Endocrine Pancreas

Diabetes Mellitus

Laboratory studies:

- Diabetes is diagnosed by any one of three criteria

1. A random blood glucose concentration of 200 mg/dL or higher, with classical signs and symptoms
2. A fasting glucose concentration of 126 mg/dL or higher on more than one occasion
3. An abnormal oral glucose tolerance test (OGTT), in which the glucose levels is 200 mg/dL or higher 2

hours after ingestion of 75 g of glucose.

Notes:

a. Persons with serum fasting glucose values < 110 mg/dL, or < 140 mg/dL for an OGTT, are considered euglycemic

b. Those with fasting glucose > 110 but < 126 mg/dL or have *impaired glucose tolerance(*OGTT values of >140 but < 200 mg/dL),, known as *prediabetes*

*1. which i*s defined as elevated blood sugar that does , not reach the criterion accepted for an outright

diagnosis of diabetes and persons with prediabetes have have a significant risk for progression to overt diabetes over time and 5% to 10% advancing to diabetes mellitus per year. for development of frank diabetes.

2.. And also,they are at *risk for cardiovascular disease*, due to abnormal carbohydrate metabolism and coexistence of other risk factors

Classification of Diabetes Mellitus

TYPE 1 Diabetes :

- It accounts for 10% of all cases
- Is an autoimmune disease destructing Pancreatic β cell leading to an absolute deficiency of insulin
- Most commonly develops in childhood, becomes manifest at puberty,
- The classic manifestations of the disease occur late in its course, after 90% of the beta cells have been destroyed

Pathogenesis:-

- The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells that may be due to defective deletion of self-reactive T cells in the thymus, and thus autoreactive T cells survive

Note

- Autoantibodies against β cell antigens, including insulin and enzyme glutamic acid decarboxylase, are detected in the blood of 70% to 80% of patients

I. Genetic factors: 20 susceptibility loci have been identified.

a. The principal susceptibility locus resides in the *locus 6p(HLA-D)* that encodes the class II MHC molecules

- 95% of white patients with diabetes have *HLA-DR3,* or *DR4,* in contrast with about 40% of normal subjects
- Despite the high relative risk in persons with particular class II alleles, most people who inherit these alleles do not develop diabetes

b. Polymorphisms in the insulin gene may reduce expression of this protein in the thymus, thus reducing the elimination of T cells reactive with this self protein

II. Additional evidence suggests that infections, may be involved and it has been proposed that certain viruses (mumps, coxsackie B viruses), may be an initiating trigger, perhaps because some viral antigens are antigenically similar to beta cell antigens leading to islets damage , but this idea is not conclusively established.

Type 2 diabetes :

Accounts for 80% to 90% of cases

- Caused by a combination of

a. Peripheral resistance to insulin action and

b. An inadequate compensatory response of insulin secretion by B-cells (*relative insulin deficiency)*

Pathogenesis :

Is a complex multifactorial disease.

1. Environmental factors, such as a sedentary life style and dietary habits, unequivocally play a role,
2. Genetic factors are also involved , as evidenced by

a. The disease concordance rate is 35% to 60% in monozygotic twins and such concordance is greater than in type 1 diabetes, suggesting an even larger genetic component in type 2 diabetes.

b. Diabetogenic genes have been identified but the but are not linked to genes involved in immune tolerance and evidence of an autoimmune basis is lacking.

Metabolic defects that characterize type 2 DM are:

I. Insulin resistance: :

- Failure of target tissues to respond to insulin and it predates the development of hyperglycemia
- It leads to

a. decreased uptake of glucose in muscle,

b. inability to suppress hepatic gluconeogenesis in the liver

Mechanism of insulin resistance

1. Functional defects in the insulin signaling pathway

- Reduced tyrosine phosphorylation of insulin receptors ,thus reduced activation of the insulin receptor and its downstream components, which attenuate signal transduction

2. Obesity and Insulin Resistance :

-Visceral obesity is common in majority of affected patients and insulin resistance is present even with simple obesity

Putative pathways leading to insulin resistance in obesity

A. *Role of excess free fatty acids* (FFAs):

- Inpatients with visceral obesity, there willl be increase in lipolysis and excess of circulating FFAs are deposited in liver and muscles
- Increased intracellular fatty acids overwhelm the fatty acid oxidation leading to accumulation of

- intermediates like diacylglycerol (DAG) and these toxic intermediates increase serine –thyronine kinase activity leading to serine phosphorylation of insulin receptor rather than tyrosine phosphorylation of insulin receptor and insulin receprior signaling proteins which attenuates insulin signaling that result in an acquired insulin resistance

b. Role of adipokines:

-Adipose tissue release *adipokines* such as leptin, resistin and adiponectin

Note: adiponectin and leptin improve insulin sensitivity while resistin decreases sensitivity of insulin receptor

In obesity

1. Release of *Adiponectin* and leptin is decreased
2. Increase release of resistin

c. *Role pf Peroxisome proliferator-activated receptor*-γ (PPARγ):

- A nuclear receptor in adipose tissue which is important in adipose tissue differentiation
- Normaly its activation leads to secretion of adiponectin that improves insulin sensitvity and shifts the deposition of FFAs in adipose tissue away from liver and skeletal muscle
- In obesity; there will be decrease in PPARγ.
- An antidiabetic drug known as thiazolidinediones acts as - agonist ligands for PPARγ so improves insulin sensitivity

II. Beta Cell Dysfunction :

- In states of insulin resistance, insulin secretion initially is higher for each level of glucose than in controls and this state is a compensation for peripheral resistance and can maintain normal plasma glucose for years but eventually, B cell compensation becomes inadequate, leads to hyper-glycemia, accompanied by absolute loss in β cells.

- The molecular mechanisms underlying B-cell dysfunction

a. Excess FFAs and glucose promote secretion of cytokines from β- cells, leading to recruitment of T-cells and macrophages into islets, resulting in β- cell death

b. Amylin, is secreted by the β- cell in conjunction with insulin, and its abnormal aggregation results in amyloid that replaces the islets

b. IAPP also engages the inflammasome and promotes IL-1β secretion, thus sustaining the inflammatory reaction in beta cells

Long term complications of Diabetes :

- There is extreme variability among patients in the time of onset , severity, and the particular organs involved but in persons with tight control of their diabetes, the onset may be delayed.

The pathogenesis of the long-term complications

I.1.Formation of advanced glycation end products

(AGEs) :Formed as a result of nonenzymatic reactions between intracellular glucose-derived precursors (glyoxal ,3-deoxyglucosone) with the

amino groups of both intra- and extracellular proteins.

- The natural rate of AGE formation is greatly accelerated in the presence of hyperglycemia.
- AGEs bind to a specific receptor (RAGE), expressed on macrophages, endothelium and vascular smooth muscle of blood vessels.

1. The effects of the AGE-RAGE signaling within vessels

a. Release of *cytokines and growth factors* from intimal macrophages

b. Generation of *reactive oxygen species* in endothelial cells

c. Enhanced *proliferation and migration of vascular smooth muscle cells into the intima and increased synthesis of extracellular matrix*

d. Can *directly cross-link extracellular matrix proteins and* AGEs cross-linked proteins can *trap*

1. Low-density lipoprotein (LDL) gets trapped within intima of large vessel walls, accelerating atherosclerosis
2. Albumin can get trapped within capillaries, accounting in part for the basement membrane thickening that is characteristic of diabetic microangiopathy

II. Activation of intracellular protein kinase C (PKC)

- Intracellular hyperglycemia can stimulate the de novo synthesis of diacyl glycerol (DAG)from glycolytic intermediates causing activation of PKC that leads to production of:

A, Vascular endothelial growth factor (VEGF),which causes neovascularization seen in diabetic retinopathy,

. b. Transforming growth factor-β, leading to increased deposition of extracellular matrix and basement membrane material

III. Disturbances in polyol pathways.

- In some tissues that do not require insulin for glucose transport (e.g., nerves, lens, kidneys, blood vessels) hyperglycemia leads to an increase in intracellular glucose that is metabolized by the enzyme *aldose reductase* to sorbitol, a polyol, and eventually to fructose, in a reaction that uses NADPH as a cofactor.

- NADPH is also required by the enzyme glutathione reductase in a reaction that regenerates reduced glutathione (GSH) which is antioxidant.
- GSH is important antioxidant and any reduction in GSH increases cellular susceptibility to *oxidative stress.that may cause damage to certain tissues like the axons of peripheral nerves.*

MORPHOLOGY in Pancreas

a. Reduction in the number and size of islets, most often in type 1

b. Leukocytic infiltration of the islets:

- seen in both type 1 and type 2 DM although it is more severe in type 1
- In both types inflammation is often absent ,by the time the disease is clinically evident

c. Amyloid replacement of islets in long-standing type 2 diabetes, appear as deposition of pink, amorphous material beginning in capillaries between cells

d. At advanced stages the islets may undergo fibrosis

e. Increase in the number and size of islets, in nondiabetic newborns of diabetic mothers, presumably, fetal islets undergo hyperplasia due to maternal hyperglycemia

Morphology and clinical manifesations of complications

1. Diabetic Macrovascular Disease.:

- The hallmark is accelerated atherosclerosis affecting the aorta , large and medium-sized arteries and it is more severe with early onset in diabetics than in nondiabetics
- Myocardial infarction due to Coronary artery athero-sclerosis is the most common cause of death in diabetics and is as common in diabetic women as in diabetic men

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- Gangrene of the lower extremities is 100 times more common in diabetics than in the general population

2. Hyaline arteriolosclerosis,

- Is the vascular lesion associated with hypertension
- Is both more prevalent and more severe in diabetics than in nondiabetics,
- but it is not specific for diabetes and may be seen in elderly persons who do not suffer from either diabetes or hypertension.

- It takes the form of hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen
- In diabetic patients, its severity is related not only to the duration of the disease but also to the presence or absence of hypertension.
- Hyaline arteriolosclerosis affects not only the afferent but also the efferent arterioles of the kidney and such efferent arteriolosclerosis is rarely if ever encountered in persons who do not have diabetes

3. Diabetic Microangiopathy. :

- Diffuse thickening of basement membranes, is most evident in the capillaries of the skin, skeletal muscle, retina and , renal glomeruli,
- It may be seen in renal tubules, nerves, and placenta.
- Despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.
- It underlies the development of diabetic nephropathy, retinopathy , and some forms of neuropathy

4. Diabetic Nephropathy.:

- Renal failure is second only to myocardial infarction as a cause of death from diabetes lesions encountered are:

1. Glomerular lesions

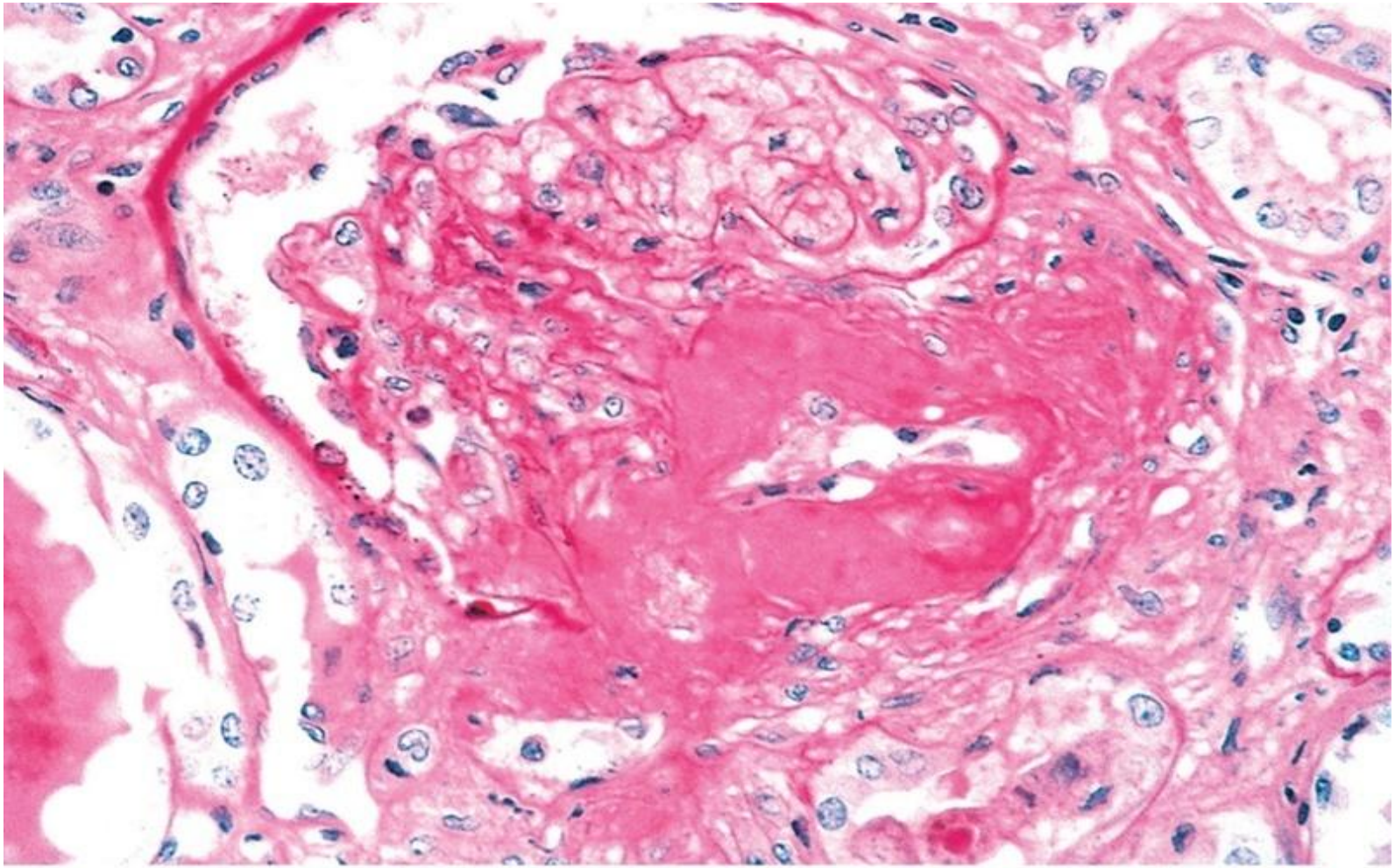
a. Capillary basement membrane thickening :can be detected by electron microscopy within a few years of onset of diabetes without any change in renal function

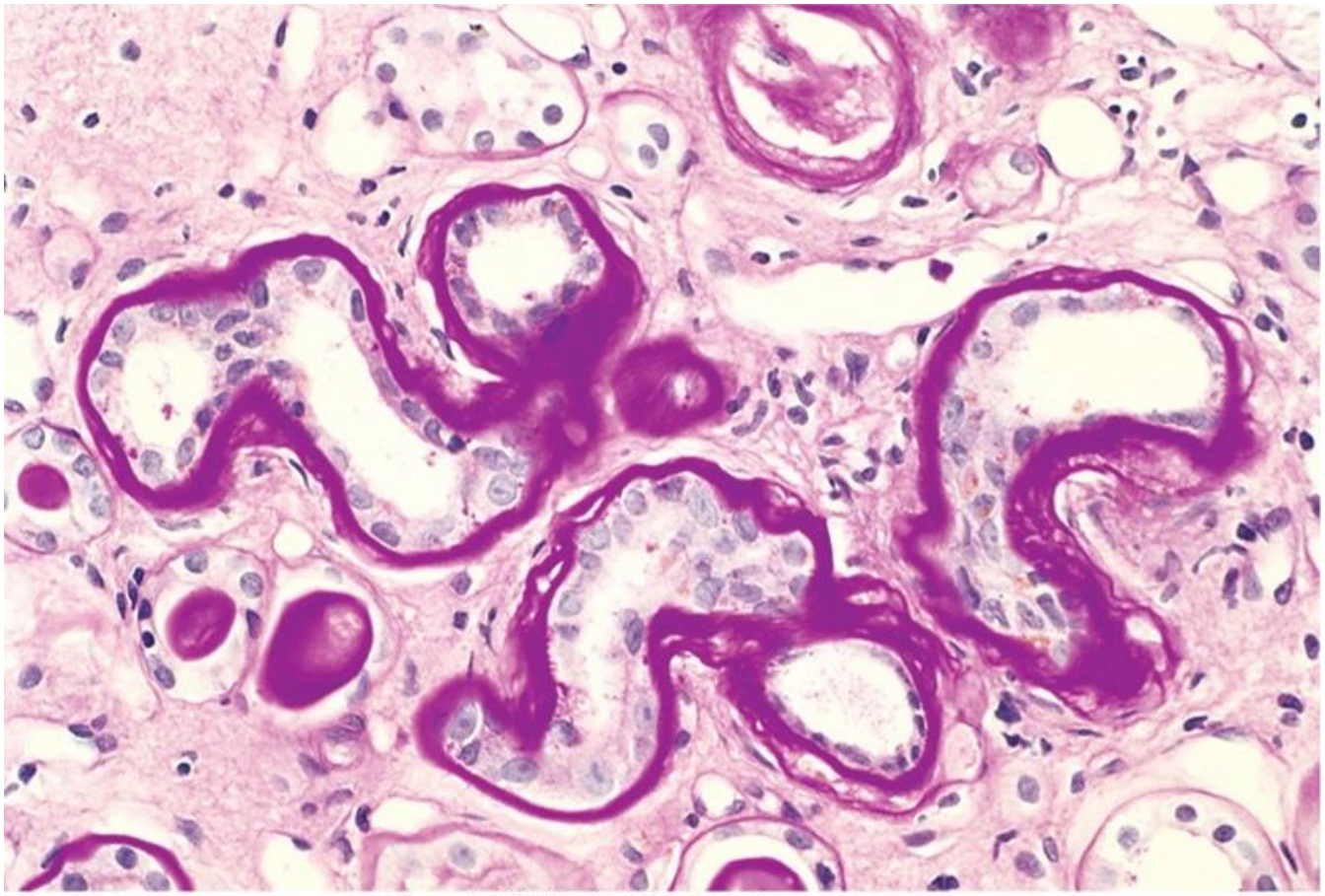
b. Diffuse mesangial sclerosis. is found in most individuals with disease than 10 years' duration

c.Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) Are ball-like deposits of a laminated matrix situated in the periphery of the glomerulus

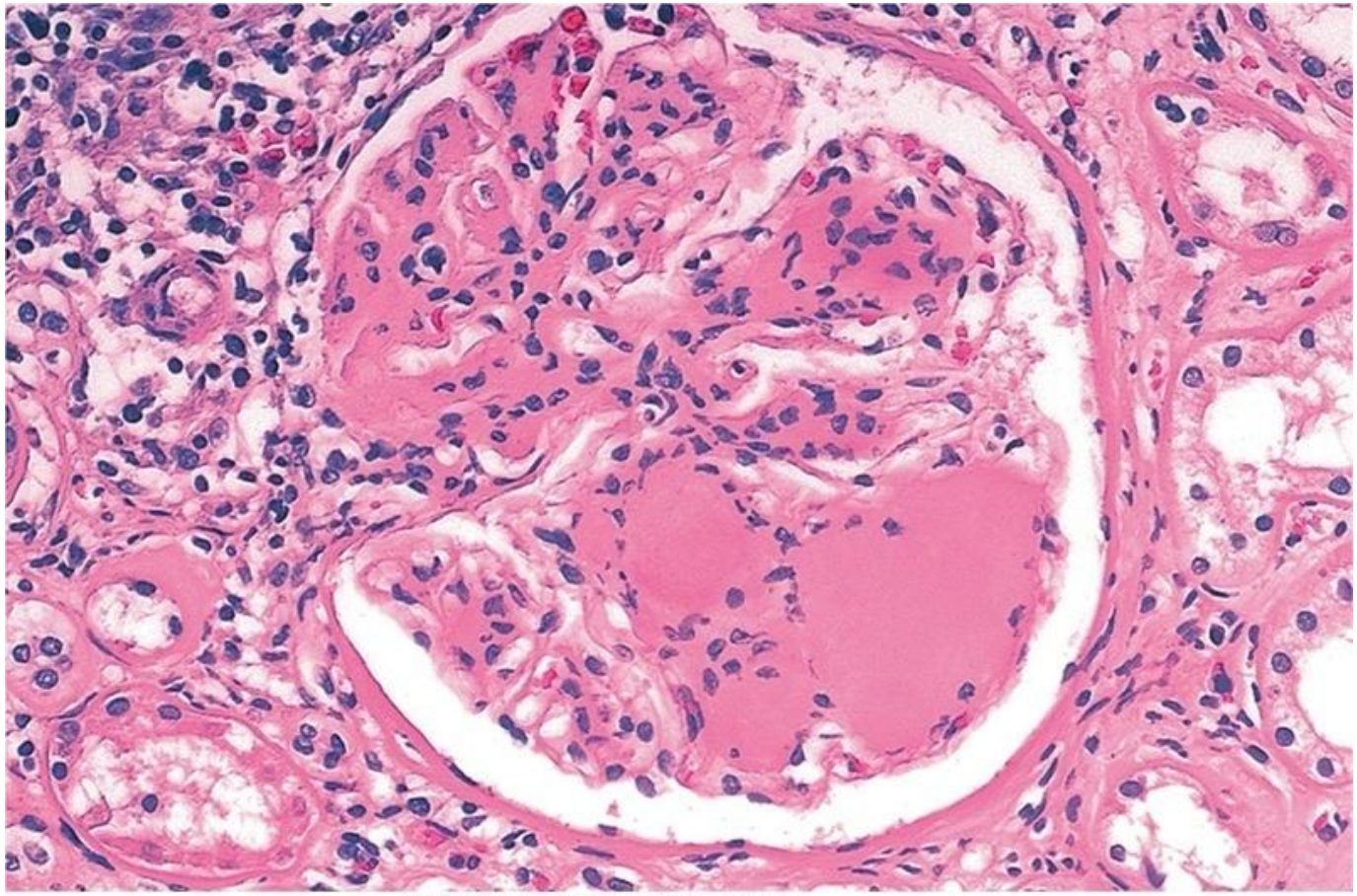
3..**Pyelonephritis**,: - Is inflammation that begins in the interstitial tissue and tubules that occur in nondiabetics as well as in diabetics but are more common and ore severe in diabetics than in the general population;

- One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics





Nodular glomerulosclerosis



- **Clinicaly: Diabetic nephropathy**:

- Is a leading cause of end-stage renal disease in USA

a. The earliest manifestation is the appearance of small amounts of albumin in the urine (> 30 but < 300 mg/day-(microalbuminuria).

- Without specific interventions, approximately 80% of patients with type 1 diabetes and 20% to 40% of those with type 2 diabetes will develop overt nephropathy

with macroalbuminuria (excretion of more than 300 mg/day) over the succeeding 10 to 15 years,.

- 20 years after diagnosis, 75% of persons with type 1 diabetes and 20% of those with type 2 diabetes with overt nephropathy will develop end-stage renal disease,

5. Ocular Complications of Diabetes:

- Visual impairment, and blindness, is one of the more feared consequences of long-standing DM
- Diabetes is the fourth leading cause of acquired blindness in USA.

Note:

- Retinopathy, the most common pattern, consists of changes that are considered by many ophthalmologists to be virtually diagnostic of the disease .

- About 60% to 80% of patients develop a form of diabetic retinopathy approximately 15 to 20 years after diagnosis and retinopathy is divided into

1. Background retinopathy
2. Proliferative retinopathy

a. Nonproliferative (background) retinopathy includes

1. Intraretinal or preretinal hemorrhages, :
2. Retinal exudates, can be either

a."soft" (microinfarcts) or

b.“ hard" (deposits of plasma proteins and lipids

3. Microaneurysms, are dilated retinal capillaries that appear through the ophthalmoscope as small red dots
4. Venous dilations and retinal edema

b. Proliferative retinopathy:

- A process of neo-vascularization and fibrosis leads to serious consequences , including blindness, especially if it involves the macula
- Vitreous hemorrhages can result from rupture of newly formed capillaries; the subsequent firosis of the hemor rhage can cause (retinal detachment)

Note- diabetic patients also have an increased propensity for glaucoma and cataract formation

6. Diabetic Neuropathy.:

a. The most frequent pattern of involvement is

a peripheral, symmetric neuropathy of the lower extremities affecting motor and sensory nerves particularly sensory

b.. Autonomic neuropathy produces disturbances in bowel and bladder function and sometimes sexual impotence,

c.. Mononeuropathy, which may manifest as sudden foot drop or wristdrop

- The neurologic changes may be the result of microangiopathy and increased permeability of capillaries that supply the nerves, as well as direct axonal damage by oxidative stress

7. Infections

- In both types of diabetes patients have enhanced susceptibility to skin infections , tuberculosis, and pyelonephritis
- and such infections cause about 5% of diabetes-related deaths

.Clinical Features of Type 1 DM

- In the initial 1 or 2 years after manifestation of overt *type 1 diabetes* ("honeymoon period"), exogenous insulin requirements may be minimal because of residual ongoing endogenous insulin secretion but thereafter the beta cell reserve is exhausted and insulin requirements increase dramatically
- Although beta cell destruction is a gradual process, the transition from impaired glucose tolerance to overt diabetes may be abrupt, heralded by an event associated with increased insulin requirements

such as infection

- The onset is marked by polyuria, polydipsia, polyphagia,

a. The hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria induces an osmotic diuresis and *polyuria,*

b. The obligatory renal water loss combined with the hyperosmolarity tends to deplete intracellular water, triggering the thirst centers of the brain and this generates intense thirst (*polydipsia*).

c. Deficiency of insulin leads to catabolism of proteins and fats which tends to induce a negative energy balance, which in turn leads to increasing appetite (*polyphagia)*

- Despite the increased appetite, catabolic effects prevail resulting in weight loss s.
- The combination of polyphagia and weight loss should point to the diagnostic possibility of diabetes

Acute complication of type 1is ***Diabetic ketoacidosis***

- Caused by deviations from normal dietary intake, unusual physical activity, infection, or stress
- The plasma glucose usually is in the range of 500 to 700 mg/dL due to absolute insulin deficiency

And unopposed effects of epinephrine and glucagon

1. The marked hyperglycemia causes diuresis and dehydration characteristic of the ketoacidotic state
2. Insulin deficiency leads to activation of lipoprotein lipase, resulting in excessive breakdown of adipose

stores , giving rise to increased FFAs which are oxidized by the liver to produce *ketones so* ketogenesis is an adaptive phenomenon in times of starvation, generating ketones as a source of energy for consumption by brain.

- The rate at which ketones are formed may exceed the rate at which they can be used by peripheral tissues, leading to *ketonemia* and *ketonuria* and if the urinary excretion of ketones is diminished by dehydration, the accumulating ketones decrease pH, resulting in metabolic ketoacidosis.

Clinical manifestations of Type 2 diabetes mellitus

- *A*lso may manifest with polyuria and polydipsia, but and patients are older than 40 years and obese
- Unfortunately, with the increase in obesity and sedentary life style type 2 diabetes is now seen in children and adolescents with increasing frequency.
- In some cases, medical attention is sought because of unexplained weakness or weight loss.
- *Most frequently, however, the diagnosis is made after routine blood or urine testing in asymptomatic persons*

Acute complication

- is called non-ketotic hyperosmolar coma

– caused by severe dehydration resulting from sustained diuresis and urinary fluid loss and the affected person is an elderly diabetic who is disabled by a stroke or infection and unable to maintain adequate water intake

- The absence of ketoacidosis and its symptoms (nausea, vomiting, respiratory difficulties) delays recognition of the seriousness of the situation until the onset of severe dehydration and coma.

- Several studies have demonstrated that complications, and the associated morbidity and mortality from diabetes are attenuated by strict glycemic control.

1. For patients with type 1 diabetes, insulin replacement therapy is the mainstay of treatment,
2. Dietary restrictions and exercise (that improves insulin sensitivity) are the "first line of defense" for type 2 diabetes.

- Most patients with type 2 diabetes will eventually

require therapeutic intervention achieved by administration of a number of agents that lower glucose levels

Note

- Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin, also known as HbA1C, which is formed by non-enzymatic addition of glucose moieties to hemoglobin in red cells.

- - HbA1C is a measure of glycemic control over long periods of time (2 to 3 months) and is relatively unaffected by day-to-day Variations and an HbA1C below 7% is taken as evidence of tight glycemic control, but patients with HbA1C levels in this range also have an increased risk of potentially life-threatening episodes of therapy-related hypoglycemia,