S. Alipour Parsa MD

Interventional Cardiologist
Associate Professor of Cardiology

Cardiovascular Research Center

Shahid Beheshti University of Medical Sciences

Vascular Complications of Diabetic Nephropathy

- Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes.

- Diabetes-associated vascular alterations include anatomic, structural, and functional changes leading to multiorgan dysfunction.

Prevelance of Vascular Complications

- **Macrovascular**:
- CAD 26%
- Peripheral artery disease 11%
- Cerebrovascular disease 8%

- **Microvascular**:
- Nephropathy 34%
- Retinopathy 20%
- Neuropathy 16%

- High incidence of complications especially microvascular and CAD occur with HbA_1C of >6.5

- Screening with simple tests such as ECG, Echo, fundoscopy and urine microalbuminuria at diagnosis for all cases of diabetes is essential to identify the complications at an early reversible stage

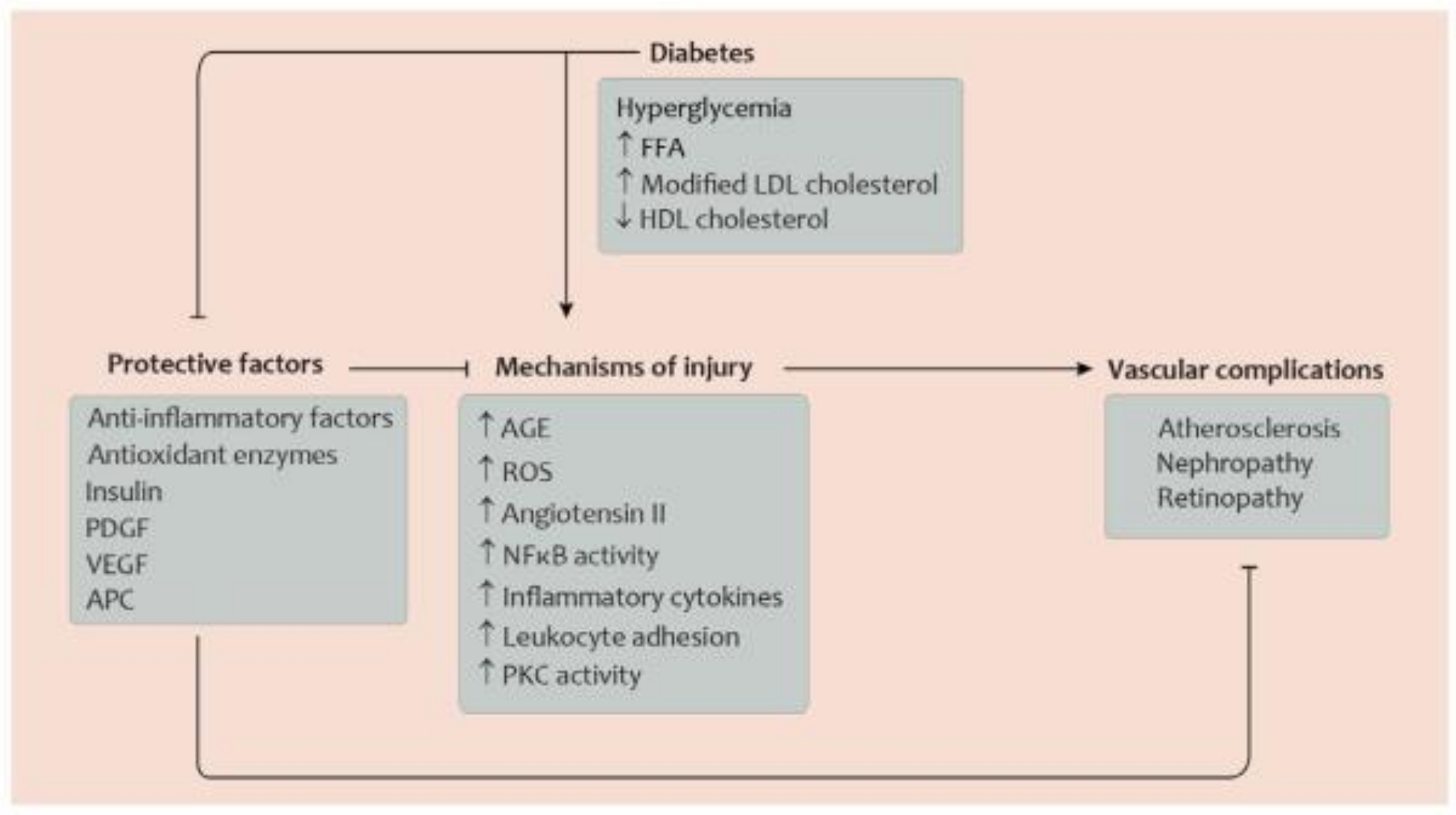
- Mechanisms for microvascular disease in diabetic nephropathy are many metabolic and structural derangements including:

- the pathologic effects of Advanced Glycation End product (AGE) accumulation
-overproduction of endothelial growth factors (EGF)
-abnormal activation of signaling cascades such as protein kinase C (PKC)
-elevated production of reactive oxygen species (ROS, oxygen-containing molecules that can interact with other biomolecules and result in damage)
-polyol pathways due to chronic hyperglycemia
-abnormal stimulation of hemodynamic regulation systems (such as the renin-angiotensin system [RAS]).

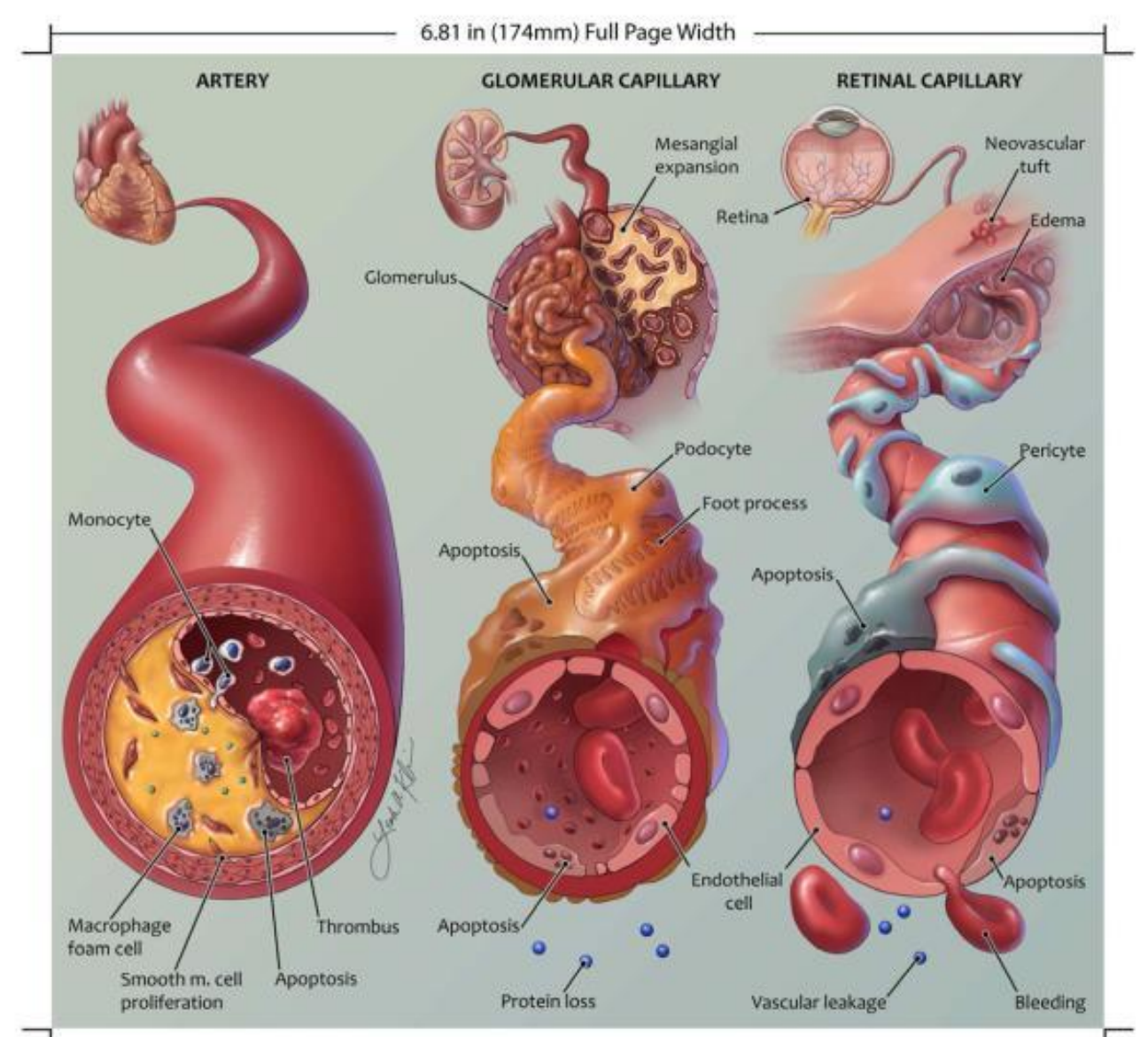
- Mechanisms for macrovascular disease in diabetes include:
  - -the pathologic effects of AGE accumulation
  - -impaired vasodilatory response attributable to NO inhibition
  - -smooth muscle cell dysfunction
  - -overproduction of EGF
  - -excess free fatty acid, and insulin resistance
  - -chronic inflammation
  - -hemodynamic dysregulation
  - -impaired fibrinolytic ability
  - -enhanced platelet aggregation (clotting)

  These cause increased oxidative stress

- There is thought to be an intersection between micro and macro vascular complications, and the two disorders seem to be strongly interconnected, with micro vascular diseases promoting atherosclerosis in macrovascular bed through processes such as hypoxia and changes in vasa vasorum.

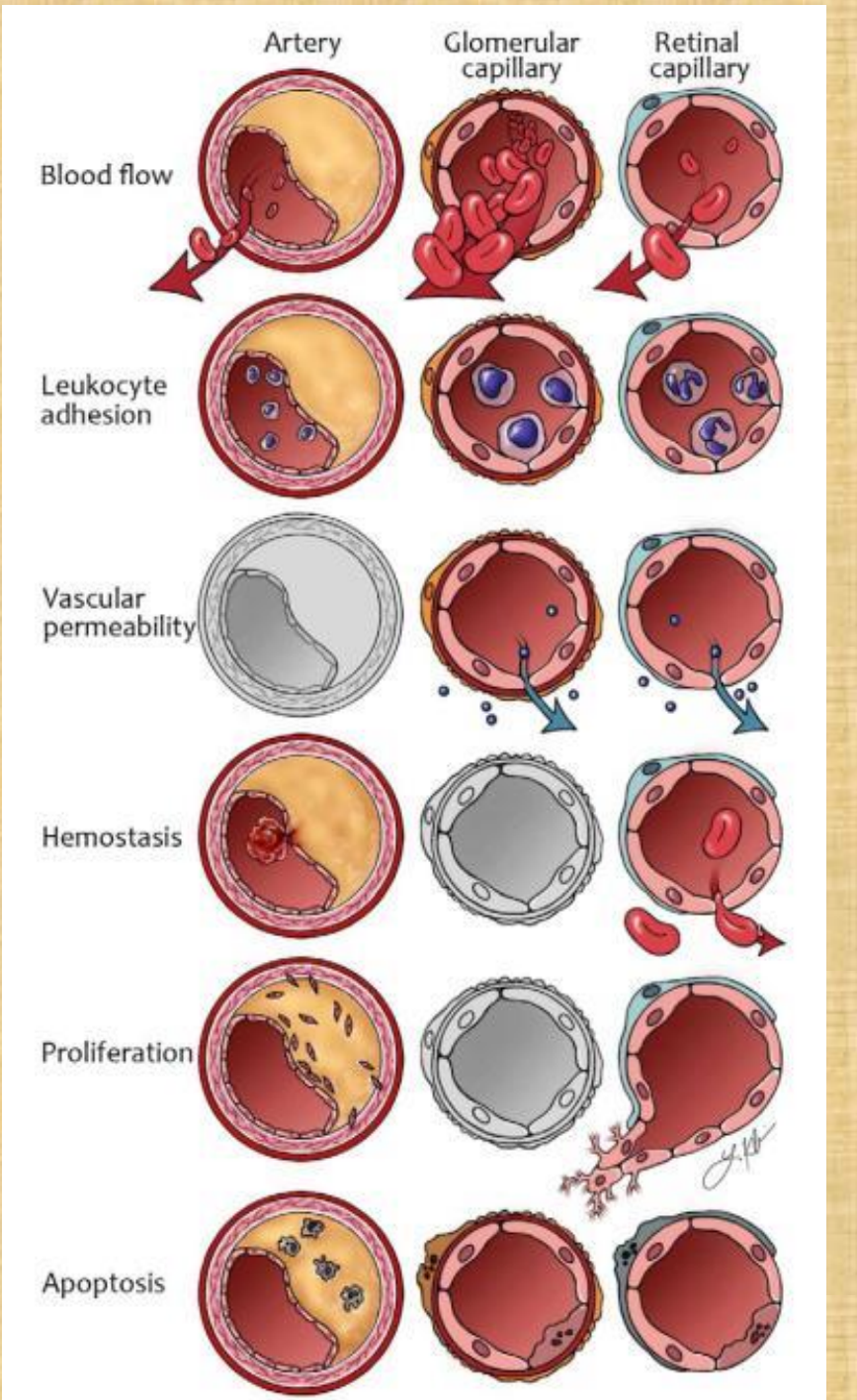

Diabetes
Hyperglycemia
↑ FFA
↑ Modified LDL cholesterol
↓ HDL cholesterol
Protective factors
Anti-inflammatory factors
Antioxidant enzymes
Insulin
PDGF
VEGF
APC
Mechanisms of injury
↑ AGE
↑ ROS
↑ Angiotensin II
↑ NFκB activity
↑ Inflammatory cytokines
↑ Leukocyte adhesion
↑ PKC activity
Vascular complications
Atherosclerosis
Nephropathy
Retinopathy

Important histopathological changes during development of atherosclerosis, nephropathy, and retinopathy in diabetes

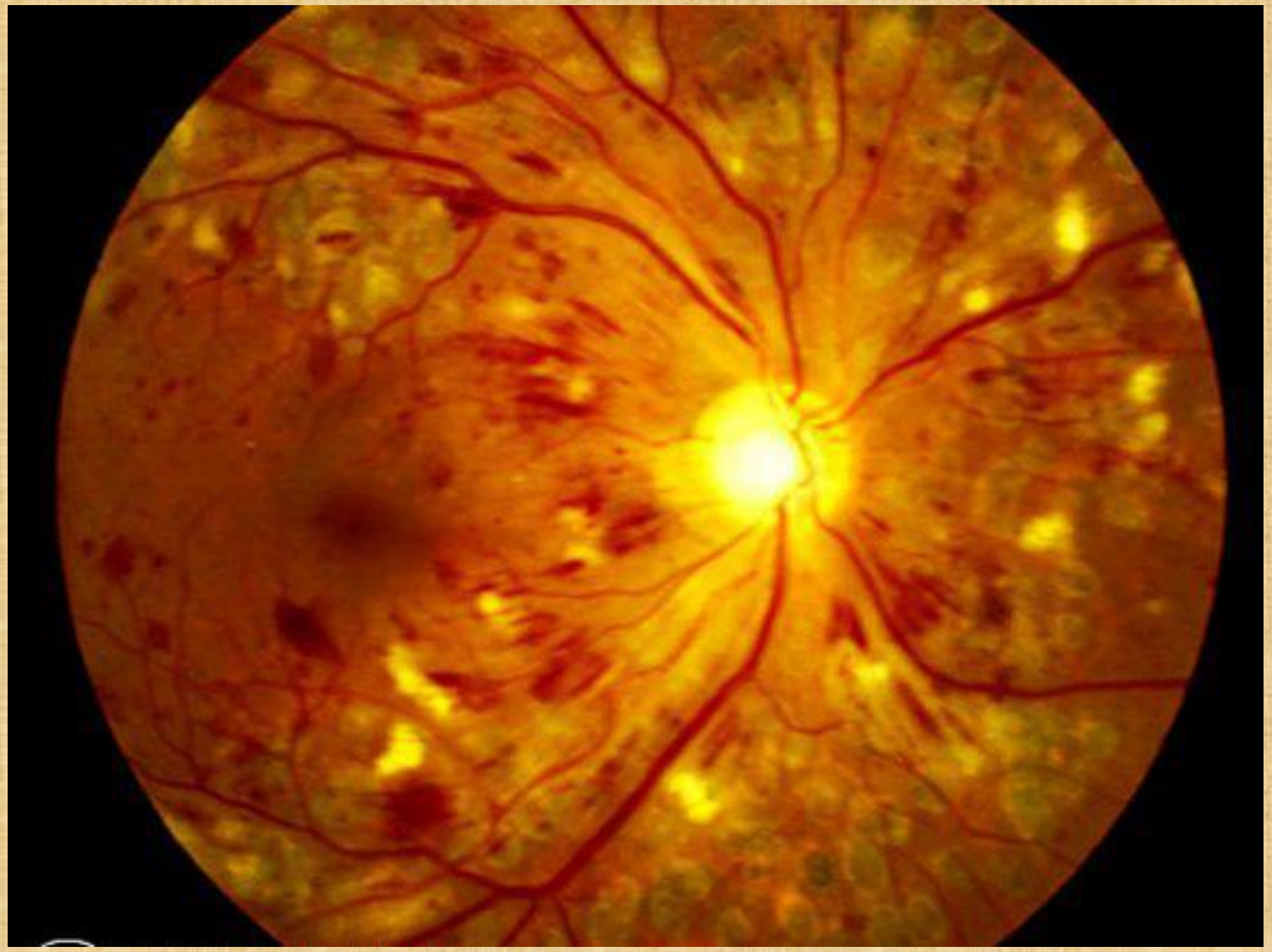


General abnormalities of vascular function in diabetes

Christian Rask-Madsen and George L. King. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab. 2013 Jan 8; 17(1): 20–33



Microvascular Complications of Diabetes



Diabetic Retinopathy

- over 95% of people with diabetes have type 2 DM
- after 30 years of diabetes over half of all diabetics had proliferative retinopathy
- people with type 1 diabetes and taking insulin had the highest prevalence of diabetic retinopathy (DR)
- Diabetic retinopathy also recently was seen in approximately 10% of people with insulin resistance (prediabetes)
- The earliest histological marker of DR is the loss of pericytes. Other microvascular changes that occur with DR include capillary basement membrane thickening, increased permeability of endothelial cells, and formation of microaneurysms

- The most significant factor in the development and progression of DR in people with diabetes appears to be poor glycemic (blood sugar) control leading to impairment of retinal blood flow, increased inflammatory cell adhesion to retinal blood vessels, and capillary blockage can result in hypoxia and damage to the retina.

Diabetic Neuropathy

- Approximately one half of people with diabetes have some form of peripheral neuropathy (PN).
- They also frequently have autonomic neuropathy, including cardiovascular autonomic dysfunction, which is manifested as abnormal heart rate (HR) and vascular control.
- Like those for DR, the risk factors for PN include poor glycemic control (ie, elevated glycation hemoglobin levels, impaired glucose tolerance and presence of microalbuminuria.
- Neuronal microvasculature is impaired in the presence of hyperglycemia,

- Diabetes-related cardiac autonomic neuropathy is frequently underdiagnosed and can include clinical abnormalities such as resting tachycardia, exercise intolerance, resting HR variability, slow HR recovery after exercise, orthostasis, “silent” myocardial infarction, and increased risk of mortality.
- poor glycemic control is also a risk factor

Diabetic Nephropathy (DN)

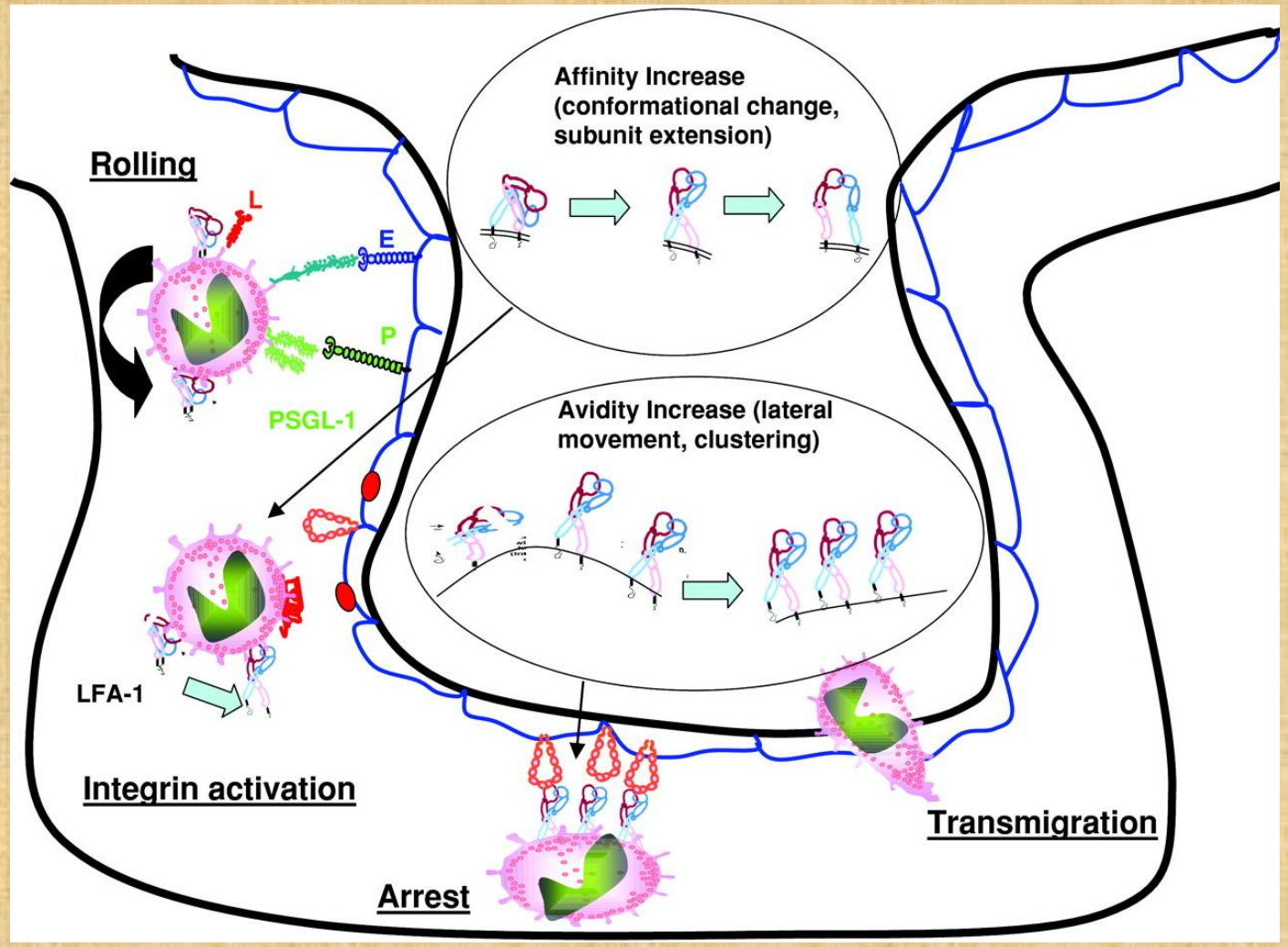
- Diabetic nephropathy (DN) is a serious and progressive complication of both type 1 DM and type 2 DM. The first manifestation of DN is typically microalbuminuria, which progresses to overt albuminuria and eventually to renal failure
- Approximately one fourth of people with type 2 diabetes have microalbuminuria or a more advanced stage of DN that worsens at a rate of 2% to 3% per year. Other characteristic features of DN include thickening of glomerular basement membranes and glomerular hyperfiltration, leading to mesangial (central part of the renal glomerulus) extracellular matrix expansion and further increases in urinary albumin excretion and progressing to glomerular and tubular sclerosis and renal failure. Hyperglycemia is also a risk factor for DN. Approximately 30% of patients with type 1 DM and 5% to 10% of those with type 2 DM become uremic. Diabetic nephropathy is a leading cause of end-stage renal disease.

- Two pathophysiologic pathways for diabetic nephropathy have been identified.
- First, diabetic nephropathy can result from increased glomerular capillary flow that, in turn, results in increased extracellular matrix production and endothelial damage. This leads to increased glomerular permeability to macromolecules. Mesangial expansion and interstitial sclerosis can ensue, which have the potential to cause glomerular sclerosis.
- A second pathway termed nonalbuminuric renal impairment is due to macrovascular and/or repeated unresolved episodes of acute kidney injury. Reduced glomerular filtration rate (GFR) and albuminuria are risk factors for cardiovascular events whereas albuminuria predicted death and progression to end stage renal disease better than GFR loss.

- The earliest sign of nephropathy is hypertension, which often coincides with the development of microalbuminuria. As nephropathy worsens, patients can develop edema, arrhythmias associated with hyperglycemia, or symptoms related to renal failure.
- Serum creatinine determinations should be performed at least annually in patients with albuminuria. When estimated glomerular filtration rate (eGFR) values are declining, more specific measures of GFR (most commonly, creatinine clearance) should be used.

- Different types of activated leukocytes play a crucial role in the pathogenesis of most kidney diseases from acute to chronic stages; however, diabetic nephropathy was not considered an inflammatory disease in the past. This view is changing now because there is a growing body of evidence implicating inflammatory cells at every stage of diabetic nephropathy. Renal tissue macrophages, T cells, and neutrophils produce various reactive oxygen species, proinflammatory cytokines, metalloproteinases, and growth factors, which modulate the local response and increase inflammation within the diabetic kidney. Although the precise mechanisms that direct leukocyte homing into renal tissues are not fully identified, it has been reported that intercellular adhesion molecule-1 and the chemokines CCL2 and CX3CL1 probably are involved in leukocyte migration in diabetic nephropathy.

Leukocyte adhesion cascade in a glomerular capillary.



Elena Galkina, and Klaus Ley JASN 2006;17:368-377

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Macrovascular Complications of Diabetes

- Patients with diabetes-associated CVD can present with stable or unstable angina pectoris, MI, or dysrhythmias; however, many patients have unrecognizable symptoms.
- Patients with cerebral vascular disease can present with a sudden onset of a focal neurologic deficit such as facial droop, hemiparesis, or isolated weakness of an arm or leg. Dizziness, slurred speech, gait difficulties, and visual loss also can be the presenting symptoms.
- Peripheral vascular disease is recognized by exertional leg pain that can progress to pain at rest and ischemic ulcers. Most cases are asymptomatic.

Macrovascular Complications of Diabetes

- First, decreased nitric oxide, increased endothelin, and increased angiotensin II cause vasoconstriction that results in hypertension and vascular smooth muscle cell growth.
- Second, decreased nitric oxide, activated nuclear factor-KB, increased angiotensin II, and activation of activated protein-1 increase inflammation, which results in the release of chemokines, cytokines, and expression of cellular adhesion molecules.
- Third, decreased nitric oxide, increased tissue factor, increased plasminogen activator inhibitor-1, and decreased prostacyclin result in thrombosis, hypercoagulation, platelet activation, and decreased fibrinolysis.
- These pathways ultimately lead to atherosclerosis, the cause of the macrovascular complications of diabetes.

Cardiovascular disease (CVD)

- People with diabetes have a 4-fold-greater risk for having a CVD event.
- People with diabetes also have a 5-fold-greater risk for a first myocardial infarction (MI) and a 2-fold-greater risk for a recurrent MI.
- The risk for an MI in diabetics who have not had an MI is similar to nondiabetic patients with previous MI.

Cerebrovascular Disease

- The presence of diabetes carries an independent risk for stroke apart from the increased presence of traditional risk factors
- Hyperglycemia appears to be a significant factor in stroke.
- Both nephropathy (proteinuria, microalbuminuria) and SDR were found to be independently increasing the risk for all subtypes of stroke.

Peripheral Artery Disease

- Peripheral artery disease is related to the duration and severity of diabetes and people with diabetes are 15 times more likely to have lower-extremity amputation than people without diabetes.
- Hyperglycemia, specifically, glycation hemoglobin, has been shown to be an independent risk factor for PAD.

- The diagnosis of peripheral arterial disease is diagnosed by determining the ankle brachial index (ABI). This is the ratio of the Doppler-determined systolic ankle pressure over the systolic brachial pressure. An ABI less than 0.9 has a sensitivity of 95% and a specificity of 100% in detecting peripheral arterial disease. An ABI greater than 1.4 reflects calcified arteries. It is associated with increased risk of foot ulcers and CVD.

- The most well-established clinical advances in preventing vascular complications of diabetes include intensive blood glucose lowering which decreases the risk of nephropathy and retinopathy, antihypertensive medicine which decreases the risk of cardiovascular disease, nephropathy, and retinopathy, panretinal photocoagulation and agents targeting vascular endothelial growth factor (VEGF) which slows the progression of diabetic retinopathy, and statin therapy which reduces the risk of cardiovascular disease.
- Although lowering blood glucose delays the onset of nephropathy and retinopathy, cardiovascular disease in diabetes shows less robust association with hyperglycemia and less benefit from glucose-lowering therapy

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