility at neutral body pH, form microprecipitates at injection site & slowly released
- **Insulin detemir**
  - forms a fatty acid chain that binds interstitial albumin at injection site; causes prolong absorption
  - dissociated detemir molecules enter circulation & again bind albumin causing further delay in distribution

Pre-mixed Insulin Products

Trade/Generic Name	Preparations	Room Temperature Expiration
Premixed insulin analogs		
Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro)	Vial, prefilled pen	Vial: 28 days; pen: 10 days
NovoLog Mix 70/30 (70% aspart protamine suspension, 30% aspart)	Vial, prefilled pen, 3-mL pen cartridge	Vial: 28 days; others: 14 days
Humalog Mix 50/50 (50% neutral protamine lispro/ 50% lispro)	3-mL pen	10 days
NPH-regular combinations		
Humulin 70/30	Vial, prefilled pen	Vial: 28 days; pen: 10 days
Novolin 70/30	Vial, pen cartridge, InnoLet[c]	Vial: 30 days; others: 10 days
Humulin 50/50	Vial	28 days

Medications that may Affect Glycemic Control

Drug	Effect on Glucose	Mechanism/Comment
Angiotensin-converting enzyme inhibitors	Slight reduction	Improves insulin sensitivity
Alcohol	Reduction	Reduces hepatic glucose production
α-Interferon	Increase	Decreases insulin sensitivity/ induces counterregulatory hormones
Atypical antipsychotics	Increase	Decrease insulin sensitivity; weight gain
Calcineurin inhibitors	Increase	Decrease insulin secretion
Diazoxide	Increase	Decreases insulin secretion, decreases peripheral glucose use
Diuretics (thiazides)	Increase	May increase insulin resistance and/or decrease insulin secretion, K^+ change may be in part responsible
Glucocorticoids	Increase	Impairs insulin action
Fluoroquinolones	Increase/ decrease	Unclear, potential drug interaction with sulfonylureas or change in insulin secretion

Medications that may Affect Glycemic Control

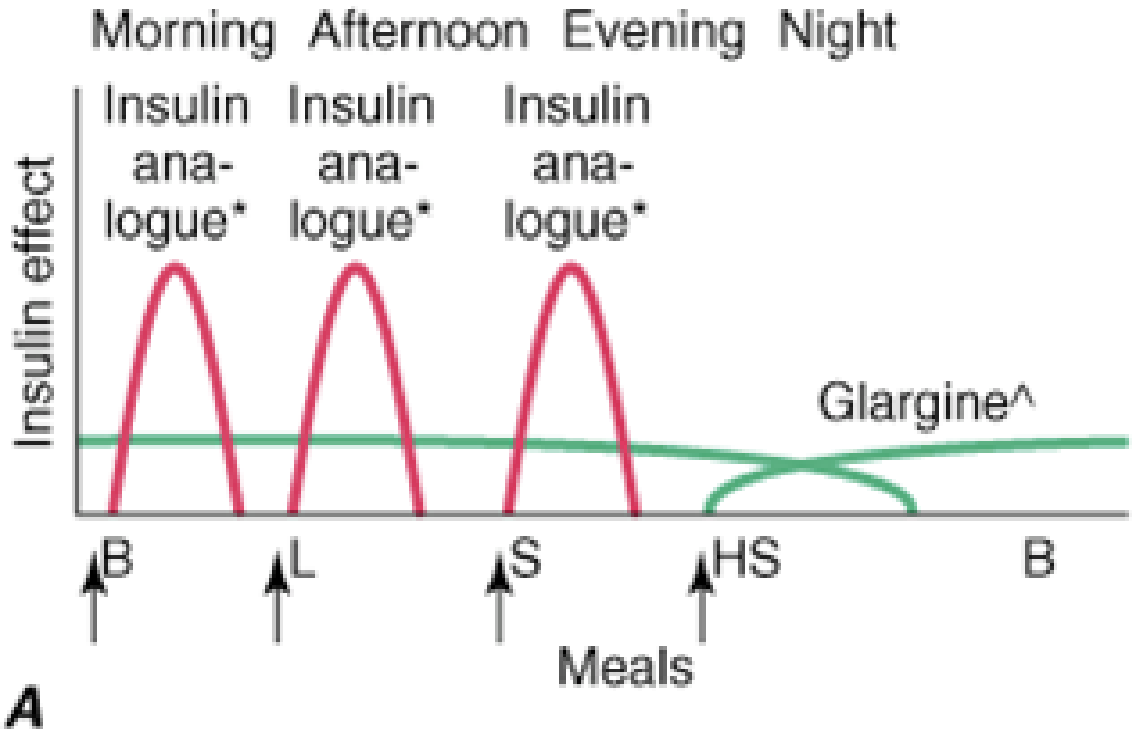
Drug	Effect on Glucose	Mechanism/Comment
Nicotinic acid	Increase	Impairs insulin action, increases insulin resistance
Oral contraceptives	Increase	Unclear
Pentamidine	Decrease, and then increase	Toxic to β cells; initial release of stored insulin, and then depletion
Phenytoin	Increase	Decreases insulin secretion
Protease inhibitors (PI)	Increase	Worsen insulin resistance/ decrease first-phase insulin release or increase lipotoxicity. Dependent on PI
β-Blockers	May increase	Decreases insulin secretion
Ranolazine	Decrease	Improves oxidative glucose disposal
Salicylates	Decrease	Inhibition of IκB kinase-β (IKK-β) (only high doses, e.g., 4–6 g/day)
mpathomimetics	Slight increase	Increased glycogenolysis and gluconeogenesis

Insulin dosing

- Individualized dosing
- Type 1 DM: average daily requirement 0.5-0.6 units/kg
  - basal insulin 50%
  - mealtime insulin 50%
- Honeymoon phase: may fall to 0.1 to 0.4 unit/kg
- Type 2 DM: doses vary depending on degree of insulin resistance
  - 0.7 to 2.5 units/kg or more

Insulin Regimens

Multiple component insulin regimen: long acting insulin for **basal** insulin coverage & **3** injections of a short-acting insulin analogue to provide glycemic coverage for each meal.



y-axis shows amount of insulin effect; the x-axis shows time of day.

B, breakfast; L, Lunch; S, supper; HS, bedtime.

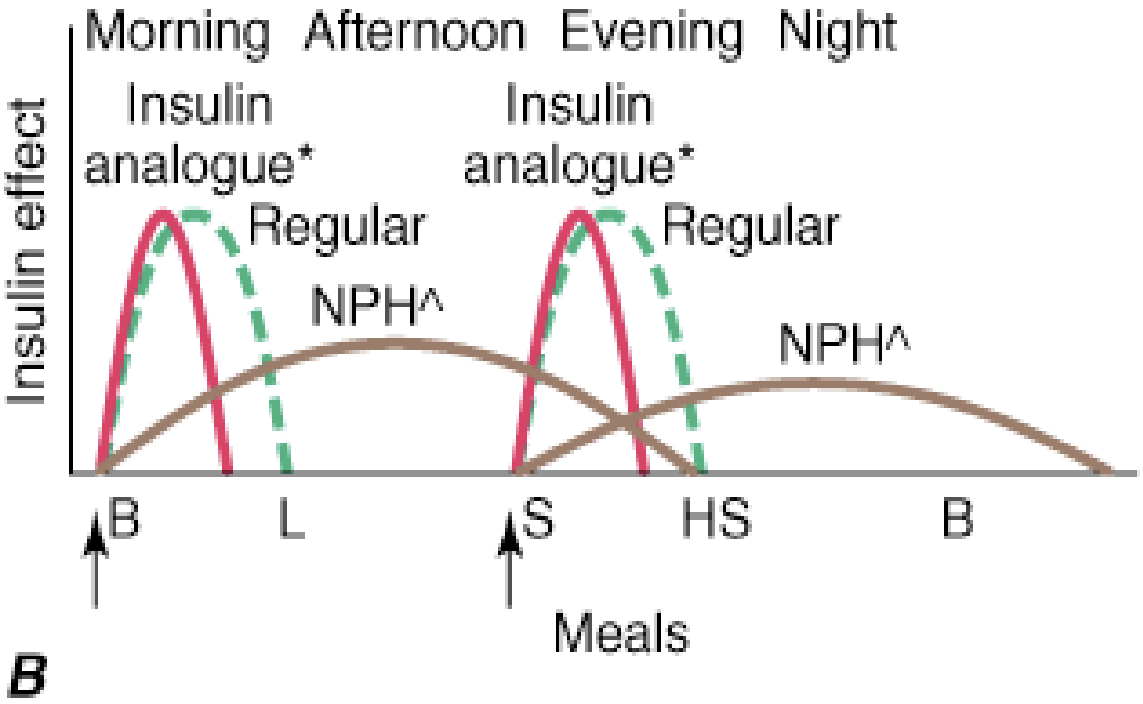
*Lispro, glulisine or insulin aspart can be used.

Time of insulin injection shown with a vertical arrow.

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Insulin Regimens…

2 injections of long-acting insulin (NPH or detemir) & short acting insulin (solid red line) or regular insulin (green dashed line).



B, breakfast; L, Lunch;

S, supper; HS, bedtime.

*Lispro, glulisine or insulin aspart can be used.

Time of insulin injection shown with a vertical arrow.

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Complications of insulin therapy

Hypoglycemia

- Symptoms of hypoglycemia
  - Confusion, agitation, loss of consciousness or coma
  - Tachycardia, tremor, sweating
- **Treatment**
  - Glucose (15–20g)PO the preferred treatment for the conscious individual
    - Any form of carbohydrate that contains glucose may be used
    - Repeat after fifteen minutes if the patient is in hypoglycemia
  - Glucagon: 0.5 to 1.0 mg SC/IM

Complications of insulin therapy…

Lipodystrophy

- **Lipohypertrophy:** a **raised** fat mass
  - Caused by many injections into the same injection site
- **Lipoatrophy:** **destruction** of fat at the site of injection
  - Due to insulin antibodies or allergic-type reactions

- Solution: Inject away from the site
  - **Rotation** of injection sites

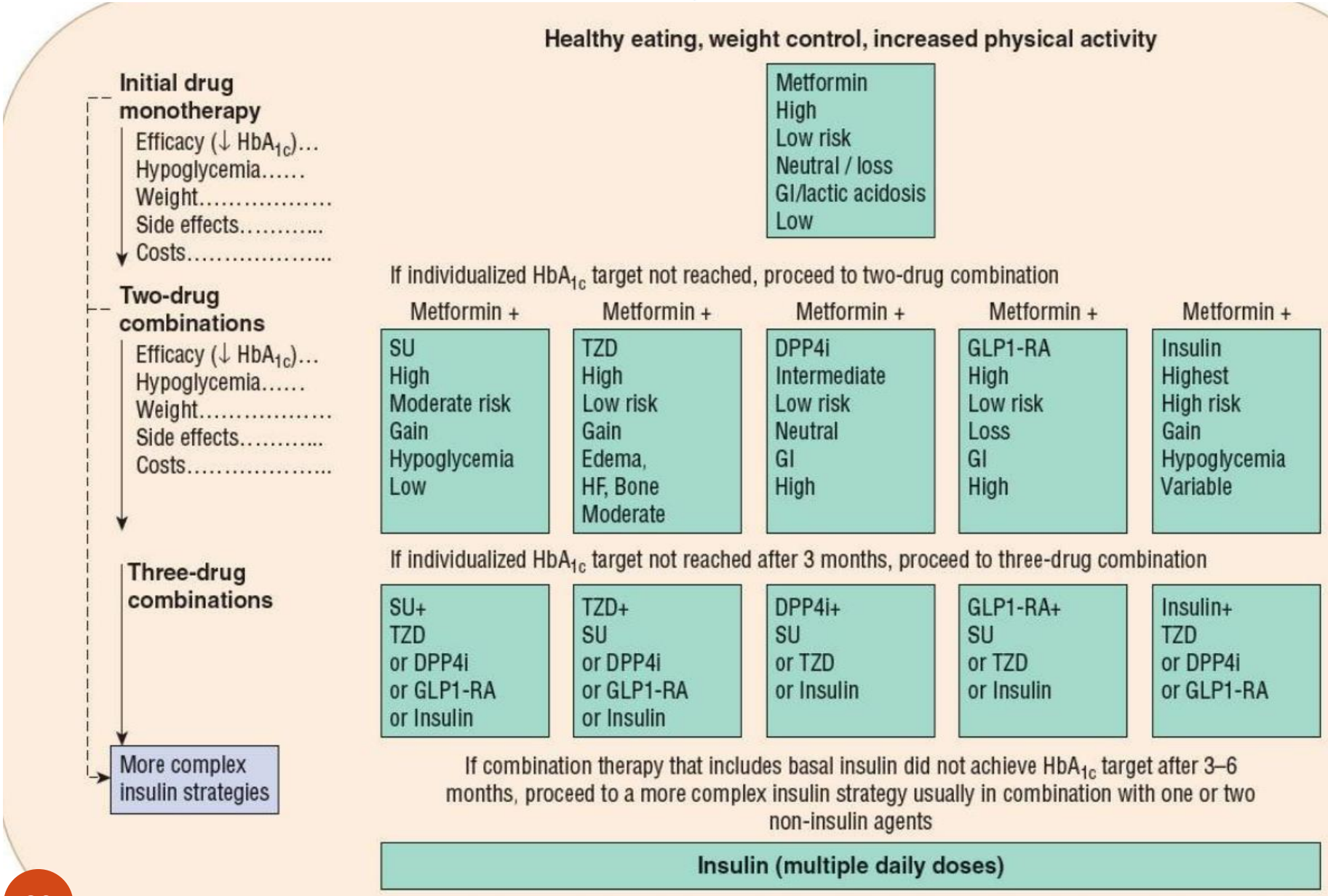
Insulin Storage

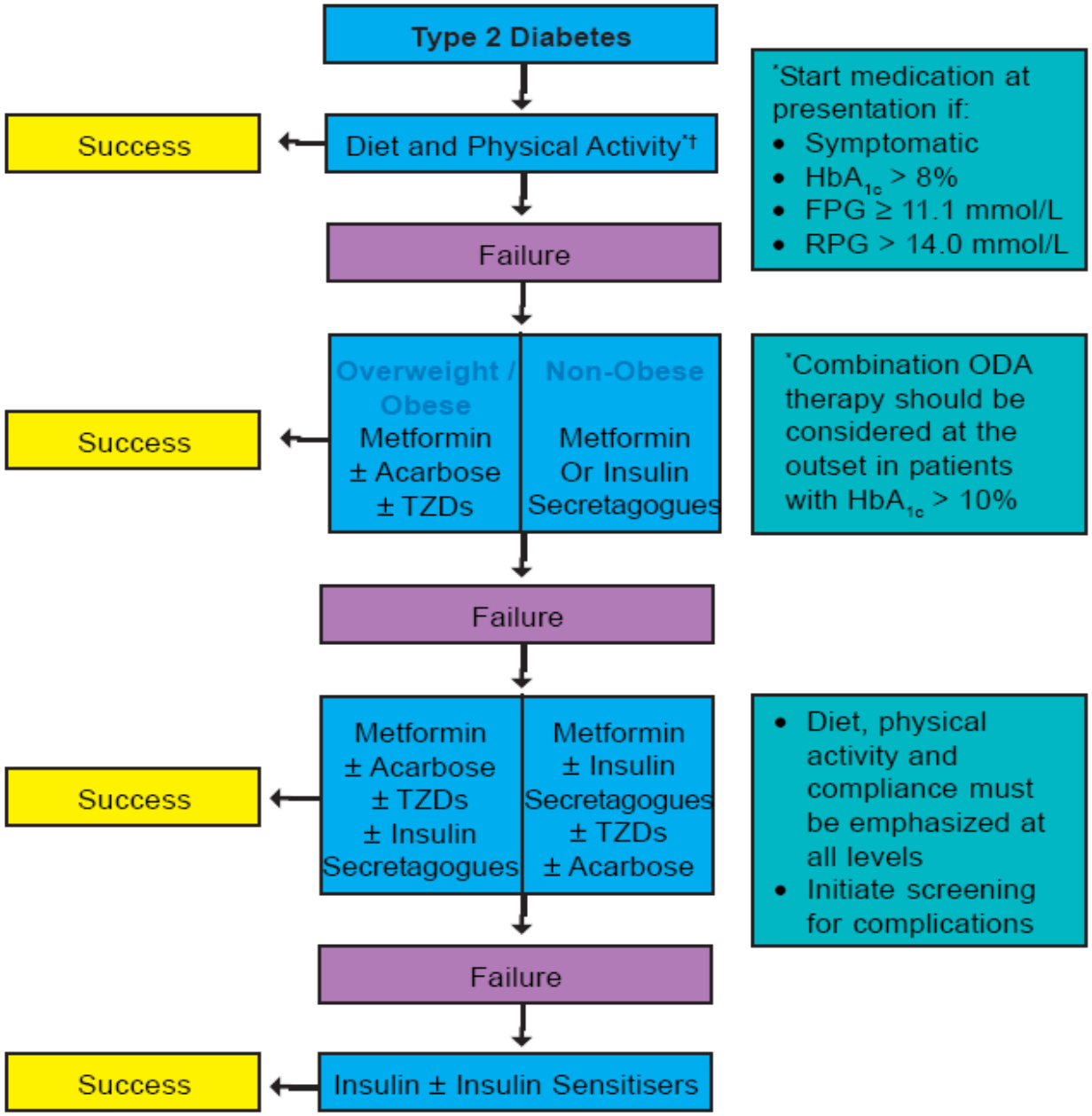
- Refrigerate unopened injectable insulin
  - 2°C to 8°C, but do not freeze
- Use unopened insulin by manufacturer's expiration date
- Opened insulin expire based on type & delivery device
  - May be kept at room temperature (15-30°C or 59-86°F)
- Inspect before use for clumping, precipitates, discoloration, etc.

Management of Type 2 Diabetes Mellitus

- **Principles of management**
  - **Symptomatic** patients: insulin or combination oral therapy
  - HbA1c ≈7% (≈0.07; ≈53 mmol/mol Hb) : single agent
  - HbA1c >7% but <8.5%; (>53 but <69 mmol/mol Hb): single oral agents, or combination therapy
  - Patients with higher initial HbA1c : **two oral agents, or insulin**

Treatment algorithm of Type 2 Diabetes Mellitus





Diabetes Management Algorithm

Biguanide

- Enhance hepatic & muscle tissue insulin sensitivity
  - increases uptake of glucose in tissues
- No direct effect on β cells
- Decrease hepatic glucose production

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Therapeutic Notes
		Nonelderly	Elderly			
Metformin	500, 850, 1,000	500 mg twice a day	Assess renal function	2,550	Up to 24 hours	No metabolism; renally secreted and excreted
Metformin ER	500, 750, 1,000	500–1,000 mg with evening meal	Assess renal function	2,550	Up to 24 hours	Take with evening meal or may split dose; can consider trial if intolerant to immediate-release

Biguanide…

- Most common adverse effects are: **GI**
  - abdominal discomfort, stomach upset, diarrhea
  - minimize with slow dose titration
  - administer with food to lessen adverse effects
  - switch to extended-release may improve tolerability
- Weight loss can occur
  - anorexia
  - stomach fullness

Biguanide…

- **Biguanide contra-indication**
  - High risk patients for lactic acidosis
  - Renal insufficiency
    - SCr ≥ 1.4 mg/dL in women
    - SCr ≥ 1.5 mg/dL in men
  - Intravenous dye procedures
    - risk of acute renal failure
    - withhold the day of procedure
    - may restart 2 to 3 days post-procedure

Biguanide…

- Average HbA1c reduction: 1.5 to 2.0%
- FBG reduction: 60 to 80 mg/dL
- Decrease plasma triglycerides & LDL by ~8%
- Increases HDL: 2%
- Weight loss: 2 to 3 kg
- Use in all type 2 DM patients, if tolerated & not contraindicated
  - The only oral antidiabetic agent proven to reduce mortality risk
    - RCTs shows metformin is **best** suited for obese type 2 DM patients; reduces mortality

Sulfonylureas

- **Enhance insulin secretion**
  - bind SUR on pancreatic β cells
  - results in suppressed hepatic glucose production
- Classification: 1st & 2nd generation
  - differences in potency, adverse effects, serum protein binding
- **Glipizide** preferred over **glyburide**
  - glyburide requires adjustment for renal dysfunction; higher risk of hypoglycemia

Sulfonylureas…

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
1st Generation						
Acetohexamide	250, 500	250	125–250	1,500	Up to 16 hours	Metabolized in liver; metabolite potency equal to parent compound; renally eliminated
Chlorpropamide	100, 250	250	100	500	Up to 72 hours	Metabolized in liver; also excreted unchanged renally
Tolazamide	100, 250, 500	100–250	100	1,000	Up to 24 hours	Metabolized in liver; metabolite less active than parent compound; renally eliminated
Tolbutamide	250, 500	1,000–2,000	500–1,000	3,000	Up to 12 hours	Metabolized in liver to inactive metabolites that are renally excreted

Sulfonylureas…

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
2nd Generation						
Glipizide	5, 10	5	2.5–5	40	Up to 20 hours	Metabolized in liver to inactive metabolites
Glipizide CR	2.5, 5, 10, 20	5	2.5–5	20	24 hours	Slow-release form; do not cut tablet
Glyburide	1.25, 2.5, 5	5	1.25–2.5	20	Up to 24 hours	Metabolized in liver; elimination ½ renal, ½ feces
Glyburide, micronized	1.5, 3, 6	3	1.5–3	12	Up to 24 hours	Equal control, but better absorption from micronized preparation
Glimepiride	1, 2, 4	1–2	0.5–1	8	24 hours	Metabolized in liver to inactive metabolites

Sulfonylureas…

- The most common side effect is : hypoglycemia
  - higher with chlorpropamide & glyburide; long $t_{1/2}$
  - high risk patients require lower doses
    - elderly
    - renal/hepatic disease
    - patients that skip meals
    - vigorous exercise
- Weight gain also common
- Less common adverse effects: rash, hemolytic anemia, GI upset,

Sulfonylureas…

- **Tolbutamide** & **chlorpropamide** may cause:
  - Hyponatremia may result from increased antidiuretic hormone
  - Disulfram-type reactions can result when alcohol is consumed
- Titrate sulfonylureas doses every 1 to 2 weeks
- At equipotent doses, all sulfonylureas equally effective at lowering blood glucose
  - All sulfonylureas are metabolized in the liver, with CYP2C9

Short-Acting Insulin Secretagogues

- Stimulate insulin secretion from pancreatic β cells
  - require presence of glucose
- Similar mechanism to sulfonylureas
  - faster onset, shorter duration

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
Nateglinide	60, 120	120 with meals	120 with meals	120 mg three times a day	Up to 4 hours	Metabolized by cytochrome P450 (CYP450), CYP2C9, and CYP3A4 to weakly active metabolites; renally eliminated
Repaglinide	0.5, 1, 2	0.5–1 with meals	0.5–1 with meals	16	Up to 4 hours	Metabolized by CYP3A4 to inactive metabolites; excreted in bile

Short-Acting Insulin Secretagogues…

- Most common adverse effect: **hypoglycemia;** (less than SU)
  - Weight gain may occur
  - May be used in patients with renal insufficiency and with caution in severe hepatic impairment
  - May be used as monotherapy or in combination with metformin or TZDs in type 2 DM
  - Dose up to 30 min prior to each meal

Thiazolidinediones (TZDs)

- Used in type 2 DM therapy
- Enhance insulin sensitivity at muscle, liver & fat tissues
- Decrease hepatic glucose production
  - Requires presence of insulin

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
Pioglitazone	15, 30, 45	15	15	45	24 hours	Metabolized by CYP2C8 and CYP3A4; two metabolites have longer half-lives than parent compound
Rosiglitazone	2, 4, 8	2–4	2	8 mg/day or 4 mg twice a day	24 hours	Metabolized by CYP2C8 and CYP2C9 to inactive metabolites that are renally excreted

TZD Adverse Effects

- May increase ALT
  - **CI,** if ALT > 2.5 times upper limit of normal
  - Discontinue if ALT > 3 times ULN
- Fluid retention
  - Edema, dilutional anemia, pulmonary edema, HF
  - **CI** in NYHA Class III & IV

TZD Adverse Effects…

- Weight Gain: 1.5 to 4 kg
  - fluid retention & fat accumulation
- Increased fracture risk
  - upper & lower limbs of postmenopausal women
- Ovulation
  - anovulatory patients can resume ovulation
    - pregnancy & contraception precautions required

α-Glucosidase Inhibitors

- Competitively inhibit enzymes in the small intestine
  - delay sucrose & complex carbohydrate breakdown
- Reduce postprandial hyperglycemia
  - Used in both type 1 & type 2 DM

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
Acarbose	25, 50, 100	25 mg one to three times a day	25 mg one to three times a day	25–100 mg three times a day	1–3 hours	Eliminated in bile
Miglitol	25, 50, 100	25 mg one to three times a day	25 mg one to three times a day	25–100 mg three times a day	1–3 hours	Eliminated renally

α-Glucosidase Inhibitors…

- **Adverse effect:**
  - GI side effects most common
    - flatulence, bloating, abdominal discomfort, diarrhea
- Contraindications:
  - IBD
  - colonic ulceration
  - intestinal obstruction
  - cirrhosis

α-Glucosidase Inhibitors…

- May be monotherapy or used with metformin, sulfonylureas, insulin
- Initiate with very low dose
  - 25 mg with one meal a day & increase gradually to maximum dose
  - 50 mg TID patients ≤ 60 kg
  - 100 mg TID patients > 60 kg
- Take with 1st bite of a meal
  - must be present to inhibit enzyme activity

DPP-IV Inhibitors

- Inhibit DPP-IV which degrades GLP-1
  - prolongs GLP-1 t½
  - GLP-1 deficient in type 2 DM
- Partially reduces elevated postprandial glucagon
- Stimulates glucose-dependent insulin secretion

Generic Name	Dose (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Duration of Action	Metabolism or Therapeutic Notes
		Nonelderly	Elderly			
Sitagliptin	25, 50, 100	100 mg daily	25 to 100 mg daily based on renal function	100 mg daily	24 hours	50 mg daily if: creatinine clearance > 30 to < 50 mL/minute 25 mg if: creatinine clearance < 30 mL/min

DPP-IV Inhibitors…

- May be used as monotherapy or in combination
- Average HbA1c reduction 0.7 to 1.0%
- Mild hypoglycemia may occur
- Post marketing reports of serious hypersensitivity reactions:
  - Anaphylaxis
  - Angioedema
  - Exfoliative skin conditions (Stevens-Johnson syndrome)

Exenatide

- Synthetic analog of amino acid peptide exendin-4
- Mechanism similar to human GLP-1
  - enhances insulin secretion
  - suppresses postprandial glucagon when blood glucose is elevated;
  - Reduces hepatic glucose production
- Slows gastric emptying, reduces food intake, promotes weight loss
- Unlike GLP-1, exenatide does not increase gastric secretions

Exenatide…

- Indication: adjunctive therapy for type 2 DM
- Not recommended in end-stage renal disease or dialysis patients
  - prolonged t½ leads to increases incidence of GI side effects
- **Adverse effects:**
  - nausea, vomiting, diarrhea
    - may improve over time
    - dose-related, slowly titrate dose

Exenatide…

- Postmarketing cases of acute pancreatitis
- May delay absorption of other medications: slow gastric emptying
- **Dose:**
  - start with 5 mcg BID
  - may titrate to 10 mcg BID when tolerated
  - inject subcutaneously within 60 min of morning & evening meals

Pramlintide

- Adjunctive therapy for patients using insulin
- Synthetic analog of amylin
  - Neurohormone co-secreted from β-cells with insulin
- Suppresses postprandial glucagon secretion
- Reduces food intake
- Slows gastric emptying

Pramlintide…

- Subcutaneous injection in abdomen or thigh
- Adverse effects:
  - GI most common
  - nausea, vomiting, anorexia; may decrease over time
  - dose-related, slowly titrate dose upwards
- May delay absorption of other medications; slow gastric emptying

Pramlintide…

- Reduce preprandial insulin dose 30 to 50% at pramlintide initiation
- Basal insulin dose may be reduced if FBG close to goal
- **Dosing**:
  - Type 2: 60 to 120 mcg prior to meals
  - Type 1: 15 to 60 mcg prior to meals

Children & Adolescents

- Increasing incidence of type 2 DM in adolescents
- Obesity, physical inactivity are causes
- 1°treatment: lifestyle modifications
- If lifestyle modifications fail:
  - metformin: labeled for use in children 10 to 16 yrs
  - sulfonylureas commonly used
  - TZDs not studied in children

Gestational DM

- Initiate insulin if FBG > 95 mg/dL, 1 hour postprandial > 155 mg/dL, 2 hour postprandial > 130 mg/dL
- Use of basal insulin over NPH still debated
- Glyburide has been used for GDM, not a labeled use
  - further studies needed to establish safety
- GDM patients at long-term risk for type 2 DM;
  - So,assess periodically

Sick Days

- Acute self-limited illness:
  - insulin sensitivity decreases; greater amount of insulin needed to control blood glucose
  - frequent SMBG, check urine ketones, use short-acting insulin to avoid diabetic ketoacidosis
  - must have glucose intake to cover insulin therapy & prevent hypoglycemia

Diabetic Ketoacidosis

- Diabetic emergency
- Precipitating Factors
  - insulin omission
  - illness, infection
  - initial DM presentation
- Diagnostic laboratory values
  - hyperglycemia
  - anion gap acidosis, ketonemia and ketonuria
  - fluid deficits
  - Na^+, K^+ deficits

Pathophysiology

- Absolute or relative insulin deficiency that is accompanied by increase in counter regulatory hormones (glucagon, cortisol, catecholamine).

- Enhances hepatic gluconeogenesis, glycogenolysis, and lipolysis.

- Hepatic metabolism of free fatty acid as alternative source of energy results in accumulation of acidic end products (acetone, β- hydroxybutyrate & acetoacetate).

Pathophysiology…

- Respiratory compensation for this acidotic condition results in rapid deep breathing(respiratory alkalosis), called kussmaul respiration
  - β– hydroxybutyrate induce nausea, and vomiting that consequently aggravate fluid and electrolyte loss
  - Acetone produces the fruity breath odor
  - Glucosuria leads to osmotic diuresis, dehydration and hyperosmolality results in electrolyte disturbance.

Treatment

- restore intravascular volume 1st
  - normal saline given acutely
  - 2–3L of 0.9% NS in 1–3 hrs.; then reduce to 250–500 mL/h
    - Switch fluids to D5W when glucose ~250 mg/dL
  - K^+ supplementation
    - potassium phosphate often used; no evidence of benefits
  - constant insulin infusion

Treatment…

- Frequent glucose & K^+ monitoring essential
  - K^+ must be WNL before insulin is administered
- Metabolic improvement: increased serum bicarbonate & pH
- Glucose will fall before the anion gap closes

Hyperosmolar Hyperglycemia

- Diabetic emergency
- Typically older type 2 DM patients
- Fluid deficits & blood glucose concentrations generally greater than DKA
- Precipitating Factors
  - infection/illness
  - prolonged hyperglycemia
  - dehydration
  - renal insufficiency

Hyperosmolar Hyperglycemia…

- Treatment
  - Fluid replacement
    - hypotonic fluids (0.45% saline) should be used if serum sodium > 150 meq/L
  - Low-dose insulin infusions (1 to 2 units/hour)
- Avoid rapid correction of glucose levels
  - no greater than 75 to 100 mg/dL
  - may result in cerebral edema

Hospitalized DM Patients

- Patients on oral agents often receive insulin therapy for adequate glycemic control during hospitalization
- Insulin dosing
  - scheduled doses of long-acting insulin
  - additional short-acting insulin doses

DM Complications

- **Retinopathy**
  - dilated eye examination annually
  - can reverse early retinopathy with improved glycemic control
  - advanced retinopathy will not improve with glycemic control; retinopathy can worsen with short-term glycemic improvements

DM Complications…

- **Diabetic peripheral neuropathy**
  - paresthesias, numbness, pain
  - feet more often than hands
  - improved glycemic control can alleviate symptoms
  - symptomatic therapy
    - topical capsaicin
    - NSAIDs, tramadol, opioids
    - low-dose tricyclic antidepressants
    - anticonvulsants: gabapentin, pregabalin

DM Complications…

- **Autonomic neuropathy**
  - resting tachycardia
  - exercise intolerance
  - orthostatic hypotension
  - constipation
  - gastroparesis
  - impaired neurovascular function
  - erectile dysfunction
  - sudomotor dysfunction
    - lack of sweating in extremities
    - increased sweating in the trunk
  - hypoglycemic autonomic failure

DM Complications…

- **Microalbuminuria & nephropathy**
  - type 2 DM: urinary screening for albumin at diagnosis
  - type 1 DM: screen patients at puberty & 5 yrs after diagnosis
  - glucose & BP control
    - prevents nephropathy
    - slows nephropathy progression
  - 1st line therapy: ACE inhibitors or ARBs
    - prevent renal disease progression in type 2 DM patients

DM Complications…

- **Peripheral vascular disease (PVD)**
- Treatment
  - smoking cessation
  - correction of dyslipidemia
  - antiplatelet therapy
  - revascularization in selected patients

DM Complications…

- **Nonhealing foot ulcers**
- Early treatment of foot lesions
  - local debridement
  - appropriate footwear
  - foot care
- DM accounts for ~71,000 lower extremity amputations annually

Hyperlipidemia in DM Patients

Parameter	Goal		Treatment (in order of preference)
LDL cholesterol	< 100 mg/dL < 70 mg/dL[a]		Lifestyle; HMG-CoA reductase inhibitors; cholesterol absorption inhibitor; or fenofibrate
HDL cholesterol	Men > 40 mg/dL	Women > 50 mg/dL	Lifestyle; nicotinic acid; fibric acid derivatives
Triglycerides	< 150 mg/dL		Lifestyle; glycemic control; fibric acid derivatives; high-dose statins (in those with high LDL)

DM Complications…

- **Coronary Heart Disease (CHD)**
  - CHD risk 2 to 4 times greater in diabetic Vs non-diabetic individuals
  - multiple-risk factor intervention reduces macrovascular events
    - lipid management
    - HTN control
    - Smoking cessation
    - Antiplatelet therapy

Hypertension & DM

- ADA & the National Kidney Foundation recommend target BP < 140/90 mmHg for DM patients
- ACE inhibitors & ARBs: generally recommended as initial therapy
- Many patients may require multiple agents to obtain goals
  - diuretics, CCBs, β-blockers: 2nd & 3rd line agents
- BP goals: more difficult to achieve than glycemic or lipid goals in most patients

Antiplatelet Agents

- Consider **aspirin** therapy (75–162 mg/day) as a primary prevention strategy
  - Patients with diabetes
    - Age≥ 50years and one additional risk factor
      - family history of premature atherosclerotic cardiovascular disease
      - Hypertension
      - Smoking
      - dyslipidemia, or
      - Albuminuria

Antiplatelet Agents…

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease
- Documented aspirin allergy: clopidogrel (75 mg/day)

The end

Thank you…..!!