Diabetes
Diabetes Mellitus

Def:

It is a state of chronic hyperglycemia due to disturbances in carbohydrate, lipid and protein metabolism caused by

- Lack of insulin secretion
- Decreased sensitivity of the tissues to insulin
Classification of diabetes mellitus

Diabetes mellitus

Primary

- Type-I or insulin dependent diabetes mellitus (IDDM) (juvenile onset diabetes mellitus)
- Type-II or non-insulin dependent diabetes mellitus (NIDDM) (Adult onset diabetes mellitus)

Secondary to other diseases or conditions

- Destructive pancreatitis, e.g., chronic pancreatitis
- Endocrine diseases, e.g., Cushing syndrome
- Drug induced, e.g., diuretics
Primary types of Diabetes mellitus

Main Types of Diabetes Mellitus (D.M.)

Type I (IDDM)
Insulin Dependent Diabetes Mellitus

Type II (NIDDM)
Non-Insulin Dependent Diabetes Mellitus
Type I Diabetes Mellitus/ (IDDM)

Onset: at about 14 years of age (juvenile diabetes mellitus).

Caused by lack of insulin secretion due to destruction of pancreatic beta cells. The cause of B-cell destruction may be due to

- Viral, Autoimmune disorders
- Hereditary tendency for B-cell degeneration

The amounts of insulin secreted are markedly reduced.
Symptoms

- Polyuria (frequent urination)
- Polydypsia (excessive thirst)
- Polyphagia (excessive hunger)
- The patients are not obese

Metabolic complication such as

- Ketoacidosis
- Hyperglycemic episodes
Type II Diabetes Mellitus/ (NIDDM)

Onset: above 40 years of age (adult onset diabetes mellitus).

caused by decreased sensitivity (decreased response to insulin) of target tissues to insulin (insulin resistance) due to inadequate insulin receptors on the cell surfaces of the target tissues.
• This syndrome is often found in obese persons, associated with multiple metabolic abnormalities.
Treatment

1. **In early stage**, by diet control, exercise and weight reduction an no exogenous insulin administration

2. **Drugs** that increase insulin sensitivity or additional release of insulin by pancreas.

3. **In the later stages,** insulin administration is Required.
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Clinical features of Diabetes mellitus

- The lack of insulin activity results in failure of transfer of glucose from plasma into the cells.

- The body responds as if it were in the fasting state with stimulation of:
  - Glycogenolysis.
  - Gluconeogenesis.
  - Lipolysis.
1- **Hyperglycemia**

The glucose adsorbed after a meal is not metabolized at the normal rate and therefore accumulates in the blood.

2- **Glucosuria**

Increased blood glucose causes loss of glucose in urine.
3- Polyuria

- The loss of glucose in the urine causes \textit{osmotic diuresis}.
- The osmotic effect of glucose in the renal tubules greatly decreases tubular reabsorption of fluid.
- The overall effect is \textit{massive loss of the fluid} in the urine (\textit{Dehydration}).
- Polyuria is associated with \textit{loss of H}_2\textit{O soluble vitamins} as well as \textit{electrolytes as K}^+, \textit{Na}^+. 
4- Polydepsia

The fluid loss and hyperglycemia increases the osmolarity of plasma, stimulating the thirst sensation.
5- ↑ rate of **catabolism of triglycerides** with mobilization of free fatty acids from adipose tissues 

(loss of weight)

6- ↑↑ **fatty acids oxidation** --> ↑ ketone bodies formation (acetoacetic acid, B hydroxybutyric acid) 

(ketonemia and ketonurea).

They are buffered in blood or other tissues ---- leads to loss of buffer cation ([HCO₃]⁻) ---- depletes (the alkali reserve) causing **ketoacidosis**.
5- ↑↑ protein catabolism  
(muscle wasting)

6- ↓↓ protein synthesis ------ ↓↓ antibodies formation ------ the patients liable for
(infections and poor wound healing)
7- **Secondary effects:**

Chronic high glucose concentration cause **tissue injury**

Eg. the functions of blood vessels in multiple tissues is **impaired** ---- inadequate blood supply to the tissue.

**This in turn leads to increased risk for:**

- heart attack
- stroke (cerebral arterial occlusion)
- nephropathy
- retinopathy and blindness
- peripheral neuropathy and cataract
- hypertension, secondary to renal injury
- Atherosclerosis, secondary to abnormal lipid metabolism
Metabolic changes of DM

Diabetes mellitus

- Insulin deficiency and glucagon excess
  - Decreased glucose uptake muscle and other tissues
    - Hyperglycemia
      - Glucosuria
        - Osmotic diuresis (Electrolyte and water depletion)
  - Increased protein catabolism
    - Increased plasma amino acids
      - Increased nitrogen loss in urine in the form of urea
        - Increased gluconeogenesis
          - Increased lipolysis
            - Increased free fatty acids oxidation
              - Increased ketogenesis
                - Ketosis
      - Dehydration
        - Dehydration
          - Diabetic ketoacidosis
            - Coma
              - Death
Diagnosis of Diabetes Mellitus

For diagnosis of type I diabetes, the diagnosis is usually early because hyperglycemia appears abruptly and accompanied by serious metabolic complications.
For diagnosis of type II diabetes, the diagnosis may be difficult because the hyperglycemia is often not severe enough for individual to notice symptoms of diabetes.
Diagnosis of DM

1- Measurement of blood Glucose conc.
2- The glucose tolerance test
3- Glycated haemoglobin
4- Glycated plasma proteins
5- Microalbuminuria
Diagnosis of Diabetes Mellitus

- Fasting plasma glucose concentration should be measured in all asymptomatic individuals at 45 years of age with subsequent follow up testing every 3 years.
Criteria for diagnosis of DM

1- Classic symptoms of diabetes and causal plasma glucose conc. $\geq 200$ mg/dl

2- Fasting plasma glucose conc. $> 126$ mg/dl on more than one occasion is diagnostic.

3- A 2 hr post-load plasma glucose conc. $\geq 200$ mg/dl during the (OGTT).
The glucose tolerance test

**Def:** Glucose tolerance means the ability of the body to utilize glucose.

GTT can be performed by 2 ways:

- **Oral GTT:** When glucose is administered by mouth
- **IV GTT:** When glucose is administered by vein

used for persons with malabsorption syndrome or previous gastric or intestinal surgery
The performance of OGTT

- **Discontinue** (when possible) medication known to affect glucose tolerance.

- The patient is instructed to eat a high carbohydrate diet for at least 3 days prior to the test.
1. **After 10-16 hours fast**, blood sample is taken for glucose determination as well as a urine sample is obtained for glucose detection.

2. **Glucose load** in a concentration of 0.75 g/kg body weight in 200 ml water is drunk.

3. Samples of blood & urine are **collected** at 30 intervals over a period of 2 hours (Their glucose content are determined & urine is tested for glucosuria).

4. The results are **plotted** for time against Bl. Glucose level (mg/dl)
Types of glucose tolerance test

- Normal glucose tolerance curve
- Abnormal glucose tolerance curve
  - Diminished glucose tolerance
  - Increased glucose tolerance
Normal glucose tolerance curve

At the start Fasting blood glucose is within the normal range 70-110 mg\%.

At half to hour Blood glucose level rises to a peak (120-140 mg/dl).

After 2 hours Blood glucose level return rapidly to normal levels.

Glucose is not present in any of the urine specimens collected for 2 hours.
I. Diminished glucose tolerance

**Def:** Decreased ability of the body to utilize glucose

**Character:**

- *Fasting blood glucose* is higher than normal limit
- *After glucose ingestion*, blood glucose level will *rise higher* exceed renal threshold (> 180 mg/dl).
- The blood glucose *remains high* for a longer time and may not return to fasting *even after 3 hours.*
The urine sample corresponding blood glucose level $> 180 \text{ mg/dl}$ shows glucosuria (+ve bendict test)

**Causes:**

- diabetes mellitus
- Certain endocrinal disorders
  - Hyperthyrodisism
  - Hyperpituitarism
  - Hyperadrenalism (cushing syndrome)
I. Increased glucose tolerance

**Def:** increased ability of the body to utilize glucose

**Character:**

- *Fasting blood glucose* is lower than normal limit
- *After hours, Only small rise in blood glucose level* (Not > 100 mg/dl).
Causes:

- Endocrinal hypoactivity disorders
  - Hypothyrodism (myxodema, critinism)
  - Hypopitutarism
  - Hypoadrenalism (addisons disease)
The glucose tolerance curve

- **type 2 diabetic**
- **normal**
Glucose reacts *spontaneously* and *non-enzymatically* with free amino group on proteins to form covalent *glycated proteins*.

**Glycated hemoglobin**
The extent of protein glycation depends on the average glucose to which the protein is exposed and on the half-life of the protein.
• Short half-life proteins such as haemoglobin A1c may undergo glycation (4.6-6.4 are saturated with glucose).

• In poorly controlled diabetics, the saturation may rise as high as 25% and provides a better outpatient index diabetic control than blood or plasma glucose, since 60 days (due to increased availability of blood glucose).
Glycated plasma protein

- Measurement of glycated plasma proteins e.g. glycated albumin (the major component of these proteins) can also be used to monitor diabetic control.

- The short half-life of albumin means that this test reflects control of blood glucose over the previous 10-15 days.
What period of time do the various clinical tests for diabetes reflect?

Blood glucose level at the time of blood sampling

Mean glycemia over the previous 3 weeks

Mean glycemia over the previous 2 months

Blood Glucose

Glycated Albumin

Glycated Hemoglobin

These differences in the period of time over which mean blood glucose level is reflected are related to the life spans (half-life) of cells and proteins.

- Blood Glucose: Several hours
- Glycated Albumin: About 2 weeks
- Glycated Hemoglobin: About 1 month and About 2 months
Microalbuminuria

- It refers to an excessive and abnormal urinary albumin loss, which is never less below the lower limit of detection of routine methods.
- The occurrence of microalbuminuria, has been shown to be a signal for progression to diabetic nephropathy.
Complications of diabetes mellitus

**Acute complications**
- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic nonketotic coma
- Diabetic lactic acidosis
- Hypoglycemic coma

**Chronic complications**
- Diabetic nephropathy
- Diabetic retinopathy
- Diabetic neuropathy
- Peripheral vascular disease
- Cataract
Biochemical changes of diabetic complications
Diabetic Keto Acidosis

Hyperglycemia

Ketones Bodies

Metabolic Acidosis
Diabetic ketoacidosis

Occur in infection, stress and decreased insulin intake

Pathogenesis:

- Severe insulin deficiency:
  interfere with glucose entry into the cells

- Hyperglycemia

- Decreased glucose utilization:
  excessive Fat utilization for energy production
  excessive formation of ketone bodies
Effect of increase of KB are:

- Excretion through lung (aceton odour)
- Excretion through kidney (Ketonuria- glucosuria - excessive water & electrolyte loss) dehydration
- Metabolic acidosis (decreased bicarbonate)
- Marked interference with insulin action vicious circuit
Coma results from the effect of the following on brain cells:

- Acidosis
- Ketonemia
- Dehydration
- Electrolyte imbalance
Normally...

Hyperglycemia → ↑Insulin → ↓Glucose production → ↓Gluconeogenesis → ↓Glycogenolysis → Normoglycemia

↑Glucose uptake
DKA

Hyperglycemia → ↑Insulin

↑Glucose production

↓Glucose uptake

↑Gluconeogenesis

↑Glycogenolysis

Hyperglycemia
D.K.A.
PATHOPHYSIOLOGY

NO INSULIN

MARKED HYPERGLYCEMIA

OSMOTIC DEHYDRATION

GLUCOSURIA

OSMOTIC DIURESIS

POLYURIA

POLYDIPSIA

WEIGHT LOSS

LIPOLYSIS

CELLULAR HUNGER

KETOACIDOSIS

POLYPHAGIA
Hyperosmolar hyperglycemic non ketotic coma

Occur in NIDDM or IDDM if insulin is given

Also, occur in older persons who live alone or impaired renal function
Pathogenesis:

Insulin is sufficient to prevent ketoacidosis but insufficient to control hyperglycemia. So,

**Hyperglycemia---diuresis-----dehydration**

occur in elderly diabetic persons who live alone, or who develop infection which worsen hyperglycemia and no adequate water intake ----

**hyperosmolarity----brain infection**
HHONK PATHOPHYSIOLOGY

Very insufficient INSULIN

MARKED HYPERGLYCEMIA

SEVERE OSMOTIC DEHYDRATION

GLUCOSURIA

OSMOTIC DIURESIS

POLYURIA

POLYDIPSIA

LIPOLYSIS Without KETOSIS

WEIGHT LOSS

CELLULAR HUNGER

POLYPHAGIA
Hypoglycemic coma

**Due to** increased insulin intake or missed diet

**Biochemical changes:**

- **Blood glucose** $\leq 50$ mg/dl----Normal Hco3.
- **Urine** ----Glucose and Ketones may be normal but first sample contain glucose because it is of the day before.
Diabetic lactic acidosis

Occur in diabetic patient recieving the oral hypoglycemic drug (biguanides)---which promote glycolysis

accumulation of lactic acid------acidosis ----

-coma
Pathogenesis of chronic complication

1- Glucose reacts spontaneously and non-enzymatically with free amino group on proteins to form covalent glycated proteins.

The extent of protein glycation depends on the average glucose to which the protein is exposed and on the half-life of the protein.
Long lived structural protein (eg lens protein) may be damaged as a result of abnormal increase in protein glycation.

Glycation of structural protein in arterial walls might be responsible for the microvascular disease (coronary heart diseases, hypertension and diabetic foot).

The amounts of these products do not return to normal when hyperglycemia is corrected; they accumulate continuously over the life span of the protein.
2. A number of tissues don't require insulin for the entry of glucose into cells. Hence the intracellular glucose of the tissues attains a level similar to that of blood, then excess glucose can be reduced to sorbitol by aldose reductase and part of it is oxidized to fructose by sorbital dehydrogenase.
Large amounts of sorbitol and fructose inside the cells will causing **hypertonicity** and **water retention**.

These are associated with pathological complication of D.M. as **cataract**, **neuropathy**, **nephropathy** and **retinopathy**.
Thank you!
Hyperosmolality
Hyperglycemia
Non-Ketonic Coma

NO Acidosis
Hyperosmolality
Hyperglycemia

Ketones Bodies