DIABETES MELLITUS
CHRONIC
COMPLICATIONS

affect many organ systems
and are responsible for the
majority of morbidity and
mortality associated with
the disease.
Chronic complications can be divided into vascular and nonvascular complications.
vascular complications of DM

- subdivided
- microvascular (retinopathy, neuropathy, nephropathy)
- macrovascular complications (coronary artery disease, peripheral vascular disease, cerebrovascular disease)
Nonvascular complications

- include problems such as:
  - Gastroparesis
  - sexual dysfunction
  - skin changes
chronic complications

- The risk increases with the duration of hyperglycemia.
- Apparent in the second decade of hyperglycemia.
- Type 2 DM may have a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.
chronic complications

Randomized, prospective clinical trials involving large numbers of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or reduces retinopathy, neuropathy, and nephropathy. Other incompletely defined factors also modulate the development of complications.
Because of these observations, it is suspected that a genetic susceptibility for developing particular complications exists. The genetic loci responsible for these susceptibilities have not yet been identified.
Three major theories

- Increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylation of cellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins.
Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when intracellular glucose is increased, some glucose is converted to sorbitol by the enzyme aldose reductase.
Increased sorbitol concentrations affect several aspects of cellular physiology (decreased myoinositol, altered redox potential) and may lead to cellular dysfunction.
However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy.
third hypothesis

- Hyperglycemia increases the formation of diacylglycerol leading to activation of certain isoforms of protein kinase C (PKC).
- Affect a variety of cellular events that lead to DM-related complications.
- Example, PKC activation by glucose alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons in vitro.
Growth factors appear to play an important role in DM-related complications.

Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications.
Finally, oxidative stress and free radical generation, as a consequence of the hyperglycemia, may also promote the development of complications.
The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM.

This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and then evaluated the development of retinopathy, nephropathy, and neuropathy.
glycemic control

- nonproliferative and proliferative retinopathy (47% reduction),
- microalbuminuria (39% reduction),
- clinical nephropathy (54% reduction)
- neuropathy (60% reduction).
intensive diabetes management

A group would experience 15.3 more years of life without significant microvascular or neurologic complications of DM as compared to individuals who received standard therapy.
NEUROPATHY AND DIABETES MELLITUS

- occurs in approximately 50% of individuals with long-standing type 1 and type 2 DM.
- It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy.
The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss. Hyperesthesia, paresthesia, and pain.
Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense. Paresthesia is characteristically perceived as a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally.
Pain typically involves the lower extremities, is usually present at rest, and worsens at night.

As diabetic neuropathy progresses, the pain subsides and eventually disappears, and a sensory deficit in the lower extremities persists.
Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness.

Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6 to 12 months.
Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve.
Can involve the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems.

multiple systems, including: the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems.
Is less than satisfactory.

Glycemic control and will improve nerve conduction velocity,

Avoidance of neurotoxins (alcohol), supplementation with vitamins for possible deficiencies (B₁₂, B₆, folate;

Symptomatic treatment are the mainstays of therapy
GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Gastroparesis

genitourinary dysfunction including cystopathy, erectile dysfunction, and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely.
Diabetes causes an array of long-term systemic complications, which have considerable impact on both the patient and the society because it typically affects individuals in their most productive years.
Ophthalmic complications

corneal abnormalities, glaucoma, iris neovascularization, cataracts, and neuropathies.

However, the most common and potentially most blinding of these complications is diabetic retinopathy.
Pathophysiology:

- The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease.
It was noted that diabetic retinopathy was reversed in women who had postpartum hemorrhagic necrosis of the pituitary gland (Sheehan syndrome).
increased erythrocyte aggregation, decreased RBC deformability, increased platelet aggregation, and adhesion, poor circulation, endothelial damage, and focal capillary occlusion.

Retinal ischemia contributes to the development of diabetic retinopathy.
Aldose reductase and vasoproliferative factors

Hyperglycemia shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (e.g., glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of its primary function (i.e., autoregulation of retinal capillaries).
Loss of function of pericytes results in weakness and eventual saccular outpouching of capillary walls.

These microaneurysms are the earliest detectable signs of DM retinopathy.

Ruptured microaneurysms (MA) result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages).
Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates.

Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy.
Another theory to explain the development of macular edema deals with the increased levels of diacylglycerol (DAG) from the shunting of excess glucose. This is thought to activate protein kinase C (PKC), which, in turn, affects retinal blood dynamics, especially permeability and flow, leading to fluid leakage and retinal thickening.
As the disease progresses, eventual closure of the retinal capillaries occurs, leading to hypoxia.

Infarction of the nerve fiber layer leads to the formation of cotton-wool spots (CWS) with associated stasis in axoplasmic flow.
More extensive retinal hypoxia triggers compensatory mechanisms within the eye to provide enough oxygen to tissues. Venous caliber abnormalities, such as venous beading, loops, and dilation.

Intraretinal microvascular abnormalities (IRMA) represent either new vessel growth or remodeling of preexisting vessels through endothelial cell proliferation within the retinal tissues to act as shunts through areas of nonperfusion.
The extracellular matrix is broken down first by proteases, and new vessels arising mainly from the retinal venules penetrate the internal limiting membrane and form capillary networks between the inner surface of the retina and the posterior hyaloid face.
Neovascularization

borders of perfused and nonperfused retina and most commonly occur along the vascular arcades and at the optic nerve head.

crEFs vessels rarely cause visual compromise. However, they are fragile and highly permeable.

These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.
These new blood vessels initially are associated with a small amount of fibroglial tissue formation.

As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections.

Traction may cause retinal edema.
Frequency:

In the US: Approximately 16 million Americans have diabetes,

- 50% of them not even aware that they have it. Of those that know, only one half receives appropriate eye care.
- diabetic retinopathy is the leading cause of new blindness in persons aged 25-74 years in the United States, responsible for more than 8000 cases of new blindness each year.
- This means that diabetes is responsible for 12% of blindness
Race: An increased risk of diabetic retinopathy

- Native American
- Hispanic
- African Americans
History:

- In the initial stages, patients are generally asymptomatic.
- In the more advanced stages of the disease, patients may experience symptoms, including blurred vision, distortion, or visual acuity loss.
Physical: Microaneurysms

- Earliest clinical sign of diabetic retinopathy
- Secondary to capillary wall outpouching due to pericyte loss
- Appear as small red dots in the superficial retinal layers
- Fibrin and RBC accumulation in the microaneurysm lumen
- Rupture produces blot/flame hemorrhages
- May appear yellowish in time as endothelial cells proliferate and produce basement membrane
n Dot and blot hemorrhages
  – Occur as microaneurysms rupture in the deeper layers of the retina such as the inner nuclear and outer plexiform layers
  – Appear similar to microaneurysms if they are small; may need fluorescein angiography to distinguish between the two

n Flame-shaped hemorrhages - Splinter hemorrhages that occur in the more superficial nerve fiber layer

n Retinal edema and hard exudates - Caused by the breakdown of the blood-retina barrier, allowing leakage of serum proteins, lipids, and protein from the vessels
- Cotton-wool spots
  - Nerve fiber layer infarction from occlusion of precapillary arterioles
  - Fluorescein angiography - No capillary perfusion
  - Frequently bordered by microaneurysms and vascular hyperpermeability
Venous loops, venous beading
- Frequently adjacent to areas of nonperfusion
- Reflects increasing retinal ischemia
- Most significant predictor of progression to Proliferative DR
Intraretinal microvascular abnormalities

- Remodeled capillary beds without proliferative changes
- Collateral vessels that do not leak on fluorescein angiography
- Usually can be found on the borders of the nonperfused retina
Macular edema

- leading cause of visual impairment.
- 75,000 new cases of macular edema are diagnosed annually.
- Possibly due to functional damage and necrosis of retinal capillaries
- Clinically significant macular edema (CSME) is defined as any of the following:
  » Retinal thickening located 500 mm or less from the center of the foveal avascular zone (FAZ)
  » Hard exudates with retinal thickening 500 mm or less from the center of the FAZ
  » Retinal thickening 1 disc area or larger in size located within 1 disc diameter of the FAZ
Mild nonproliferative diabetic retinopathy - Presence of at least 1 microaneurysm

Moderate nonproliferative diabetic retinopathy
- Presence of hemorrhages, microaneurysms, and hard exudates
- Soft exudates, venous beading, and IRMA less than that of severe NPDR

Severe nonproliferative diabetic retinopathy (4-2-1)
- Hemorrhages and microaneurysms in 4 quadrants
- Venous beading in at least 2 quadrants
- IRMA in at least 1 quadrant
the more advanced stages of NPDR reflect the increasing retinal ischemia setting up the stage for proliferative changes.
Causes: Risk factors

Duration of the diabetes

- In patients with type I diabetes, no clinically significant retinopathy can be seen in the first 5 years after the initial diagnosis of diabetes is made.
- After 10-15 years, 25-50% of patients show some signs of retinopathy.
- This prevalence increases to 75-95% after 15 years and approaches 100% after 30 years of diabetes.
In patients with type II diabetes, the incidence of diabetic retinopathy increases with the duration of the disease.

- Patients with type II diabetes:
  - 23% have NPDR after 11-13 years
  - 41% have NPDR after 14-16 years
  - 60% have NPDR after 16 years
Lab Studies:

- Fasting glucose
- Hemoglobin A1c (HbA1c)
Imaging Studies:

Fluorescein angiography is an invaluable adjunct in the diagnosis and management of diabetic retinopathy.

- Microaneurysms would appear as pinpoint hyperfluorescence that does not enlarge but rather fades in the later phases of the test.
- Blot and dot hemorrhages can be distinguished from microaneurysms because they appear as hypofluorescent rather than hyperfluorescent.
- Areas of nonperfusion appear as homogenous dark patches bordered by occluded blood vessels.
- IRMA is evidenced by collateral vessels that do not leak, usually found in the borders of the nonperfused retina.
multiple microaneurysms.