Diabetes Mellitus: chronic complications

Assistant of Department Tetiana V. Zolotarova

Candidate of Medicine, Associate Professor of Department Ella V. Karnaukh

Head of the Department of Propaedeutics of Internal Medicine and Physical Rehabilitation, Candidate of Medicine

Mariia S. Brynza

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DM: Complications

A summary of the features of diabetes-related complications includes the following:

- Duration and degree of hyperglycemia correlate with complications
- Intensive glycemic control is beneficial in all forms of DM
- Blood pressure control is critical, especially in type 2 DM
- Survival in patients with type 1 DM is improving, and diabetes-related complications are declining
- Not all individuals with diabetes develop diabetes-related complications.

DM: Complications

Four theories, which are not mutually exclusive, on how hyperglycemia might lead to the chronic complications of DM include the following pathways.

- (1) Increased intracellular glucose leads to the formation of advanced glycosylation end products, which bind to a cell surface receptor, via the nonenzymatic glycosylation of intra- and extracellular proteins, leading to cross-linking of proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and altered extracellular matrix composition
- (2) Hyperglycemia increases glucose metabolism via the sorbitol pathway related to the enzyme aldose reductase.
- (3) Hyperglycemia increases the formation of diacylglycerol, leading to activation of protein kinase C, which alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons
- (4) Hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production, leading to altered function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor β (TGF-β) or plasminogen activator inhibitor-1.

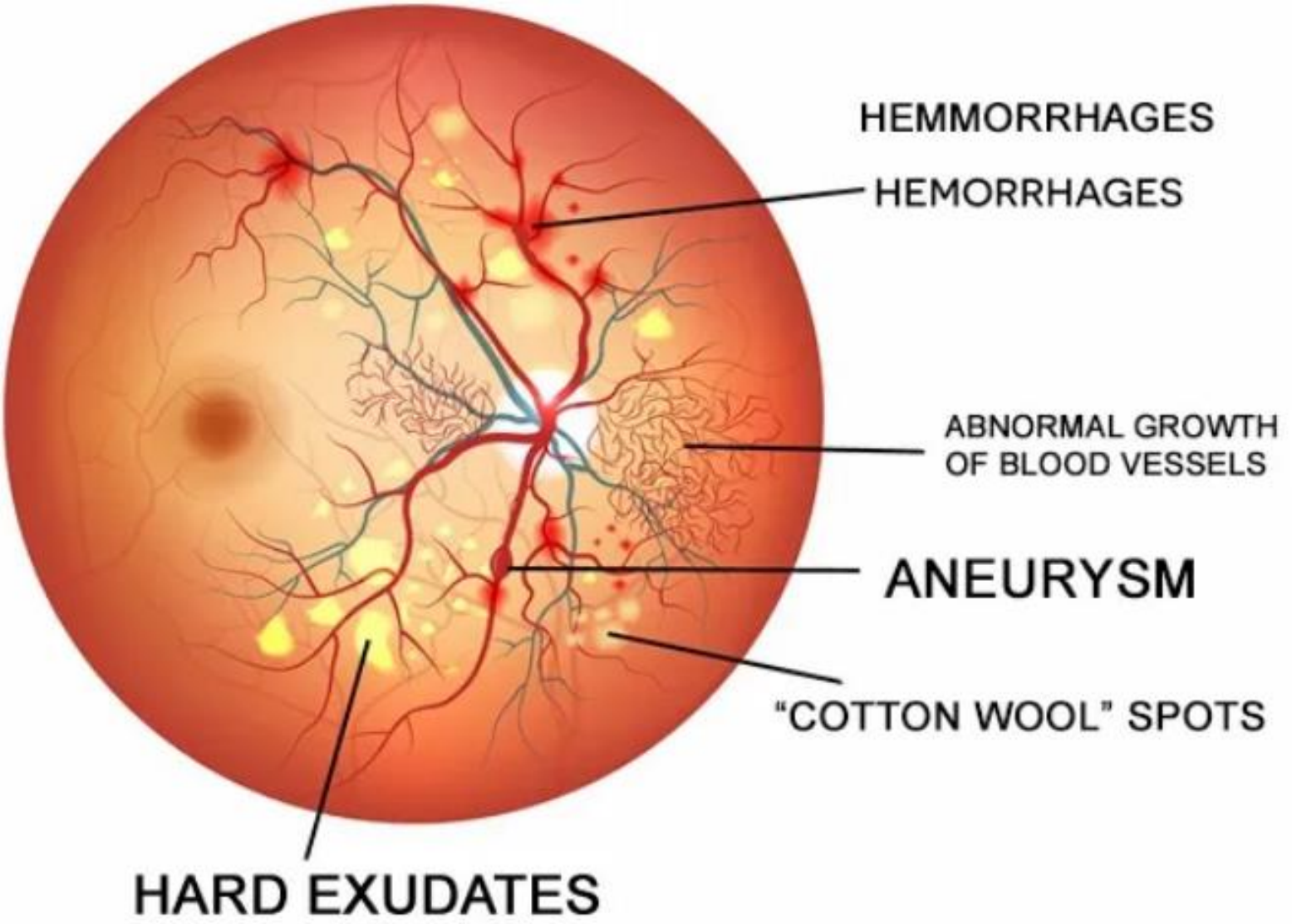
DM : Complications

- Diabetes-related complications affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease
- Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 DM
- **The vascular complications of DM are further subdivided into microvascular** (retinopathy, neuropathy, nephropathy) and **macrovascular** complications (coronary heart disease, peripheral arterial disease [PAD], cerebrovascular disease).

Diabetic retinopathy

- DM is the leading cause of blindness between the ages of 20 and 74 in the United State
- Diabetic retinopathy is classified into two stages: nonproliferative and proliferative

Diabetic retinopathy

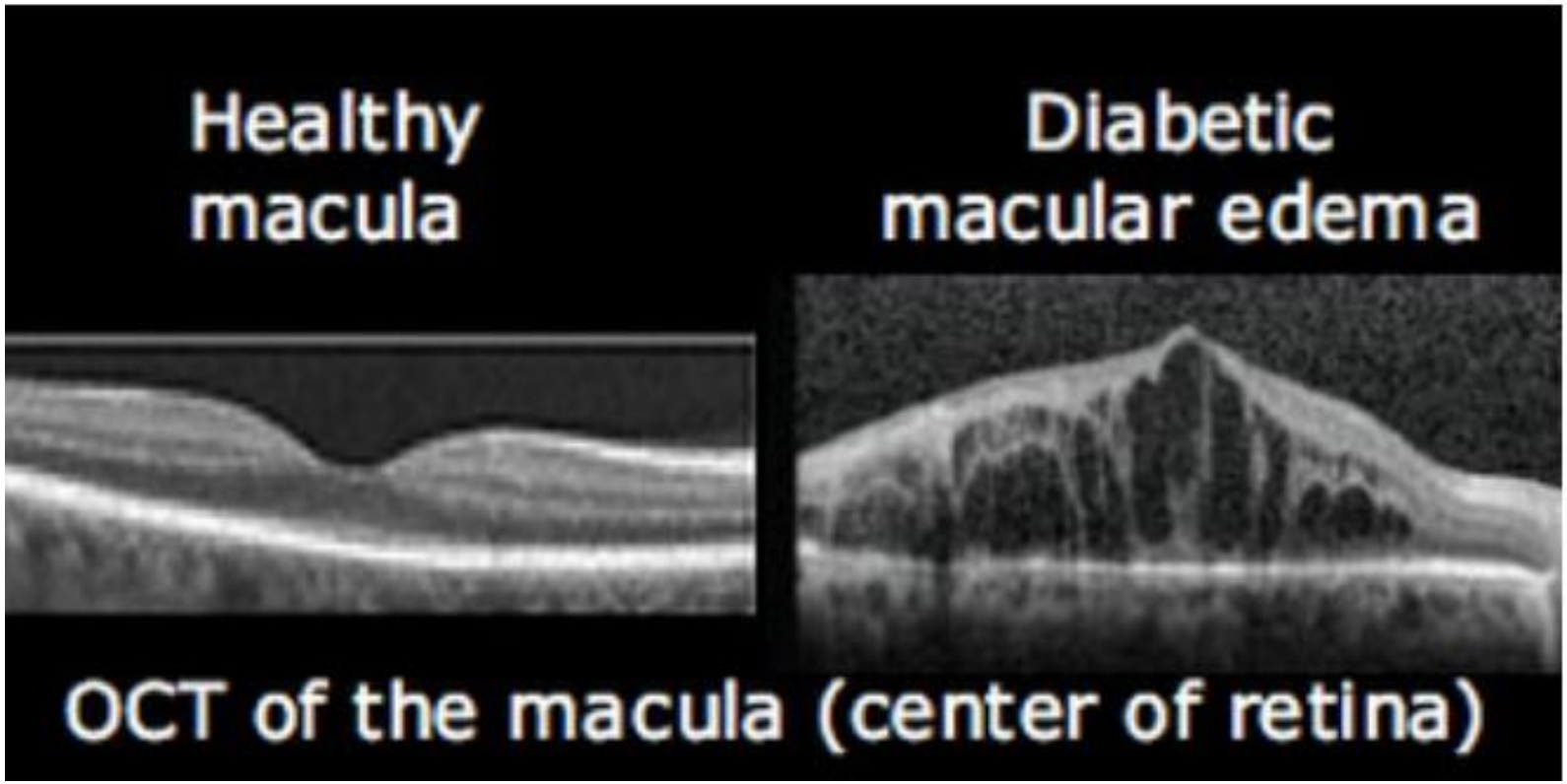


https://drlleung.com/blog/f/how-does-diabetic-retinopathy-cause-vision-loss

Diabetic retinopathy: **Nonproliferative Diabetic Retinopathy (NPDR)**

NDPR occurs when the retinal blood vessels start to leak, causing blood or fluid to seep into the retina. The retina becomes thick and swollen and does not work correctly. If the leaking happens in the macula, (the central part of the retina), vision will be blurred. If the leaks occur in the periphery of the retina, there may be no impact to vision.

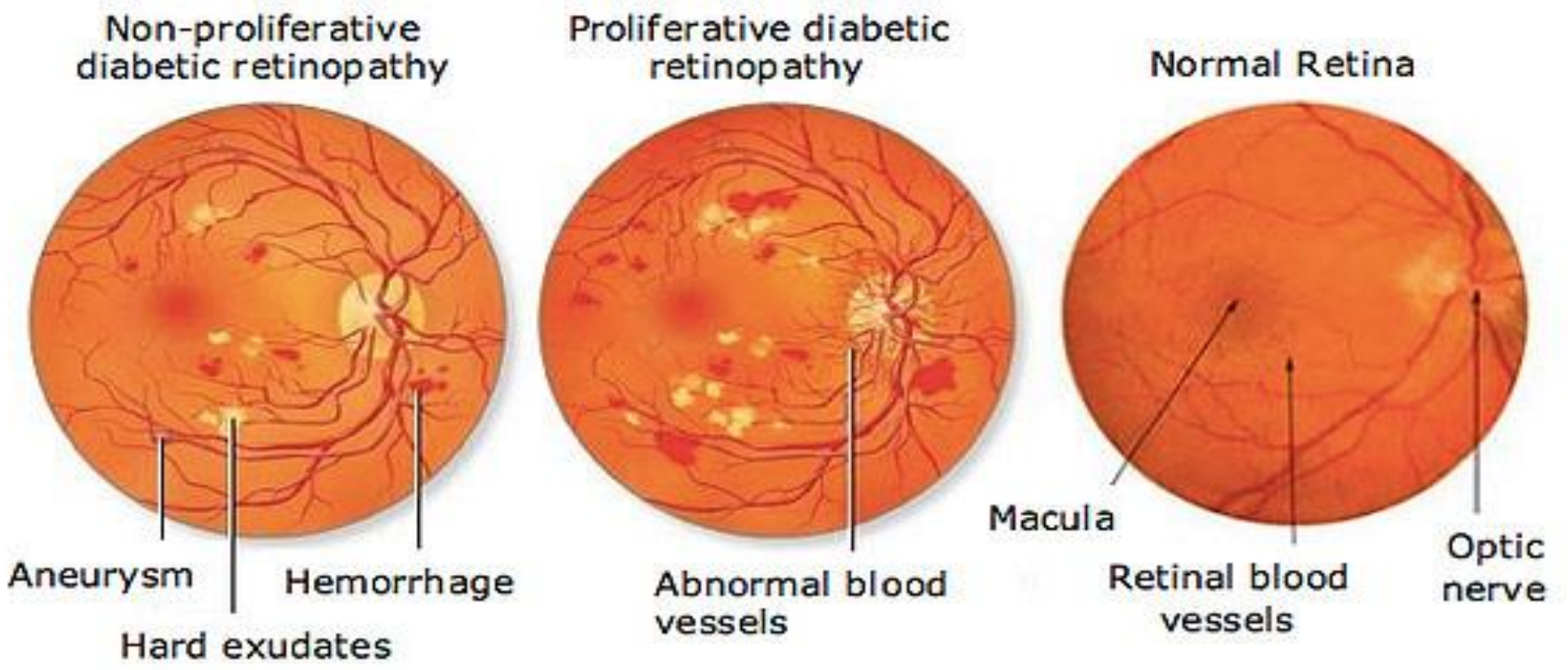
- Nonproliferative retinopathy is found in many individuals who have had DM for >20 years



https://www.retinamd.com/diseases-and-treatments/retinal-conditions-and-diseases/diabetic-retinopathy/

Diabetic retinopathy: **Proliferative Diabetic Retinopathy (PDR)**

- PDR occurs when the retinal blood vessels close, cutting off nutrition to the retinal tissue. The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy
- These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment.



https://www.retinamd.com/diseases-and-treatments/retinal-conditions-and-diseases/diabetic-retinopathy/

Diabetic retinopathy: TREATMENT

The most effective therapy for diabetic retinopathy is prevention!!!

- Intensive glycemic and blood pressure control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 D
- Regular, comprehensive eye examinations are essential for all individuals with DM
- Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation and anti–vascular endothelial growth factor therapy (ocular injection)

Outpatient Glucose Targets for Nonpregnant Adults

Parameter	Treatment Goal
A1C, %	Individualize on the basis of age, comorbidities, duration of disease, and hypoglycemia risk: • In general, ≤6.5 for most* • Closer to normal for healthy • Less stringent for "less healthy"
FPG, mg/dL	<110 (6.1 mmol/l)
2-Hour PPG, mg/dL	<140 (7.8 mmol/l)

*Provided target can be safely achieved.

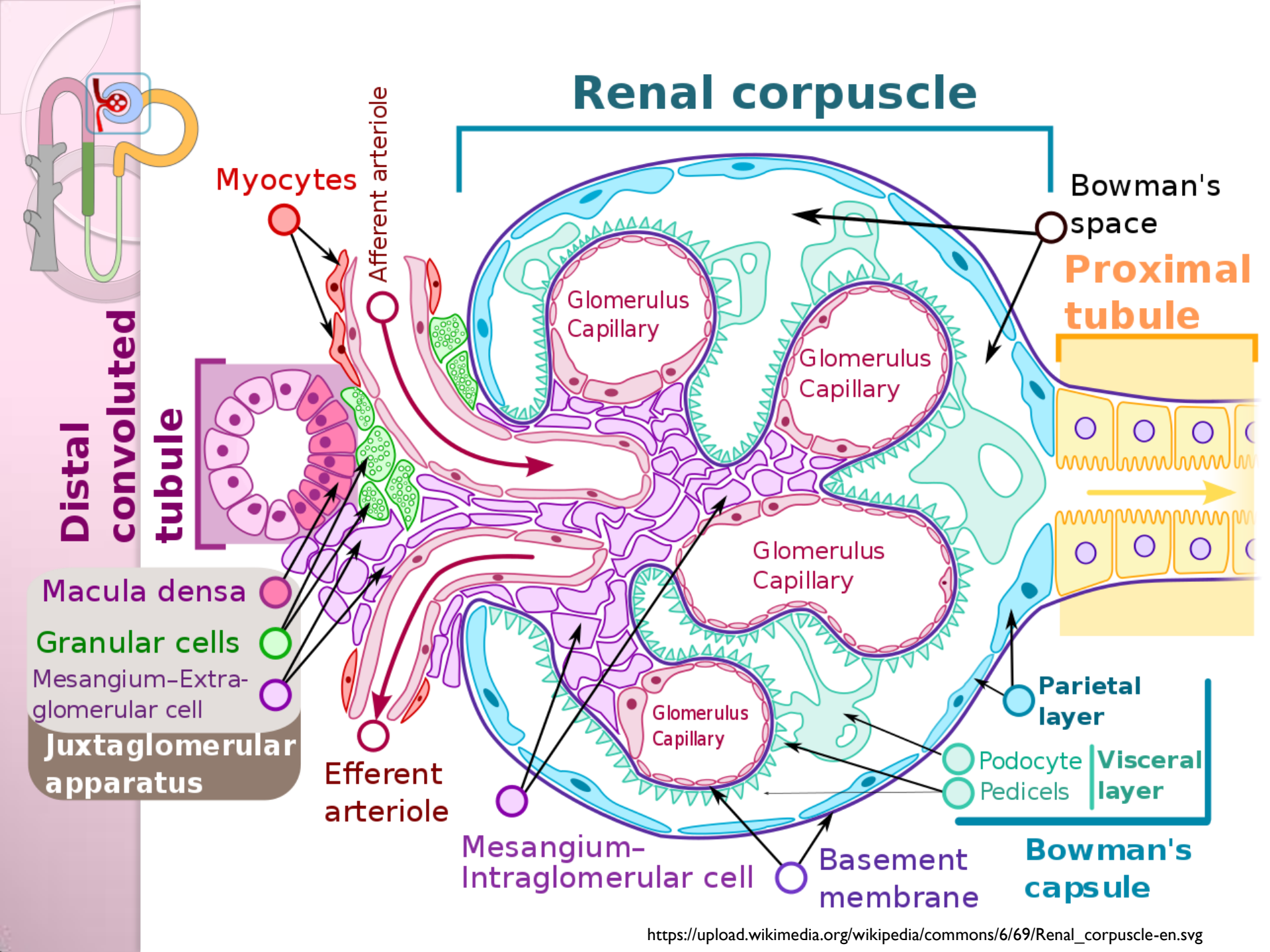
FPG = fasting plasma glucose; PPG = postprandial glucose.

Diabetic nephropathy

Diabetic nephropathy **is the leading cause of chronic kidney disease** (CKD), ESRD, and CKD requiring renal replacement therapy

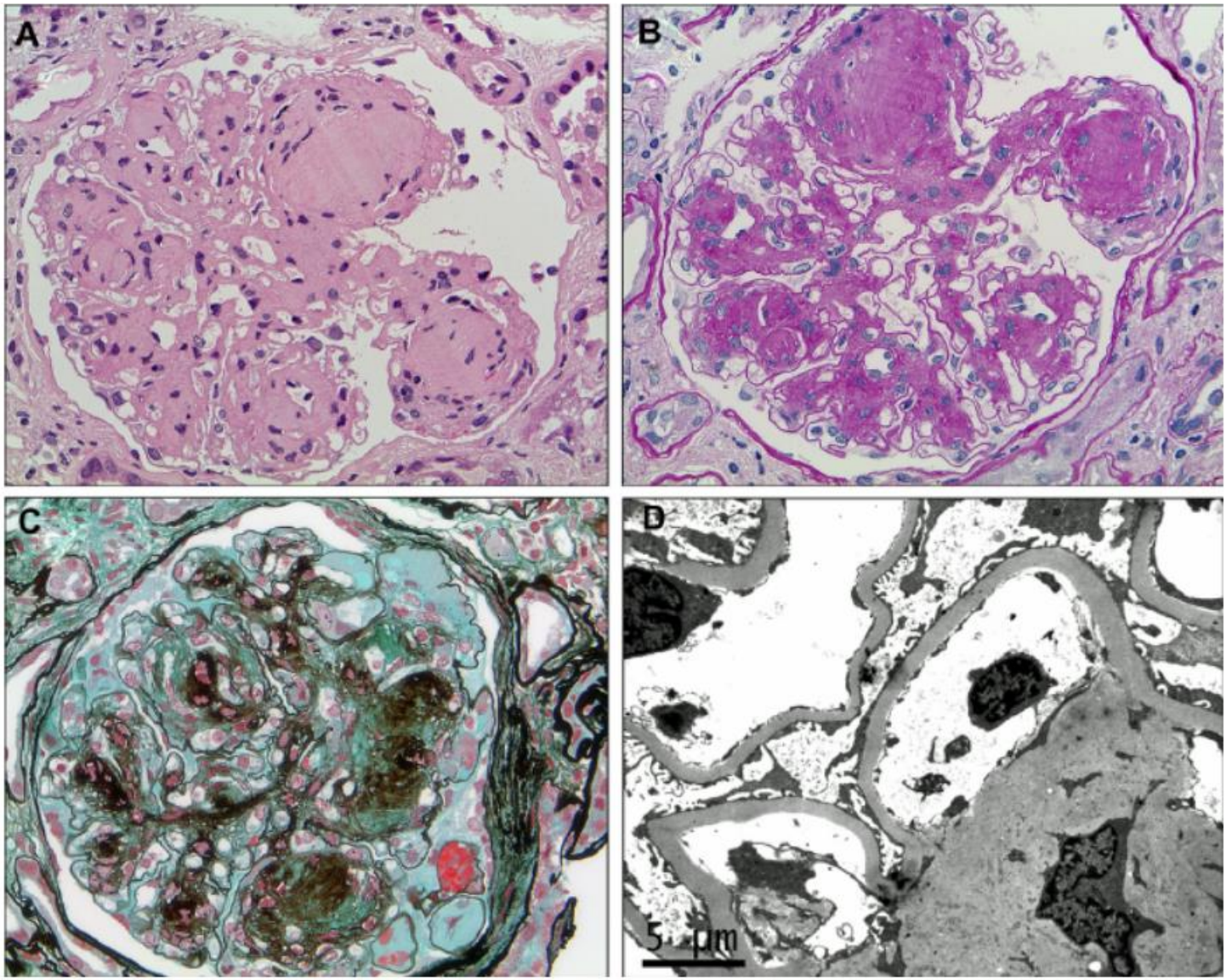
Diabetic nephropathy

- ***The mechanisms*** by which chronic hyperglycemia leads to diabetic nephropathy, although incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, advanced glycation end products [AGEs]), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis)



https://upload.wikimedia.org/wikipedia/commons/6/69/Renal_corpuscle-en.svg

Diabetic nephropathy



https://www.researchgate.net/figure/Characteristic-histological-features-of-diabetic-nephropathy-Notes-In-advanced-diabetic_fig1_267731120

Diabetic nephropathy

- Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the glomerular filtration rate (GFR)
- During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal
- After 5–10 years of type 1 DM, many individuals begin to excrete small amounts of albumin in the urine (persistent albuminuria (≥300 mg/24 h))
- **Once macroalbuminuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7–10 years**
- Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible
- The serum creatinine to estimate GFR should also be performed

Diabetic nephropathy: TREATMENT

The optimal therapy for diabetic nephropathy is prevention by **control of glycemia**

Interventions effective in slowing progression of albuminuria include

- (1) improved glycemic control
- (2) strict blood pressure control
- (3) administration of an ACE inhibitor or ARB
- Dyslipidemia should also be treated

Diabetic neuropathy

- Diabetic neuropathy occurs in ~50% of individuals with long-standing type 1 and type 2 DM
- It may manifest as polyneuropathy, mononeuropathy,and/or autonomic neuropathy
- It most frequently presents with distal sensory loss and pain, but up to 50% of patients do not have symptoms of neuropathy
- Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally

Diabetic neuropathy: TREATMENT

- Chronic, painful diabetic neuropathy is difficult to treat but may respond to duloxetine, amitriptyline, gabapentin, valproate, pregabalin, or opioids.

Diabetic neuropathy: TREATMENT

Painful Diabetic Neuropathy		
Class of Medication	**Medication**	**Typical Target Dose**
Antidepressants (oral)	Amitriptyline	25-150 mg at bedtime
	Desipramine	25-150 mg daily
	Nortriptyline	25-150 mg at bedtime
	Duloxetine[a]	60 mg daily
Anticonvulsants (oral)	Gabapentin	1800-3600 mg daily
	Pregabalin[a]	300 mg daily
Opioids (oral)	Tramadol	50-100 mg daily
	Oxycodone controlled release	10-60 mg daily
Topical	Lidocaine 5% patch	Up to 3 patches/12 hr, followed by 12 hr off
	Capsaicin 0.075%	Apply 3-4 times daily

[a]FDA-approved to treat diabetic neuropathy.
Adapted from references 2,4

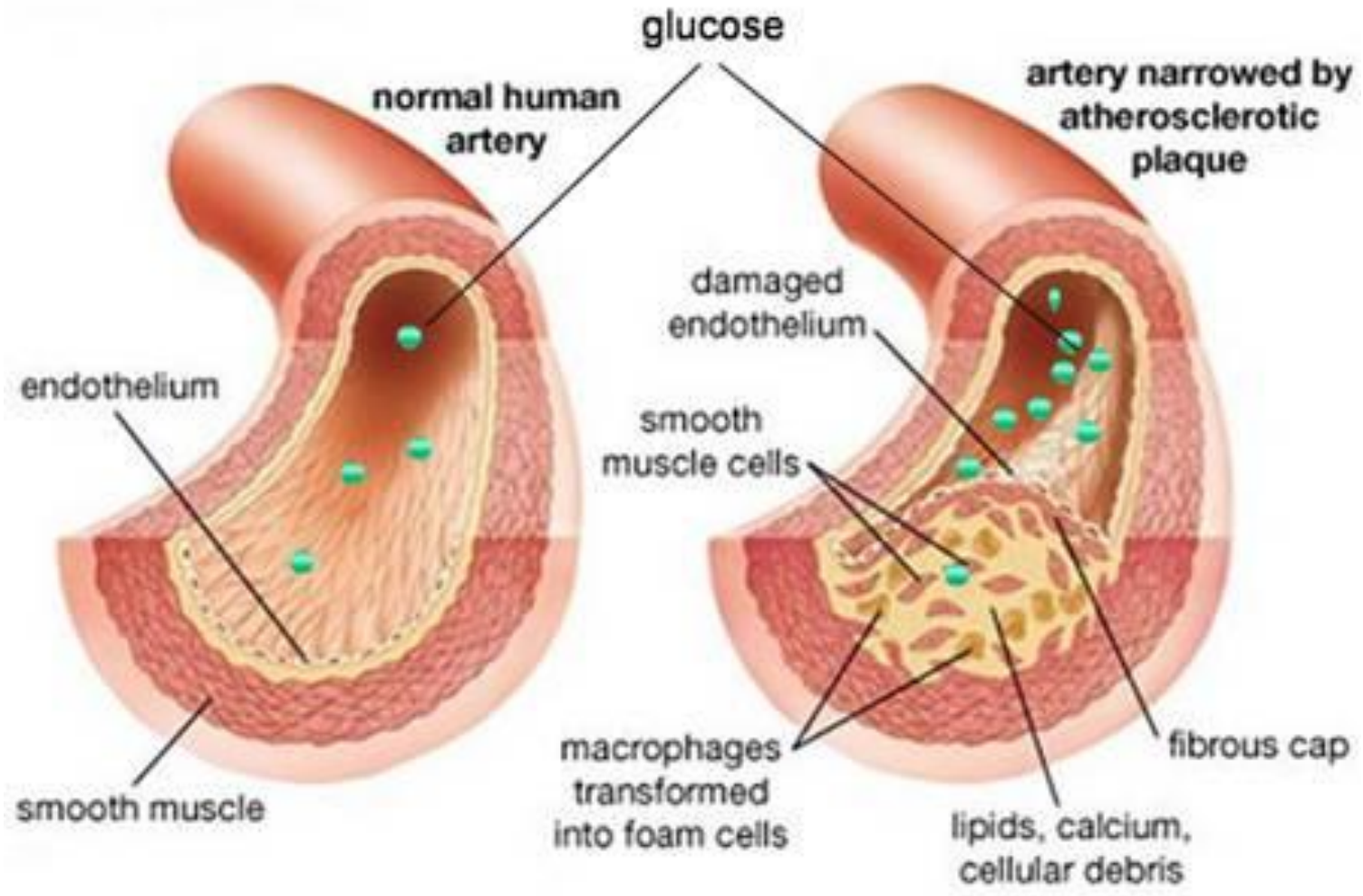
https://www.pharmacytimes.com/publications/issue/2008/2008-10/2008-10-8712

DM and Coronary artery disease

- Coronary artery disease (CAD) is a major determinant of the long-term prognosis among patients with DM
- Amongst adults with DM there is a prevalence of 75% to 85% of hypertension, 70% to 80% for elevated LDL, and 60% to 70% for obesity
- CAD is the main cause of death in both type 1 and type 2 DM, and DM is associated with a 2 to 4-fold increased mortality risk from heart disease
- The American Heart Association has designated DM as a "CHD risk equivalent," and type 2 DM patients without a prior myocardial infarction (MI) have a similar risk for coronary artery–related events as nondiabetic individuals who have had a prior MI

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4672945/#:~:text=Coronary%20artery%20disease%20(CAD)%20is,worse%20overall%20prognosis%20with%20CAD.

DM and CAD



http://www.lifelinehealthcarebd.org/Heart-Diseases-129

DM and CAD

- Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking
- Additional risk factors more prevalent in the diabetic population include microalbuminuria, macroalbuminuria, an elevation of serum creatinine, abnormal platelet function and endothelial dysfunction
- Diagnosis of CAD should be done according current guidelines for CAD management

Harrison's Principles of Internal Medicine, 20ec

DM and CAD: Treatment

- Aggressive cardiovascular risk modification in all individuals with DM and glycemic control should be individualized
- In patients with known CAD and type 2 DM, an ACE inhibitor (or ARB), a statin, and acetylsalicylic acid (ASA; aspirin) should be considered

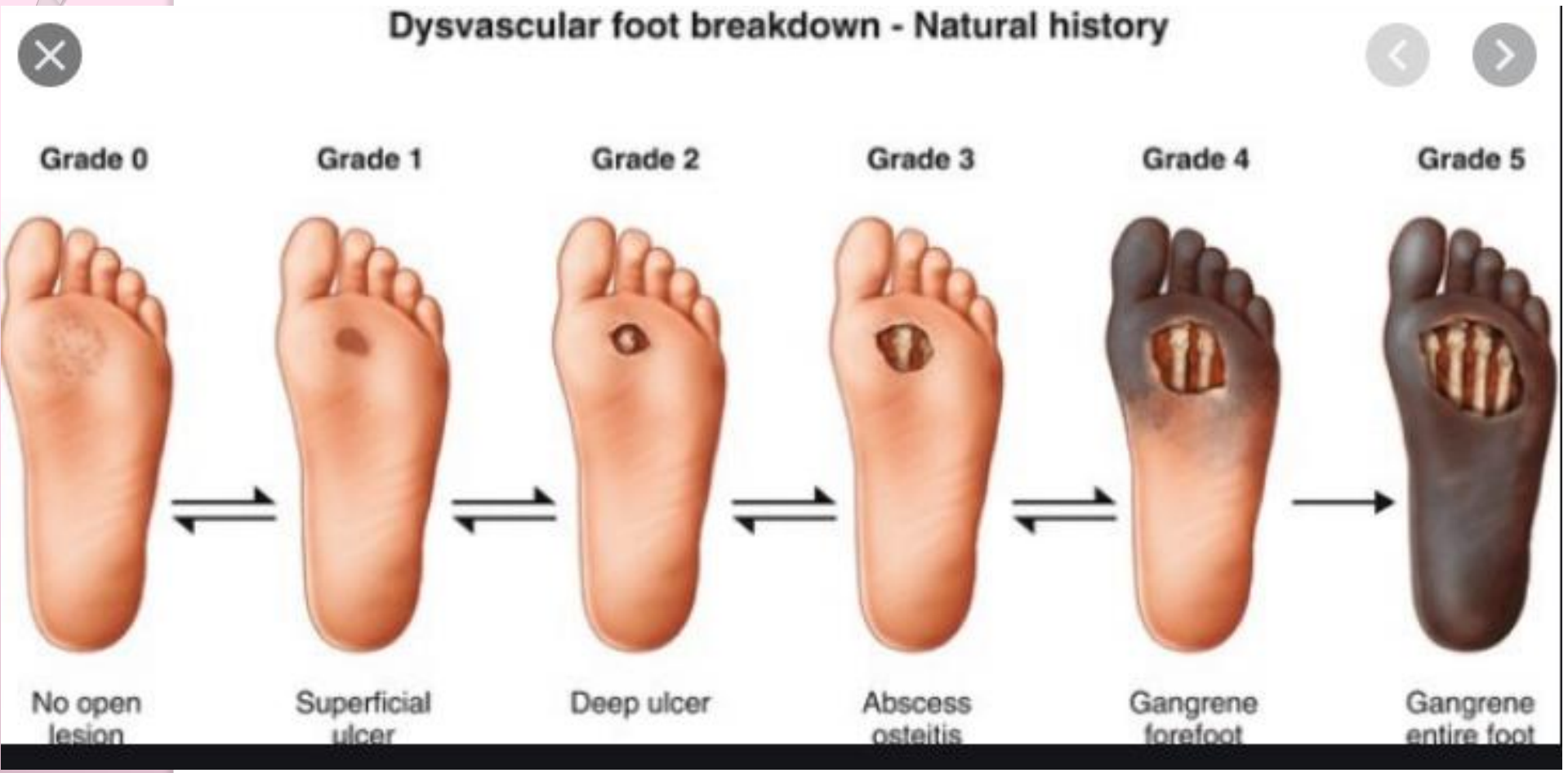
DM and CAD: Treatment

- In general, the treatment of coronary disease is not different in the diabetic individual (**see** 2019 Guidelines on Chronic Coronary Syndromes https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes)
- Revascularization procedures for CAD, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual
- Initial success rates of PCI in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies

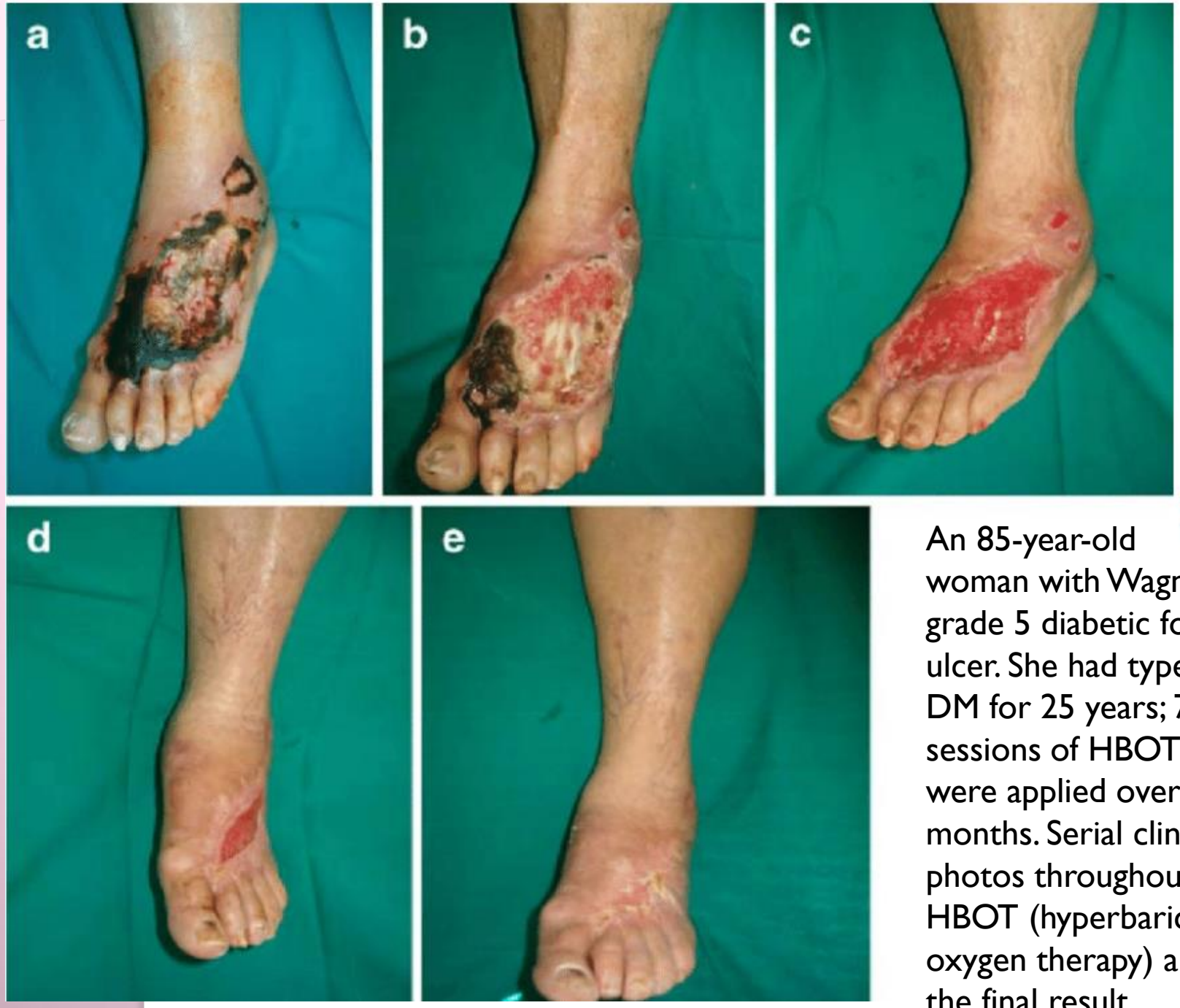
LOWER EXTREMITY COMPLICATIONS

- DM is the leading cause of nontraumatic lower extremity amputation in the United States
- Foot ulcers and infections are also a major source of morbidity in individuals with DM
- The reasons for the increased incidence of these disorders in DM involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, PAD, and poor wound healing.

Diabetic foot



https://www.vitad.org/tiki-index.php?page=Diabetic%20Foot%20Ulcer%203.2%20X%20or%203.6%20X%20more%20likely%20if%20low%20vitamin%20D%20%E2%80%93%20meta-analyses%202019



An 85-year-old woman with Wagner grade 5 diabetic foot ulcer. She had type 2 DM for 25 years; 75 sessions of HBOT were applied over 3 months. Serial clinical photos throughout HBOT (hyperbaric oxygen therapy) and the final result

DOI: 10.1007/s00264-008-0623-y

CASE STUDY 1.3.

TYPE II DIABETIC FOOT

- Type of Wound: Diabetic Foot Ulcer
- Patient: 61 year-old male
- A 61 year-old male, with a medical history notable for Type II diabetes, hypertension and hypercholesterolemia, presented with an ulcer on the lateral aspect of the left midfoot
- On physical exam, there was an abscess which tracked medially across the entire plantar midfoot (Image #1-2)
- The patient was admitted emergently for antibiosis, and the wound was debrided and abscess drained in the OR (Image#3)
- The right lower extremity was subsequently revascularized
- The tunneled track was filled with the single layer Integra™ Matrix and covered and fixated with the Integra™ Bilayer Matrix 31 days later (Image #4)

CASE STUDY 2.3.

Image 1

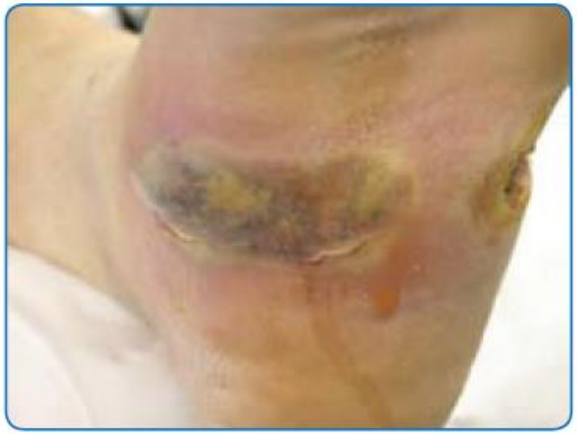


Image 2

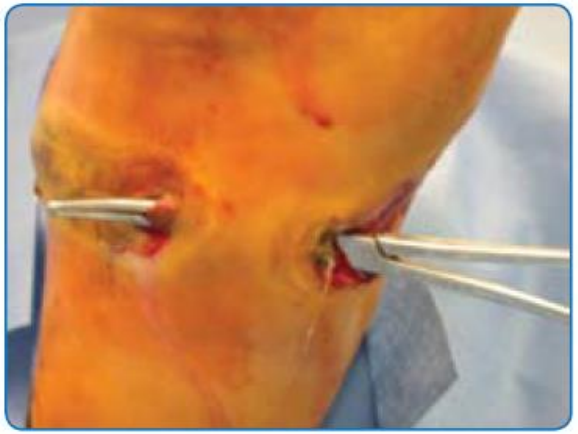


Image 3

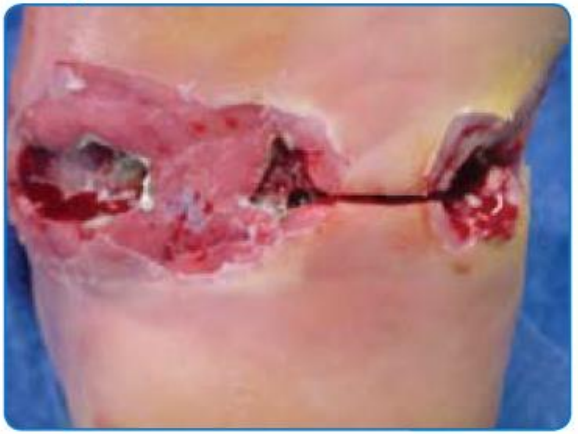


Image 4

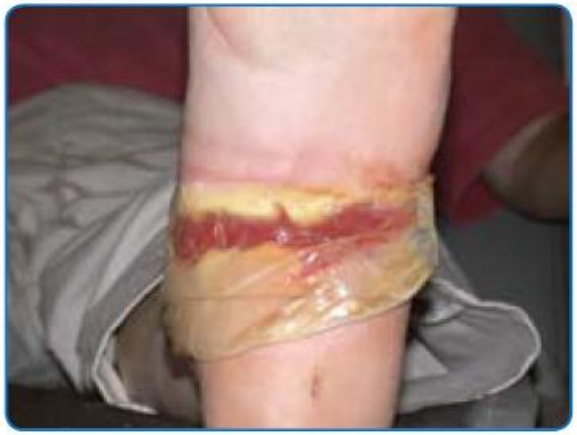


Image 5

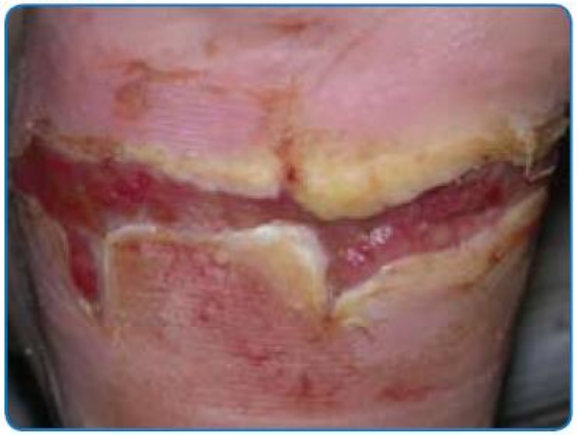
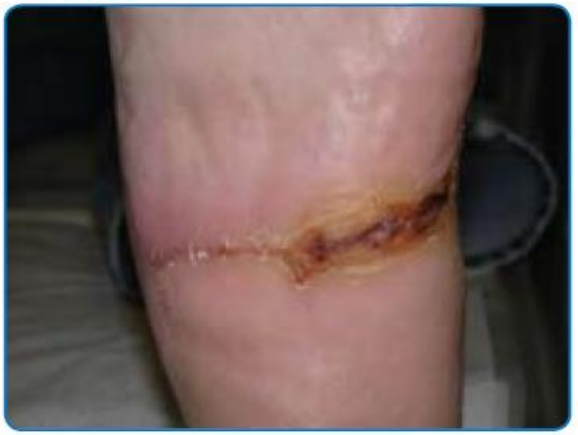


Image 6



DIABETIC SKIN ULCER
INTEGRA™ MATRIX WOUND DRESSING • INTEGRA™ BILAYER MATRIX WOUND DRESSING

CASE STUDY 3.3.

- The graft was completely integrated by post-op day 50 (images #5 and 6), with complete closure at post-op day 113 (Image #7)
- The patient was fitted for a custom-molded brace for ambulation
- Wound closure has been maintained without incident for 2 years (images #8 and 9)

Image 7

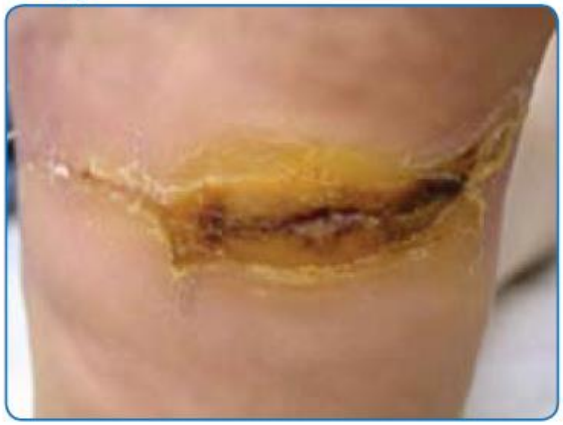


Image 8

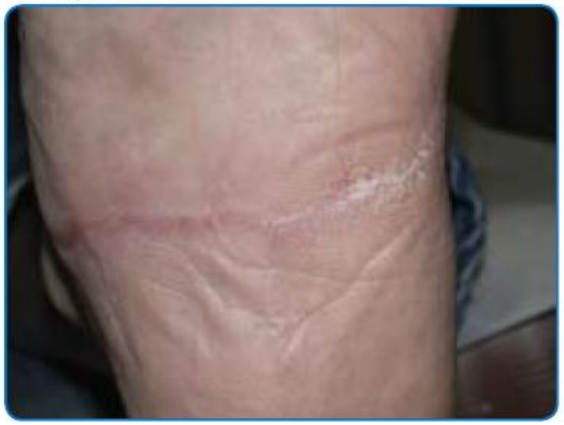


Image 9