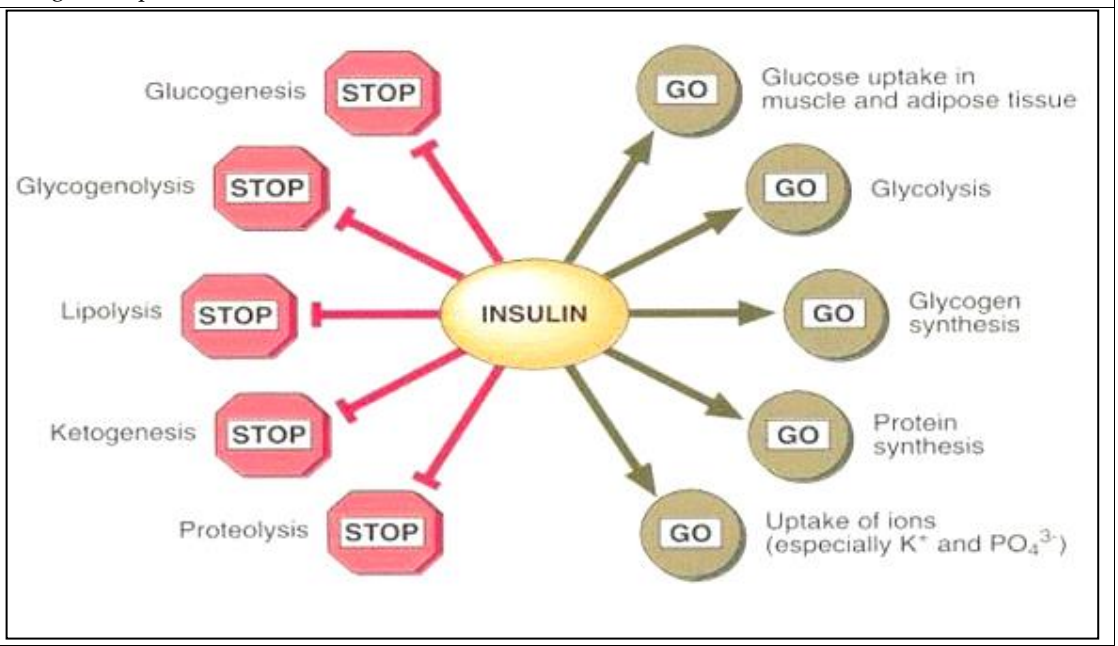
DIABETES MELLITUS

Introduction	• Refers to a group of common metabolic disorders that share the phenotype of hyperglycemia • Characterized by metabolic abnormalities and by long-term complications involving the eyes, kidneys, nerves, and blood vessels • Hyperglycemia induced by reduced insulin secretion, decreased glucose utilization, and increased glucose production
Actions of Insulin	
Diagnosis	Diagnosis is confirmed by: • *either* plasma glucose in random sample or 2 hrs after a 75 g glucose load ≥ 11.1 mmol/L (200 mg/dL) *or* • fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) *or* • HbA1c ≥ 48 mmol/mol **Pre- diabetes is classified as:** • impaired fasting glucose = fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL) and < 7.0 mmol/L (126 mg/dL) • impaired glucose tolerance = fasting plasma glucose < 7.0 mmol/L (126 mg/dL) *and* 2-hr glucose after 75 g oral glucose drink 7.8–11.1 mmol/L (140–200 mg/dL)
Classification	**Primary** • *Type 1: Insulin dependent DM:* B cell destruction (A-immune mediated & B- Idiopathic). • *Type 2: Non-insulin dependent:* Insulin Resistant Diabetes Mellitus **Secondary** • Pancreatic disease • Hormonal abnormalities • Chemical induced diabetes • Insulin receptor abnormalities • Diabetes with genetic syndromes **Etiologic classification:** **I. Type 1 diabetes** (immune-mediated beta cell destruction, usually leading to absolute insulin deficiency) **II. Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance) **III. Specific types of diabetes** **A. Genetic defects of beta cell development or function characterized by mutations in:**

	1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1) 2. Glucokinase (MODY 2) 3. HNF-1α (MODY 3) 4. Insulin promoter factor-1, HNF-1β, NeuroD1, and others leading to other forms of MODY 5. Insulin, subunits of ATP-sensitive potassium channel leading to permanent neonatal diabetes 6. Mitochondrial DNA 7. Other pancreatic islet regulators/proteins such as *KLF11, PAX4, BLK, GATA4, GATA6, SLC2A2* (GLUT2), *RFX6, GLIS3* **B. Transient neonatal diabetes** **C. Diseases of the exocrine pancreas**—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase **D. Genetic defects in insulin action**, including type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome, Lipodystrophy syndromes **E. Endocrinopathies**—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma **F. Drug- or chemical-induced**—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine **G. Infections**—congenital rubella, cytomegalovirus, coxsackievirus **H. Uncommon forms of immune-mediated diabetes**—"stiff-person" syndrome, anti-insulin receptor antibodies **I. Other genetic syndromes** sometimes associated with diabetes—Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome **IV. Gestational diabetes mellitus (GDM)**

Pathogenesis of Type 1 DM

- T-cell mediated autoimmune disease
- Presence of islet-directed autoimmunity
- Autoimmune destruction induced by an environmental factor (viral infection)

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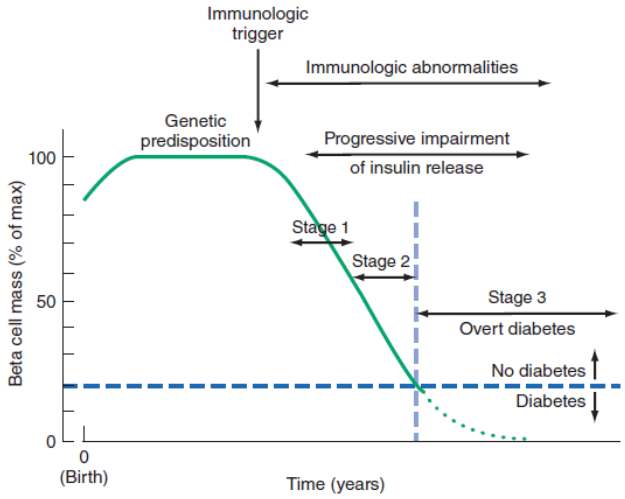
autoimmune inflammation and gradual destruction of the beta cells with time

⬇

insuline levels drop until it is not enough to control blood sugar

⬇

clinical disease appears



Pathogenesis of Type 2 DM

- Has a strong genetic component & a strong familial predisposition
- Characterized by
  - Impaired insulin secretion
  - Peripheral insulin resistance
  - Excessive hepatic glucose production

Obesity (visceral or central) is very common in type 2 DM

Prevention of Type 2 DM

- Life-style modifications prevents or delays the onset
- High risk individuals must maintain a normal body mass index and engage in regular physical activity

Clinical features

- Symptoms of hyperglycemia include
  - Polyuria
  - Polydipsia
  - Weight loss
  - Fatigue
  - Weakness
  - Blurry vision
  - Frequent superficial infections (vaginitis, fungal skin infection)
  - Slow healing of skin lesions after minor trauma
- Metabolic derangements due to hyperglycemia (osmotic diuresis, reduced glucose entry into muscle)
- catabolic state of the patient (urinary loss of glucose and calories, muscle breakdown due to protein degradation and decreased protein synthesis).
- Blurred vision due to change in water content of the lens and resolves with control of hyperglycemia
- Characteristics of type 1 DM:
  - Onset of disease before the age of 30 years
  - Lean body
  - Requirement of insulin as the initial therapy
  - Liability to develop ketoacidosis
  - An increased risk of other autoimmune disorders (autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, and vitiligo)
- Characteristics of type 2 DM:
  - Develop diabetes after the age of 30
  - Are usually obese (80% are obese, but elderly individuals may be lean)
  - Might not require insulin therapy initially
  - May have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or polycystic ovary syndrome
- Insulin resistance is often associated with abdominal obesity and hypertriglyceridemia.

Laboratory Assessment	**Criteria of diagnosis of DM** • Fasting (overnight): Venous plasma glucose concentration: **126 mg/dL** on at least two separate occasions. • Two-hour plasma glucose concentration: 200 mg/dL during oral glucose tolerance test. • Random blood sugar: 200 mg/dL + symptoms of diabetes (polyuria, polydipsia, and weight loss)
Treatment	• Goals of therapy for type 1 or type 2 DM are to o Eliminate symptoms related to hyperglycemia. o Reduce or eliminate the long-term microvascular and macrovascular complications of DM. o Achieve as normal a life-style as possible. • Type 2 Diabetes Mellitus o Goals of therapy for type 2 DM are like those in type 1: - Improved glycemic control with near normalization of the HbA1c. - Care of obesity, hypertension, dyslipidemia, cardiovascular disease and detection & management of DM-related complications. o Begin with diet therapy for one month, start drug therapy if doesn't subside o Oral glucose lowering drugs are to be used in type 2 diabetes only **Oral Drugs** • Increase insulin secretion: - Sulphonylurea - Glybenclamide (daonil) - Glipizide (diamicron) - Glimepride (amaryl) - Side effects: hypoglycemia, weight gain. • Biguanides: - Increase glucose utilization - Decrease hepatic glucose production - Promote weight loss (metformine = glucophage) • Alpha glucosidase inhibitors: Prevent glucose absorption (acarbose = glucobay). • Thiazolidinediones: New group reduce insulin resistance, increase glucose utilization (rosiglitazone = avandia). Side effects: weight gain. **Insulin therapy in Type2 DM** • Considered in lean individuals or those with severe weight loss, underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in acutely ill individuals • Pregnancy, patients with transplanted kidney • Started as single dose of S.C intermediate acting insulin at bedtime; it can be combined with oral drugs. **New treatment** • Pancreatic transplantation • Pancreatic islet cell transplantation

COMPLICATIONS OF DM

Acute Complications:

1. Diabetic Keto Acidosis (DKA)	
Introduction	Seen mainly in type 1 DM more than type 2 DM Potentially associated with serious complications if not treated promptly
Symptoms	• Nausea and vomiting are often present

	• Thirst and polyuria due to hyperglycemia and glucosuria leading to dehydration • Tachycardia and hypotension • Abdominal pain • Altered mental state • Rapid acidotic breathing
Physical Signs	• Tachycardia • Reduced skin elasticity & Dry mucous membranes • Dehydration & Hypotension • Tachypnea • Kussmaul's respirations &an acetone odor on the patient's breath (both secondary to metabolic acidosis) are classic signs of the disorder • Abdominal tenderness • Fever, Lethargy & CNS depression may evolve into coma with severe DKA. • Cerebral edema (extremely serious complication of DKA), seen most frequently in children.
Precipitating Factors	• Inadequate insulin intake • Infection • Infarction (coronary, cerebral, peripheral) • Drugs
Pathophysiology	**Results from:** Insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). Both insulin deficiency and glucagon excess, in particular, are necessary for DKA to develop. ⇩ **Results in:** - Increased gluconeogenesis - Glycogenolysis - Ketone body formation in the liver - Increasing substrate delivery from fat &muscle (free fatty acids, amino acids) to the liver. *Ketosis* occurs due to marked increase in free fatty acid release from adipocytes, with a resulting shift toward ketone body synthesis in the liver.
Laboratory alterations	DKA is characterized by: - Hyperglycemia - Ketosis, and metabolic acidosis - Serum bicarbonates are reduced - Body stores of electrolytes are reduced (sodium, chloride, phosphorous, &magnesium).
Treatment	• Confirm diagnosis (hyperglycemia, metabolic acidosis, and ketone bodies). • Hospital admission, better intensive care. • Continue laboratory assessment for electrolytes, acid base and kidney function. • Replace fluids- normal saline 1-2 liters in the first few hours, then half normal saline, then 5% dextrose plus half normal saline if the RBS reach 250 mg%. • Regular insulin IM or IV 10-20 units, then 5-10 units/hour by IV infusion. • Treat precipitating factors: Infection, infarction, drugs (Cociane). • Correct electrolytes, especially K • Continue treatment until the patient is stable, acidosis disappear, blood sugar between 150-250 mg %. • Once the patient start to eat, shift to long acting or combined insulin.
Complications of DKA	• cerebral edema, often seen in children • Venous thrombosis and adult respiratory distress syndrome
2. **Non Ketotic Hyperosmolar State**	
Pathophysiology	• Insulin deficiency is less severe than DKA

	• osmotic diuresis resulting from hyperglycemia leads to profound intravascular volume depletion, exacerbated by inadequate fluid replacement, causing little to no ketosis (insulin / glucagon does not favor ketosis) • Marked hyperglycemia (>1000 mg%).
Clinical Features	Most commonly seen in elderly individuals with type 2DM. Prominent features include: - Polyuria - Orthostatic hypotension - neurologic symptoms -altered mental status, lethargy, seizure, and possibly coma.
Treatment	• Hypotonic saline infusion (0.45% saline) should be used. • After hemodynamic stability is reached, correct the free water deficit using hypotonic fluids (0.45% saline initially then 5% dextrose in water). • Calculated free water deficit (which averages 9 to 10 L) should be reversed over the next 1 to 2 days. • Potassium repletion • Fluid therapy lowers glucose initially • Insulin therapy is less required than DKA, insulin 5 to 10 units first followed by intravenous constant infusion rate (3 to 7 units/h).
3. ***Hypoglycemia*** **-** The most serious complication of diabetes mellitus therapy	
Symptoms	Behavioral changes, confusion, fatigue, seizure, loss of consciousness, and death Hypoglycemia-induced autonomic responses include palpitations, tremor, and anxiety and cholinergic symptoms like sweating, hunger, and paresthesia.
Treatment	Oral treatment with glucose tablets or glucose-containing fluids, candy, or food. A reasonable initial dose is 20 g of glucose. Parenteral therapy- Intravenous glucose (25 g) given using a 50% solution followed by a constant infusion of 5 or 10% dextrose.

Chronic complications:

1. Ophthalmologic Complications		
Introduction	• Leading cause of blindness between the ages of 20 and 74 in the United States. • Duration of DM and degree of glycemic control are the best predictors for retinopathy development	
Types	***Non-proliferative diabetic retinopathy***	**Age of occurrence:** • Almosy all individuals who have had DM for >20 years. • Appears between the first and second decade. **Changes include:** • Retinal vascular microaneurysms • Blot hemorrhages • Cotton wool spots, leading at the end in retinal ischemia.
	Proliferative diabetic retinopathy	**Occurrence:** • Not in every patient. **Appearance:** • Neovascularization in response to retinal hypoxia is the hallmark • Ruptured vessels leads to vitreous hemorrhage, fibrosis, and ultimately retinal detachment.
2. Renal Complications		
Introduction	• Diabetic nephropathy is the leading cause of end stage renal failure • Proteinuria is associated with markedly reduced survival and increased risk of cardiovascular disease. • Individuals always have diabetic retinopathy also.	
Cause	Due to:	

<table>
<tr><td></td><td colspan="2">• Chronic hyperglycemia that causes hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration, increased glomerular capillary pressure), and structural changes in the glomerulus.
• Smoking accelerates the decline in renal function.</td></tr>
<tr><td>Features</td><td colspan="2">• 5 to 10 years of type 1 DM 40% of individuals begin to excrete small amounts of albumin in the urine: microalbuminuria which is defined as 30 to 300 mg/d in a 24-h collection.
• Appearance of microalbuminuria (incipient nephropathy) in type 1 DM is a very important predictor of progression to overt proteinuria (>300 mg/d).</td></tr>
<tr><td colspan="3">3. Neuropathy</td></tr>
<tr><td>Introduction</td><td colspan="2">Diabetic neuropathy occurs in approximately 50% of individuals with long-standing type 1 and type 2 DM Development correlates with the duration of diabetes and glycemic control.</td></tr>
<tr><td rowspan="3">Types</td><td>Polyneuropathy</td><td>• Most common form is distal symmetrical polyneuropathy. presents with distal sensory loss.
• Hyperesthesia, parathesia, and pain may also occur.
Physical examination reveals:
• Sensory loss
• Loss of ankle reflexes
• Abnormal position sense.
• Paresthesia is characteristically perceived as a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally.
• Neuropathic pain occasionally preceded by improvement in their glycemic control.
• Pain typically involves the lower extremities, is usually present at rest, and worsens at night.</td></tr>
<tr><td>Mononeuropathy, polyradiculopathy, and autonomic neuropathy</td><td>• Mononeuropathy is pain and motor weakness in the distribution of a single nerve, most commonly the third cranial nerve which starts by diplopia.
• Physical examination reveals:ptosis and opthalmoplegia with normal papillary constriction to light.</td></tr>
<tr><td>Diabetic polyradiculopathy</td><td>It is a syndrome characterized by:
• Severe disabling pain in the distribution of one or more nerve roots, accompanied by motor weakness.
• Intercostal or truncal radiculopathy causes pain over the thorax or abdomen.
• Involvement of the lumbar plexus or femoral nerve may cause pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors.
• It is a self-limiting condition within a year.</td></tr>
<tr><td colspan="3">4. Gastrointestinal Complications</td></tr>
<tr><td colspan="3">• Longstanding DM may affect the motility and function of the gut,through autonomic neuropathy.
• Gastroparesis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal distension.
• Causes nocturnal diarrhea, alternating with constipation</td></tr>
<tr><td colspan="3">5. Genitourinary Complications</td></tr>
<tr><td colspan="3">• Cystopathy begin with an inability to sense a full bladder and a failure to void completely.
• Erectile dysfunction and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication).</td></tr>
<tr><td colspan="3">6. Lower limbs complications</td></tr>
<tr><td colspan="3">• Diabetes is the leading cause of nontraumatic lower extremity amputation.
• Foot ulcers and infections are also a major source of morbidity
• Many factors are involved in the pathogenesis of these complications:
1. Neuropathy interferes with normal protective mechanisms and allows the patient to sustain repeated trauma to the foot
2. Peripheral vascular disease leading to poor wound healing.</td></tr>
</table>

- **Autonomic neuropathy results in:**
  - Anhidrosis promoting drying of the skin, fissure formation, and hence skin ulceration.
- **Risk factors for foot ulcers or amputation include:**
  - Male sex
  - History of diabetes >10 years duration
  - Peripheral neuropathy
  - Abnormal structure of foot (bony abnormalities, callus & thickened nails)
  - Peripheral vascular disease
  - Smoking
  - History of previous ulcer or amputation

7. Diabetic skin complications

- Most common skin complication are:
  - Protracted wound healing
  - Skin ulceration
- Diabetic dermopathy also termed pigmented pretibial papules, or "diabetic skin spots," begins as an erythematous area then ends in a circular hyperpigmentation. Sometimes pretibial bullae.
- Results from minor mechanical trauma in the pretibial region and are more common in elderly men with DM.
- Necrobiosis lipoidica diabeticorum, a rare lesion affects young women with type 1 DM starts as erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration.
- Acanthosis nigricans (sometimes a feature of severe insulin resistance), hyperpigmented velvety plaques seen on the neck or extensor surfaces.
- Lipoatrophy occuring at insulin injection sites, scleredema (areas of skin thickening on the back or neck at the site of previous superficial infections) and granuloma annulare (erythematous plaques on the extremities or trunk).

Management:

- It involves treating hyperglycemia to prevent long term complications.

Principles of treatment:

a. Urgent treatment with insulin for type I DM
b. Lifestyle modification and diet changes in type II DM
c. Oral hypoglycemic agents are then prescribed depending on the glycol Hb levels
d. Prompt referral to specialists to rule out complications.

Oral hypoglycemic agents:

- Metformin is the first drug of choice as it decreases truncal obesity and improves insulin sensitivity. If target glycol Hb is not reached within three months, dual therapy is started.
- The second drug may be a sulphonylurea, thiazolidinedione, dipeptidyl peptidase inhibitor, GLP 1 receptor agonist or insulin. This decision is made based on patient's lifestyle, hypoglycemia risk and weight loss intended.
- If adequate glycol Hb is not achieved in 3 months, triple therapy should be advocated.

a. Sulphonylureas: these are insulin secretagogues, they increase insulin secretion from the islet cells of pancreas. They do so by closing ATP sensitive K+ channels and thus decreasing K+ influx and thus, triggers insulin secretion. The main side effects are weight gain and in creased risk of hypoglycemia. Glibenclamide, gliclazide are the common ones.
b. Biguanides: Metformin is the only drug in this class. It increases sensitivity of tissues to insulin, reduces gluconeogenesis, increases insulin mediated glucose uptake by cells and increases weight loss. It is also helpful in microvascular diseases. The usual dose is 500-1000mg twice daily.
c. Alphaglucosidase inhibitors: acarbose is an example. They inhibit carbohydrate metabolsim in the gut.
d. Thiazolidinediones or PPRA gamma agonists: they bind to and activate peroxisome proliferator activated receptor on the nuclear surface of adipose tissues. Common drugs are rosiglitazone and pioglitazone. Risk of hypoglycemia is less.
e. DPP inhibitors and GLP receptor agonists: these drugs bring about their desired effect by behaving like incretin hormone: incretins are peptides released in the gut following intake of food. They increase insulin secretion. As a result, the risk of hypoglycemia is increased. Common drugs are sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. Currently available GLP agonists are exenatide, liraglutide, lixisenatde.

f. Sodium and glucose transporter 2 inhibitors: dapagliflozin, canagliflozin and empagliflozin ar available for use. These drugs inhibit reabsorption of glucose by the proximal tubule. Side effcts include calorie loss and increased genitourinary infections.

g. Insulin therapy:

Rapid acting insulin	Insulin lispro, aspart and glulisine
Short acting insulin	Insulin regular
Intermediate insulin	Insulin isophane, lente
Long acting insulin	Insulin ultralente

The choice of insulin regimen depends on the desired degree of glycemia.