

# *Diabetes mellitus*

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- **Hyperglycemia due to deficiency of insulin secretion or resistance of body's cells to action of insulin, or combination → disturbances of carbohydrate, fat and protein metabolism**
- **Normal blood glucose = 72-126 mg/dl**
- **Symptoms of hyperglycemia :-**
  - thirst, polydipsia, polyuria**
  - weight loss**
  - tiredness and malaise**
  - constipation (due to dehydration)**
  - recurrent or refractory infections**
  - visual disturbance**
  - paresthesia (due to peripheral nerve damage)**
  - pruritus, cramp (due to diuresis)**

# *Diabetic complications*

- Eye – retinopathy, maculopathy, cataract, squint
- Ear – deafness
- Kidney – nephropathy, renal failure, chronic pyelonephritis
- Nerve – peripheral, autonomic neuropathy
- Heart - coronary artery disease, heart failure
- Leg – peripheral vascular disease
- Brain – stroke
- Feet – ulcer, infection, gangrene
- Skin – dermopathy, necrobiosis lipoidica

# *American diabetes association diagnostic criteria for diabetes mellitus*

- **Diabetes mellitus (DM)** –
  - symptoms of DM + casual plasma glucose  $\geq 200$  mg/dl
  - repeated fasting plasma glucose  $\geq 126$  mg/dl
  - repeated plasma glucose  $\geq 200$  mg/dl at 2 hours after 75 gm oral glucose challenge (not recommended for routine use)
- **Impaired fasting glucose** –
  - fasting plasma glucose 110-126 mg/dl
- **Normal fasting glucose** –
  - fasting plasma glucose  $< 110$  mg/dl

■ **Goals of diabetic control** :-

1. prevent ketoacidosis and hyperosmolar coma
2. prevent hyperglycemic symptoms (eg. polyuria) and catabolism (eg. fatigue, weight loss, hyperphagia)
3. prevent long-term complications eg. atherosclerosis, retinopathy, nephropathy, neuropathy

■ **Mainstays of DM control** = weight loss, diet, exercise

■ **Recommended diet** = low fat, high complex carbohydrate, high fiber and low salt diet, with calorie restriction and avoid sweet foods and drinks

# *Age-adjusted goals of treatment of DM*

	<b>preprandial blood sugar (<u>mg/dl</u>)</b>	<b>postprandial blood sugar (<u>mg/dl</u>)</b>	<b><u>HbA1c</u></b>	<b><u>urinary glucose and ketones</u></b>
<b>toddlers/ preschoolers</b>	<b>150-160</b>	<b>&lt; 250</b>	<b>7.5-8.5%</b>	<b>glycosuria but rare ketonuria</b>
<b>children/ adolescent/ adults</b>	<b>140-150</b>	<b>&lt; 160</b>	<b>6.5-7.4%</b>	<b>intermittent glycosuria, rare ketonuria</b>
<b>elderly with neurologic or cardiovascular Dysfunction</b>	<b>150-160</b>	<b>&lt; 250</b>	<b>7.5-8.5%</b>	<b>„</b>

**HbA1c = glycosylated glucose attached to hemoglobin indicating  
glycemic load during 120 day lifespan of red blood cell**

# *American diabetes association*

## *classification of diabetes mellitus*

- **Type 1 DM (5-10%)**: caused by pancreatic beta cell destruction, often immune mediated → loss of insulin secretion (absolute insulin deficiency). Common in children and adolescent, characterized by abrupt onset of severe symptoms, need insulin to sustain life, prone to ketosis. Markers of autoimmune destruction = antibodies to islet cells and insulin, glutamic acid decarboxylase etc.
- **Type 2 DM (90-95%)**: caused by genetic and nongenetic factors (eg. age, high calorie intake, overweight, central obesity, sedentary lifestyle etc) → insulin resistance and relative (not absolute) insulin deficiency

## ■ ***Other specific types of DM***

***(1-2%) :***

causes include genetic defects affecting beta cell function or insulin action, endocrinopathies, drugs, infection etc.

## ■ ***Gestational DM(3-5%):***

caused by insulin resistance and relative insulin deficiency associated with pregnancy

# *Type 1 diabetes mellitus*

- **Type 1A = immune mediated, type 1B = etiology unknown**
- **Familial predisposition**
- **Antiislet antibodies, cytokines → pancreatic beta cell destruction → hyperglycemia**
- **Associated with other autoimmune diseases:**  
eg. autoimmune polyglandular syndrome I (Addison disease, hypoparathyroidism, mucocutaneous candidiasis), X-linked polyendocrinopathy (autoimmune thyroiditis, enteropathy, hemolytic anemia, atopic dermatitis), pernicious anemia, celiac disease, vitiligo, autoimmune hepatitis etc.
- **Need insulin therapy. If inadequate, may add oral hypoglycemic drugs such as metformin, glitazones or acarbose**

# *Type 2 diabetes mellitus*

## **Risk factors for type 2 diabetes mellitus:-**

- Genetic factors (family history of diabetes)
- Old age (diminished homeostatic control of glucose metabolism)
- High glucose level, low insulin secretion, insulin resistance
- Physical inactivity, obesity
- Smoking
- Depression
- Intake of high calorie, alcohol, fat, low fiber, high glycemic index, low vegetable, low whole grain diet

# *Therapy of type 2 diabetes mellitus*

## *Insulin secretagogues*

*(sulfonylureas, meglitinides,  
phenylalanine derivatives)*

- Mechanism of action = stimulate insulin secretion
- Side effects = hypoglycemia, weight gain, fluid retention
- Contraindication = type 1 DM, pregnancy, major surgery, severe infection, stress or trauma, history of severe adverse reaction to sulfonylurea, predisposition to hypoglycemia (eg. patients with significant liver or kidney disease)

# *Metformin*

- **Mechanism of action** = improve insulin sensitivity in liver, skeletal muscle and adipose tissue
  - inhibit hepatic gluconeogenesis
  - enhance insulin receptor kinase activity → stimulate glucose transport by increasing activity of glucose transporter
- **Clinical use** = prevent progression of impaired glucose tolerance to overt type 2 DM and metabolic syndrome
- **Side effects** = gastrointestinal disturbance (eg. nausea, vomiting, diarrhea, anorexia), lactic acidosis (very rare), body weight loss, increase fibrinolytic activity

## ***Peroxisome proliferator-activated receptor (PPAR) modulators eg. Thiazolidinediones***

- Mechanism of action = improve insulin sensitivity and pancreatic beta cell function
- Side effects = body weight gain, hepatic dysfunction, fluid retention and edema (so not use in heart failure)

### ***alpha-glucosidase inhibitors***

- Mechanism of action = inhibit absorption of carbohydrate from small intestine
- Side effects = gastrointestinal eg. flatulence, diarrhea

## ***Glinides eg. Nateglinide (Starlix), repaglinide (Novonorm)***

- Mechanism of action = stimulate insulin secretion
- Side effects = hypoglycemia, weight gain (lesser than that of sulfonylureas)

## ***Insulin therapy for type 2 DM***

- Reserved for type 2 DM not controlled by diet, exercise and oral hypoglycemic agents
- Combination therapy = oral hypoglycemic drugs + single injection of intermediate-acting insulin at bedtime

# *Acute complication of DM*

## *(1) Hypoglycemia*

= common problem in diabetics and seriously ill patients

**Diagnosis** = plasma glucose 45-60 mg/dl

### **Symptoms of hypoglycemia:-**

- (1) **Autonomic** = palpitation, diaphoresis, anxiety, hunger, irritability, pallor, nausea, angina
- (2) **Neuroglycopenic** = headache, weakness, fatigue, confusion, amnesia, blurred vision, focal neurologic deficit, seizure, coma

- **Predisposing factors** = excessive dose of insulin or oral hypoglycemic drugs, inadequate or delayed food intake, sudden or prolonged exercise, renal and hepatic failure, diabetic gastroparesis, age, pregnancy, drugs, alcohol, medical conditions (heart failure, cardiogenic shock, starvation, sepsis, lactic acidosis, adrenal insufficiency etc.)

## *(2) Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS)*

- **DKA classically occurs in young type 1 DM, many are older and type 2 DM. HHS usually occurs in middle or old age type 2 DM. Some patients have features of HHS and DKA. Etiology = insulin deficiency + excess glucose counterregulatory hormones (catecholamines, glucagon, cortisol, growth hormone) → decrease peripheral glucose utilization → increase lipolysis (→free fatty acid for ketone body production) and proteolysis (→gluconeogenesis)**

■ **Diagnosis:-**

**DKA = hyperglycemia (usually  $\geq 300$  mg/dl), elevated blood ketones**

**HHS = hyperglycemia (usually  $\geq 600$  mg/dl), mild acidemia, profound dehydration (serum osmolarity  $\geq 320$  mOsm/Kg) in absence of severe ketosis**

■ **Precipitating factors:-**

**coexistent medical illness (eg. infection, silent myocardial infarction, stroke, pancreatitis, mesenteric ischemia), drugs (diuretics, sedative), insulin omission and eating disorder**

- **Symptoms** = nausea, vomiting, thirst, polyuria, abdominal pain, signs of dehydration, acidotic respiration, ketones on breath, hypothermia, deficits in electrolytes (Na, K, Mg, PO<sub>4</sub>), conscious disturbance.
- **Treatment** = hydration, correction of potassium deficiency, continuous insulin infusion, and treatment of underlying causes

## *Chronic complication of diabetes mellitus* *Macrovascular complications*

- **Coronary artery disease, stroke and peripheral vascular disease**

### *Microvascular complications*

- **Diabetic retinopathy:-**
- **Pathophysiology =**
  - a) formation of microaneurysm**
  - b) excessive vascular permeability**
  - c) vascular occlusion**
  - d) proliferation of new blood vessels and fibrous tissue on retina**
  - e) contraction of fibrovascular proliferation and vitreous**
- **Microvascular complication associated with risk factors (hyperglycemia, hypertension, dyslipidemia, anemia, fibrinogen etc)**
- **Leading cause of blindness**



- **Diabetic nephropathy:-**

- Microvascular complication associated with risk factors (hyperglycemia, hypertension, proteinuria, molecular mediators eg. transforming growth factor, insulin-like growth factor, vascular endothelial growth factors etc.)

- **Diabetic neuropathies:-**

- Most common = distal symmetric polyneuropathy affecting somatic sensory or motor nerves and autonomic nervous system
- Symptoms often begins in feet and progress proximally to hands

- Etiology = metabolic, vascular, autoimmune, neurohormonal growth factor deficiency. Persistent hyperglycemia → accumulation of sorbitol and fructose in nerves → nerve damage
- **Dyslipidemia and atherosclerosis**
- **Skin:-**
- Most common = skin ulceration (due to impaired wound healing)