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Diabetes mellitus complications

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Objectives:

- Distingue between micro- and macrovascular lesions and what they cause.
- Understand the other complications associated with DM.
- Identify the mechanisms by which hyperglycemia can cause long-term complications of diabetes.
- Understand why good DM control reduces the incidence of complications.

Epidemiology:

Diabetes mellitus
"A disease with many faces
and few voices „

Daily around the world because of DM:

- 512 people die
- 66 people are blind
- 77 people need dialysis
- 153 people need amputations.

Diabetes around the world in 2021:

537 million adults (20-79 years) are living with diabetes - 1 in 10. This number is predicted to rise to **643 million** by 2030 and **784 million** by 2045.

Over 4 in 5 (81%) adults with diabetes live in low- and middle-income countries.

Diabetes is responsible for **6.7 million** deaths in 2021 - 1 every 5 seconds.

Diabetes caused at least **USD 966 billion** dollars in health expenditure – a 316% increase over the last 15 years.

541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes..

www.who.int/diabetes/global-report #diabetes World Health Organization

Classification:

I. Acute complications:

- ***Ketoacidosis***
- ***Hypoglycemia***
- ***Hyperglycemic hiperosmolar syndrome***
- ***Lactat acidosis***

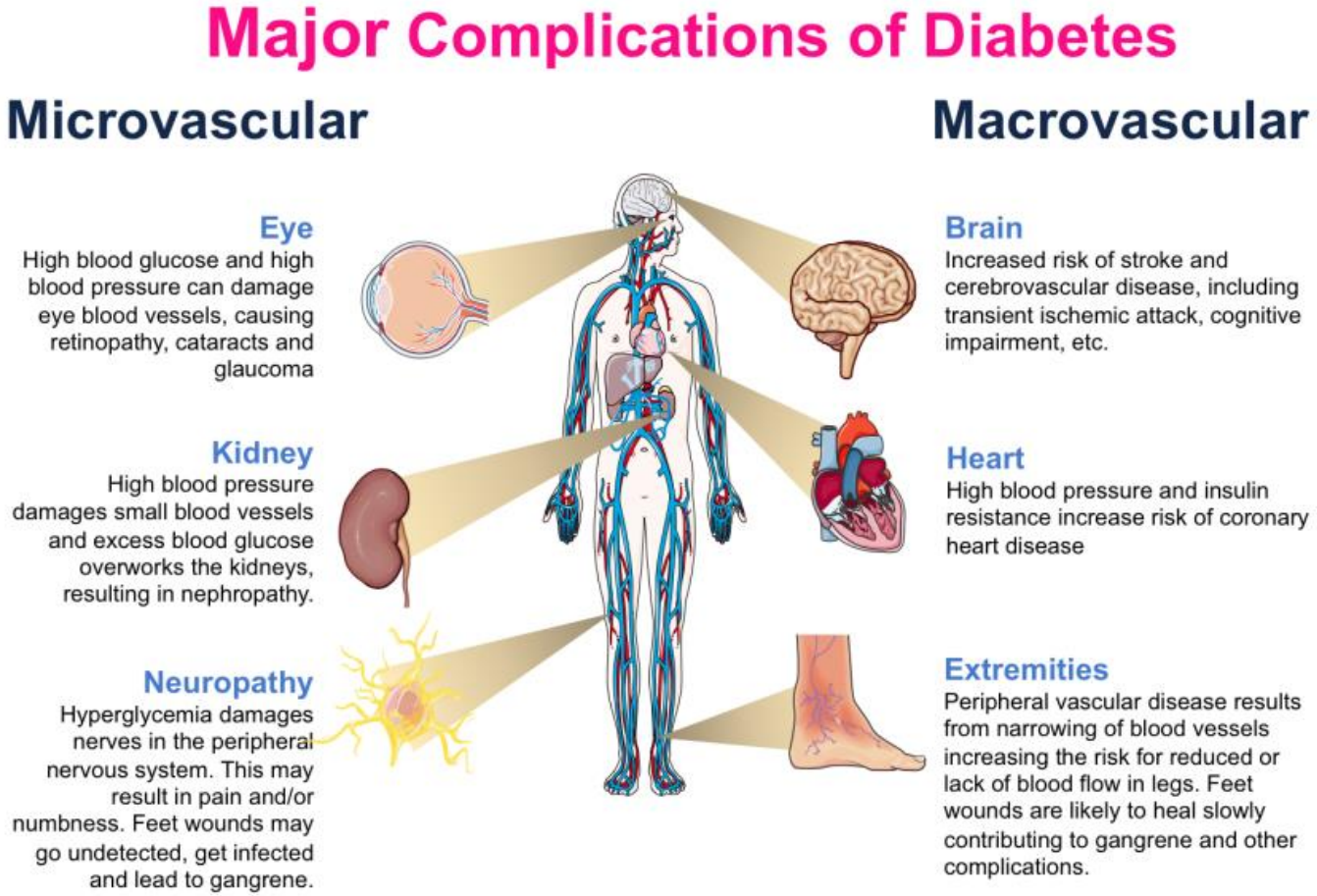
II. Chronic complications:

a. Microvascular

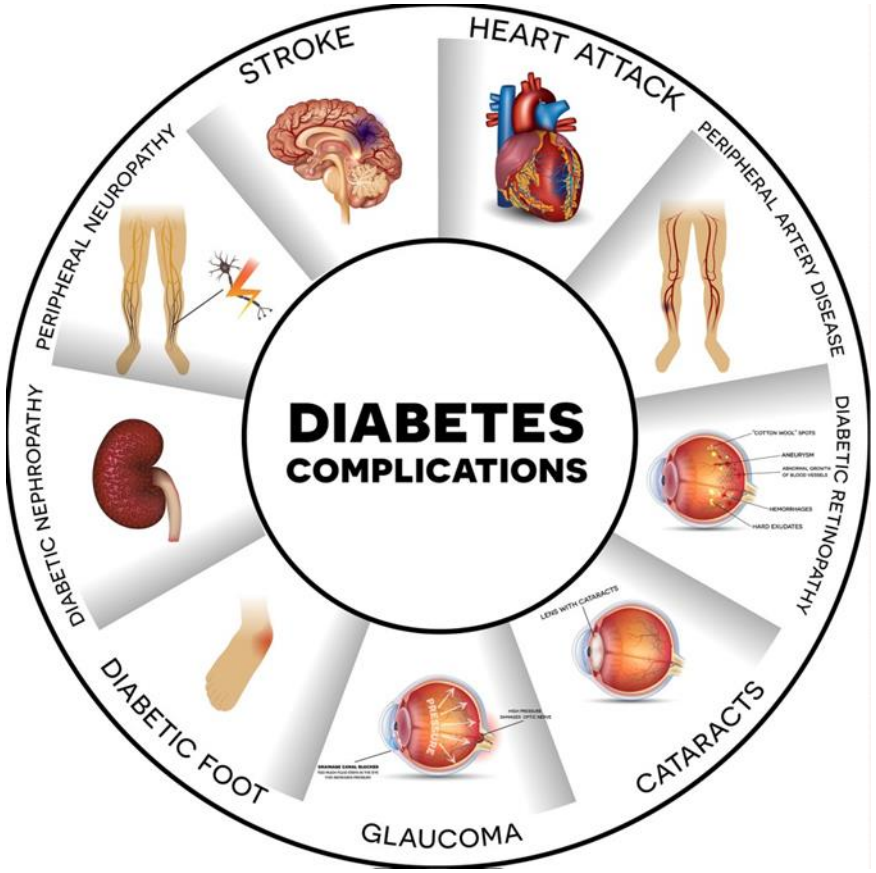
- ***Retinopathy***
- ***Nephropaty***
- ***Neuropathy***
- ***Diabetic foot***

b. Macrovascular

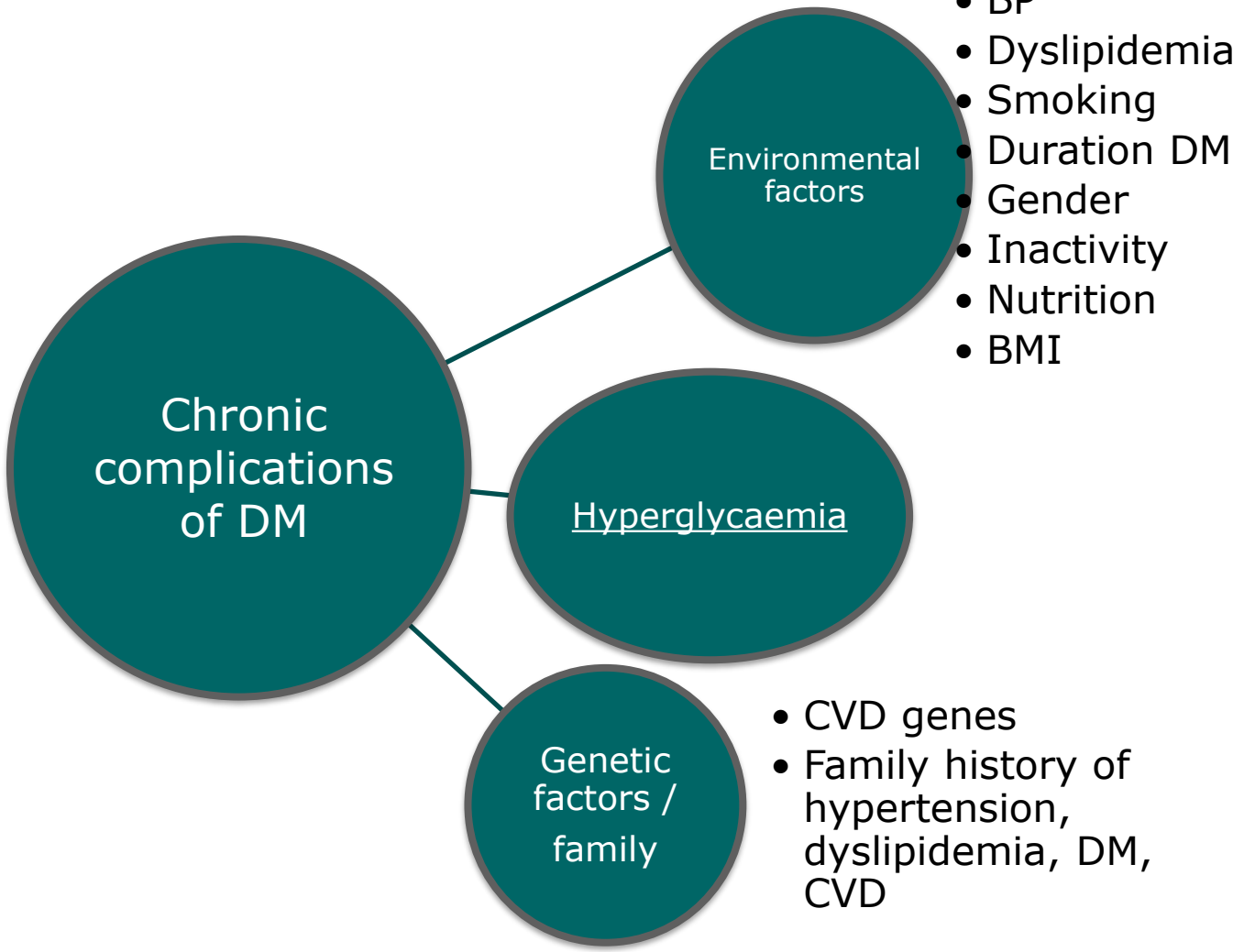
- ***Cerebrovascular disease***
- ***Coronary artery disease***
- ***Peripheral vascular disease***



Chronic DM complications



Risk factors for chronic complications

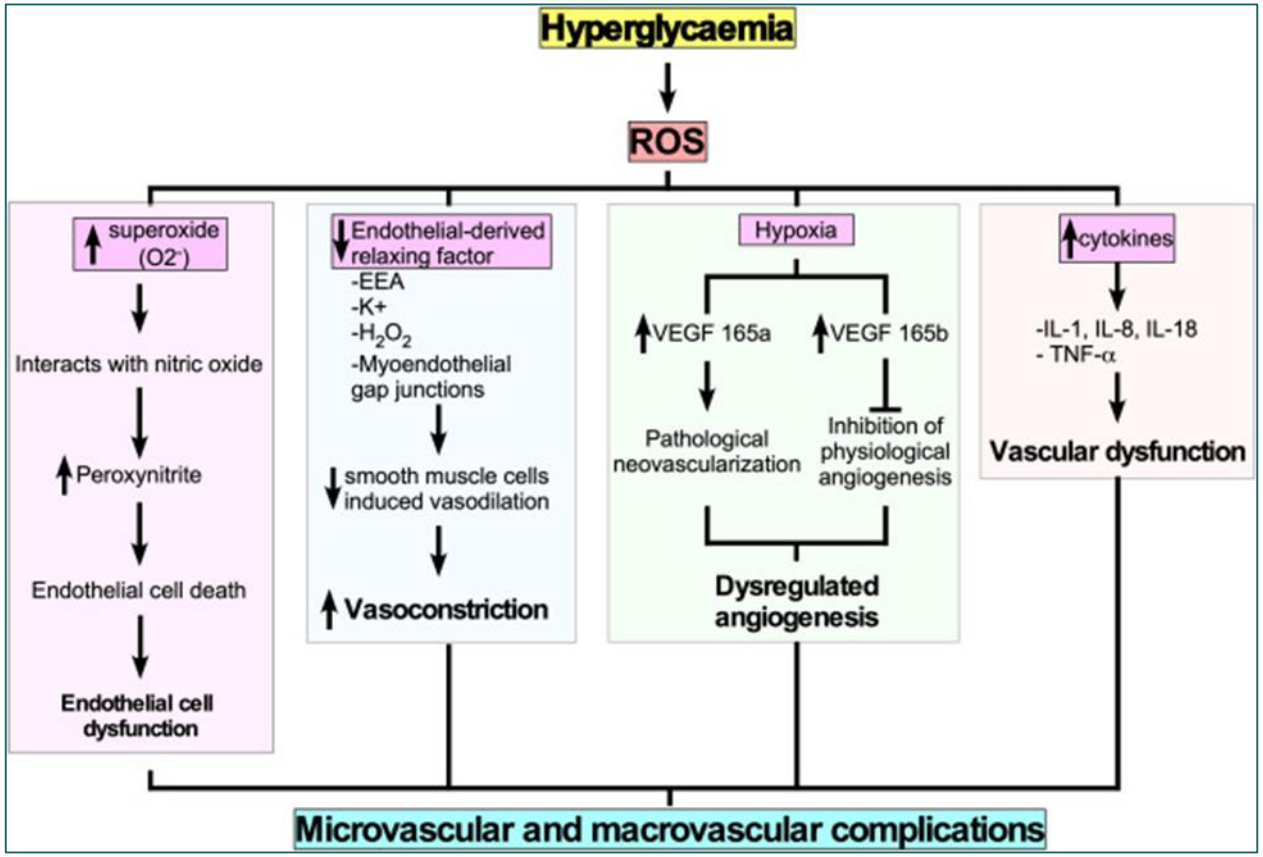


Risk factors for chronic microvascular complications

Controllable	Uncontrollable
Hyperglycaemia Hypertension Dyslipidemia Smoking Body weigh	Duration of DM DM type (T1DM) Insulin therapy Nephropathy Genetic factors Puberty Pregnancy

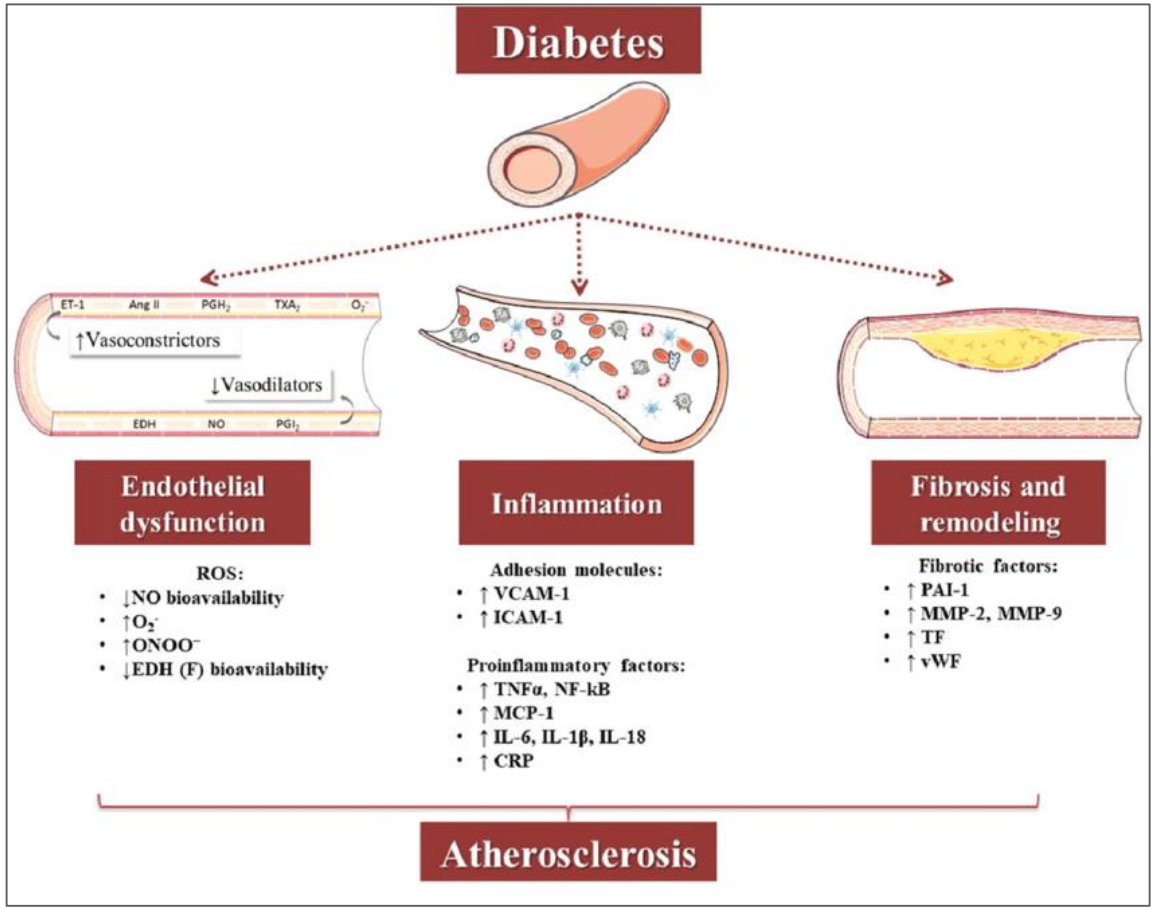
Pathogenesis

- Reactive oxygen species and endothelial cell damage
- Polyol pathway
- Advanced Glycation End products (AGE) pathway
- Protein Kinase C pathway
- Hexosamine pathway
- Dysregulation of growth factors, cytokines.

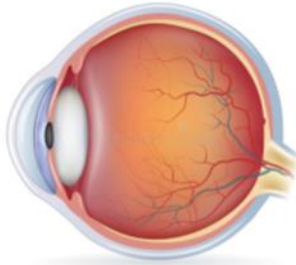


The mechanisms of macrovascular disease

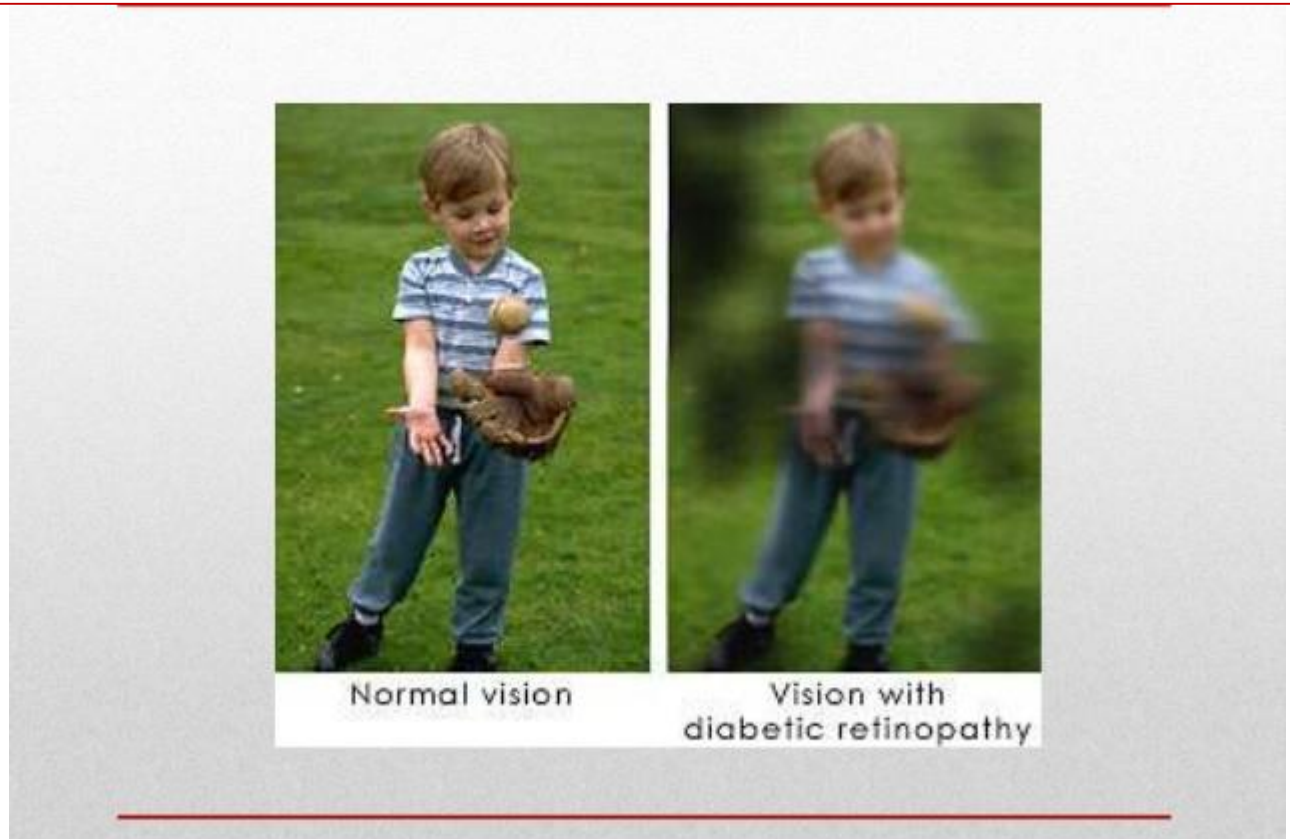
- Accumulation of oxidized lipids, resulting from LDL particles.
- Angiotensin II promotes their oxidation.
- Monocytes infiltrate the arterial wall and differentiate into macrophages, which absorb oxidized lipids and form foam cells → stimulate macrophage proliferation and attract T lymphocytes → proliferation of striated muscles of arterial walls and accumulation of collagen → atheroma plaque → acute vacular infarction.



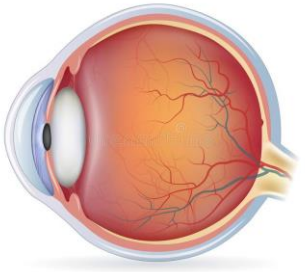
Diabetic retinopathy (DR) - Definition



Progressive dysfunction of the retinal blood vessels caused by chronic hyperglycaemia.

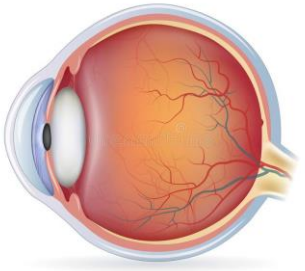


Diabetic retinopathy (DR)



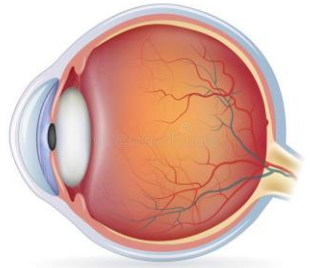
- 1 preventable cause of blindness in patients with diabetes.
- 50% of patients with T1DM after 10 years of DM.
- 90% after 30 years of T1DM.
- 5% of patients with T2DM at the time of diagnosis.
- Glaucoma, cataracts and other ocular pathologies - appear earlier, more frequently, with atypical and more severe evolution in people with diabetes.

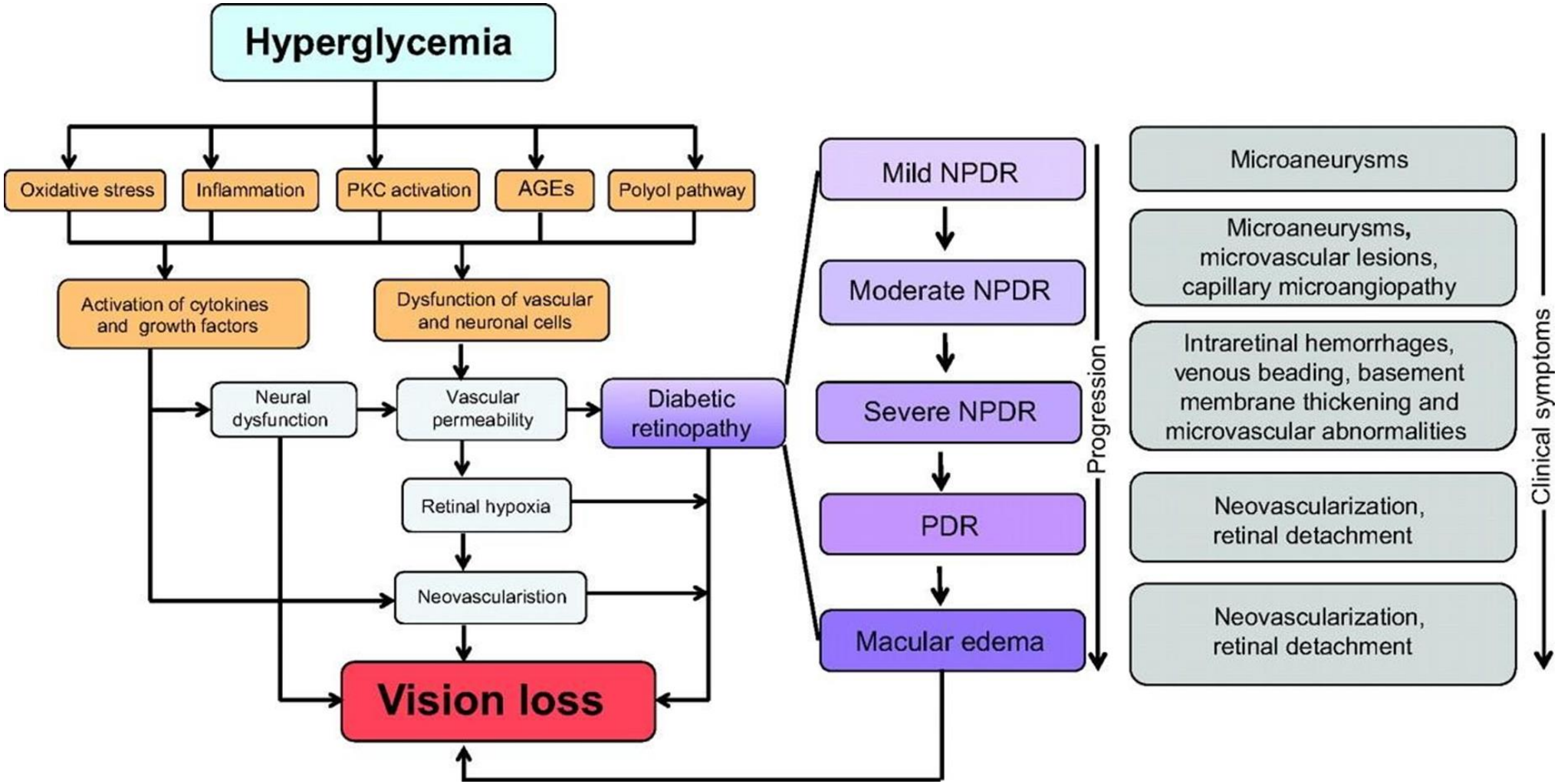
Risc Factors for DR



- Hyperglycaemia
- Duration of diabetes
- Hypertension
- Hyperlipidaemia
- More in females than males
- Pregnancy may accelerate DR
- Smoking, Obesity, Anaemia
- Poor metabolic control
- Hereditary – more on proliferative DR

DR – pathogenesis, classification





Classification DR (**ETDRS (**Early Treatment Diabetic Retinopathy Study**))**

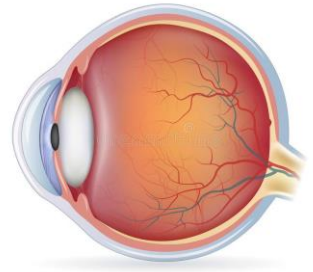
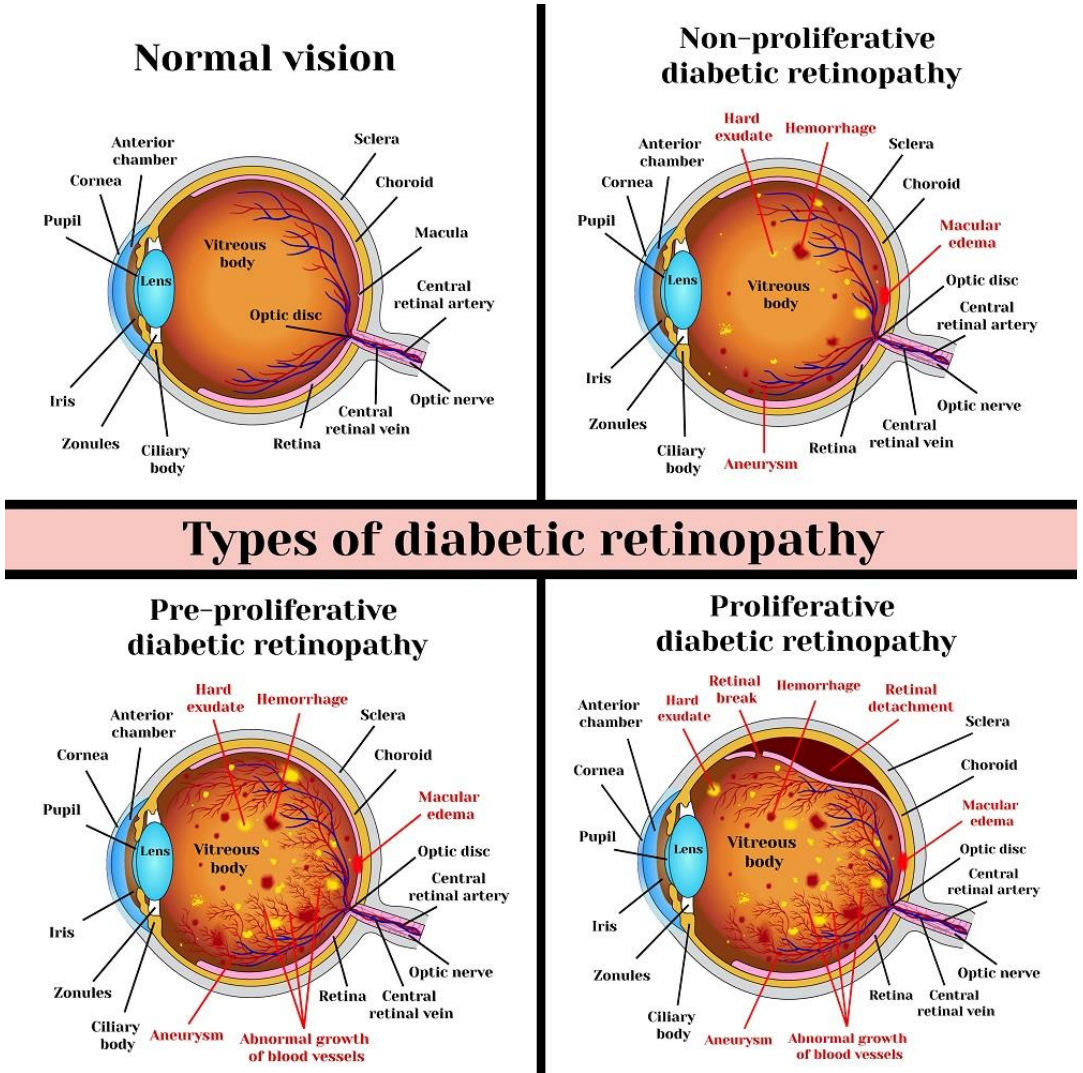


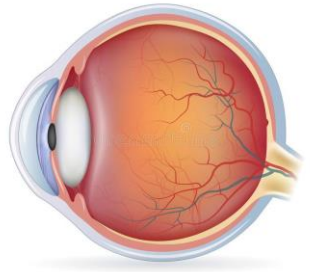
TABLE. Diagnosing Diabetic Retinopathy

DIABETIC RETINOPATHY LEVEL	RETINAL FINDINGS
Mild NPDR	MAs only
Moderate NPDR	At least one hemorrhage or MA and/or at least one of the following: • Retinal hemorrhages • Hard exudates • Cotton wool spots • Venous beading
Severe NPDR	Any of the following but no signs of PDR (4-2-1 rule): • > 20 intraretinal hemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants
PDR	One of either: • Neovascularization • Vitreous/preretinal hemorrhage

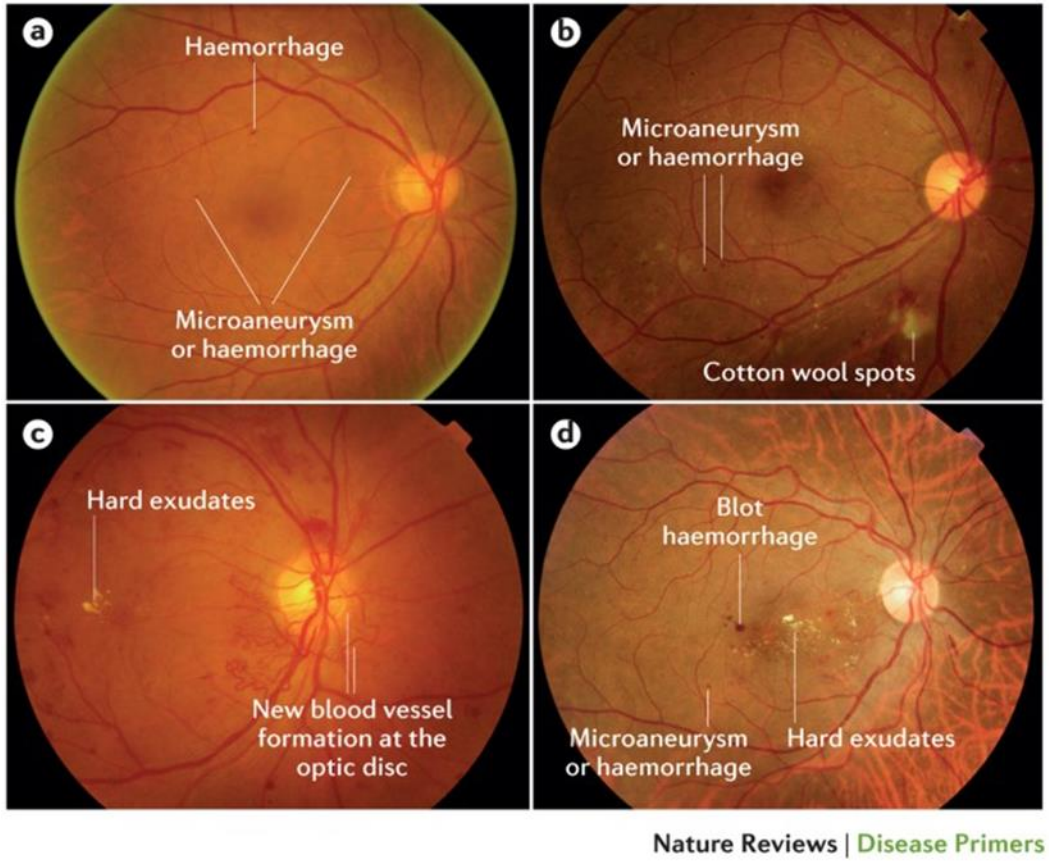
Abbreviations: IRMA, intraretinal microvascular abnormality; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy



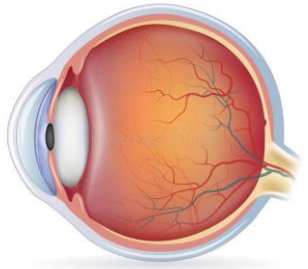
Changes and the development of DR



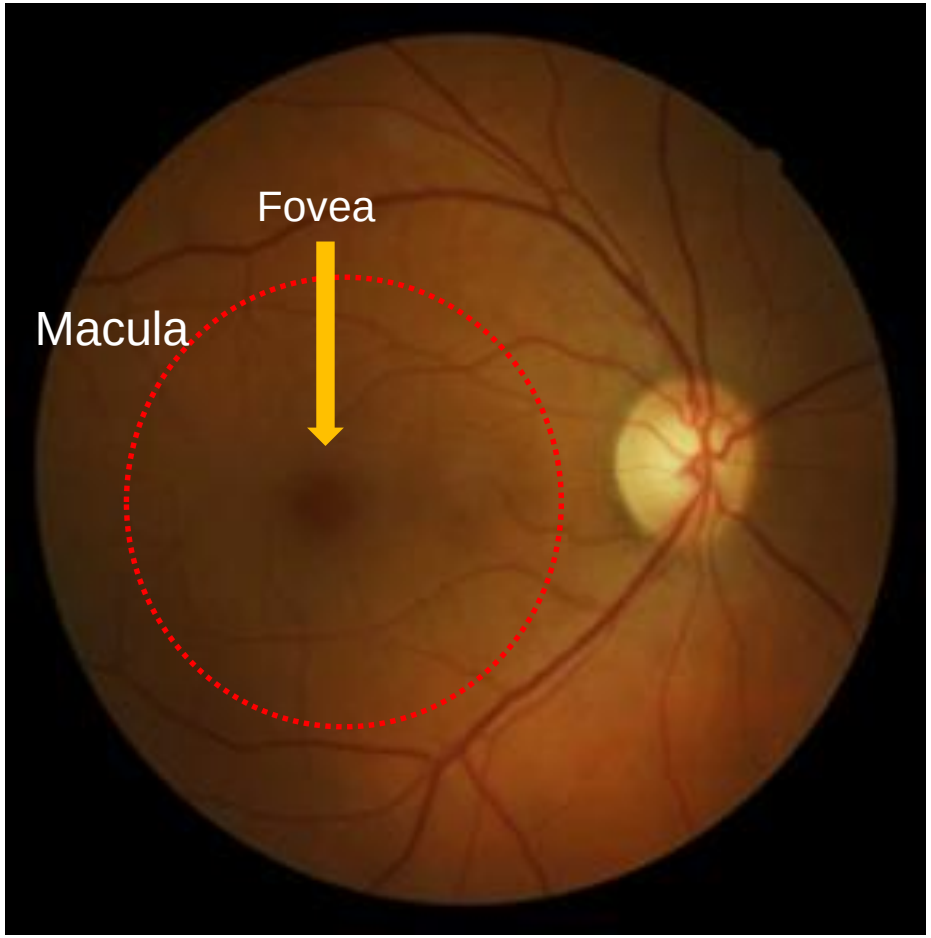
- **Small hemorrhages - "dots"** and therefore are frequently referred to as "dot hemorrhages."
- **Hard exudates** - caused by lipid deposition that typically occurs at the margins of hemorrhages.
- **Microaneurysms** - small vascular dilatations, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination.
- **Retinal edema** may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. The appearance is one of grayish retinal areas.



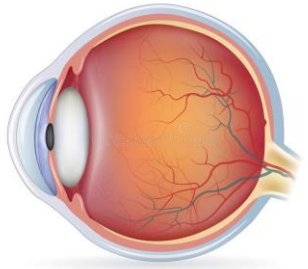
Maculopathy



- A common cause of blindness!
- It produces 80% of cases of blindness due to DR
- The macula is responsible for central vision
- Diabetic macular edema may be asymptomatic at the begining. As the macular edema moves to the fovee (the center of the macula) the patient will have blurred central vision, the ability to read and recognize faces will be compromised.



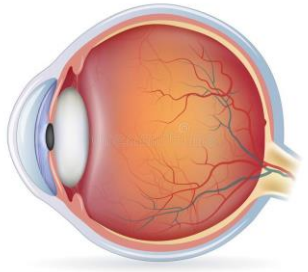
SYMPTOMS of DR



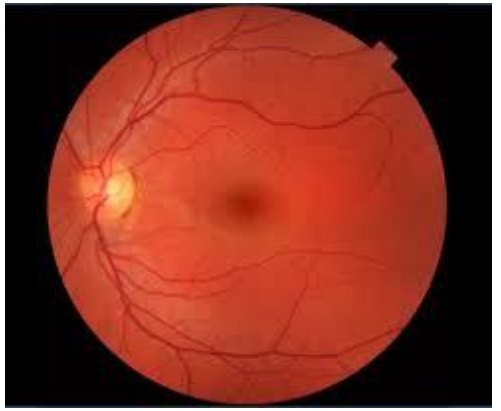
- DR is asymptomatic in early stages of the disease.

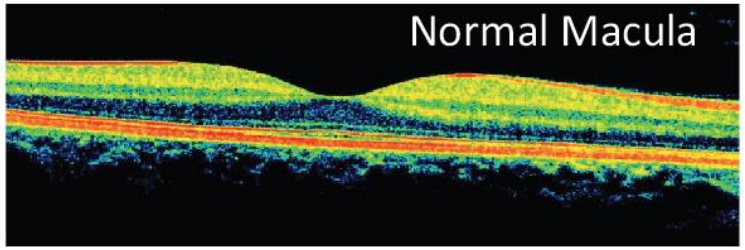
- As the disease progresses symptoms may include:
  - Blurred vision
  - Floaters and flashes
  - Fluctuating vision
  - Distorted vision
  - Dark areas in the vision
  - Poor night vision
  - Impaired color vision
  - Partial or total loss of vision

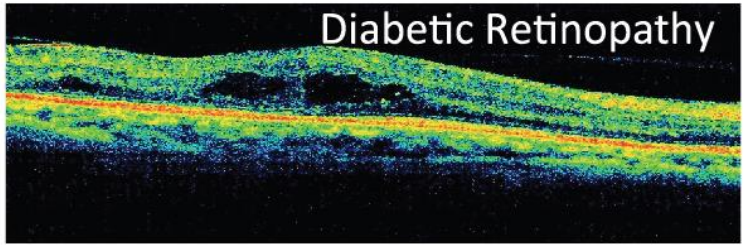
DR - Screening



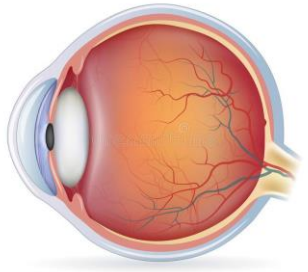
- **T1DM:**
  - The first screening 5 years after the onset and then annually.
- **T2DM:**
  - At the time of the diabetes diagnosis.
- **Screening and diagnostic methods:**
  - Ophthalmoscopic Exam
  - Fluorescein angiography (FA)
  - Optical coherence tomography (OCT)
  - Ocular ultrasonography







Risc factors management

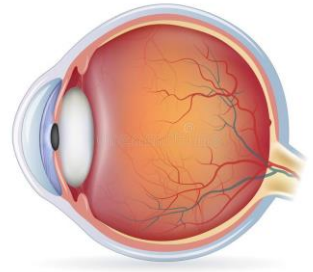


- **Good glycemic control:**
  - HbA1c < 7% vs. 7,9% - reduces the risk of microvascular complications by 25%

- **BP control:**
  - TAs < 140 mmHg – reduces the risk of DR progression by 34%

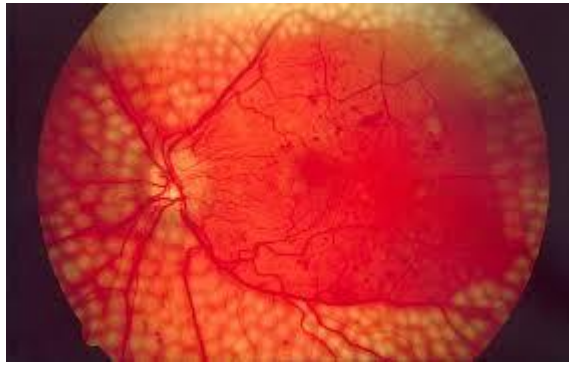
- **Lipides control:**
  - TG<150 mg/dl, LDL colesterol < 100 mg/dl, Col Tot < 200 mg/dl
  - With:
    - Atorvastatin
    - Fenofibrat

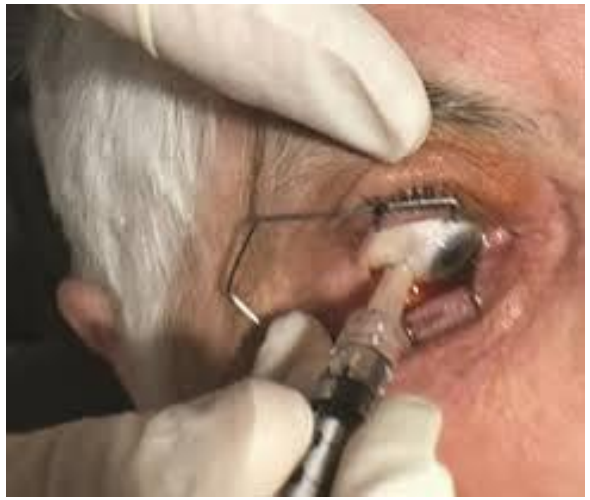
DR Treatment



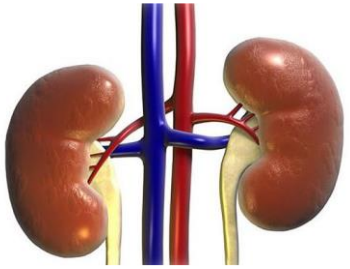
- **Panretinal laser photocoagulation therapy,** is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy.

- **Intravitreous injections of anti–vascular endothelial growth factor** are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy.
  - Ranibizumab
  - Aflibercept
  - Bevacizumab

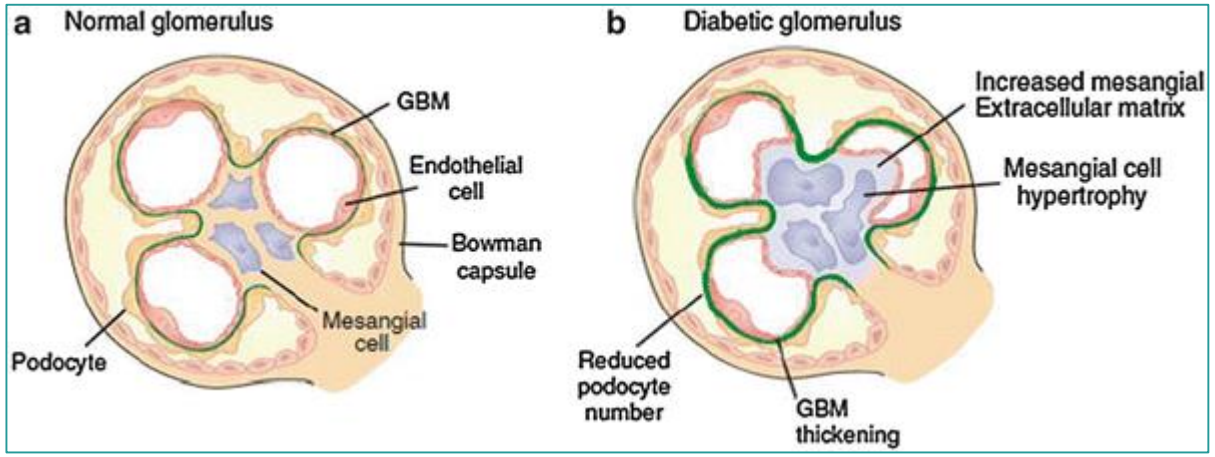




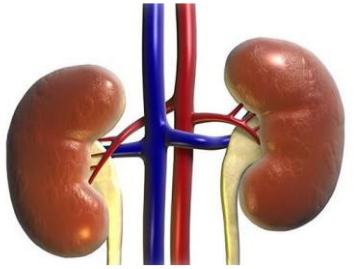
Diabetic nephropathy (DN)



Diabetic nephropathy (DN) or diabetic kidney disease is a syndrome characterized by ***the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and loss of glomerular filtration rate (GFR)*** in diabetics.

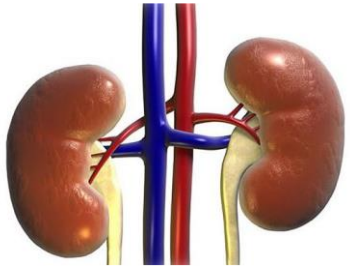


Chronic Diabetic Kidney (CDK)



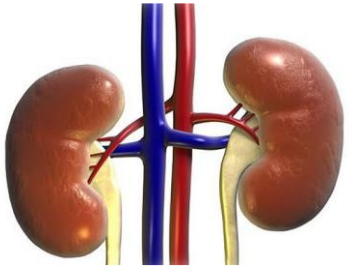
- Occurs in 20-40% of diabetic patients.
- 30% of patients with T1DM develop CDK within 20 years, may be present at diagnosis of type 2 diabetes..
- It is the leading cause of progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation.
- 20% of those with CDK get dialysis.
- It is associated with increased cardiovascular mortality.

Risk factors

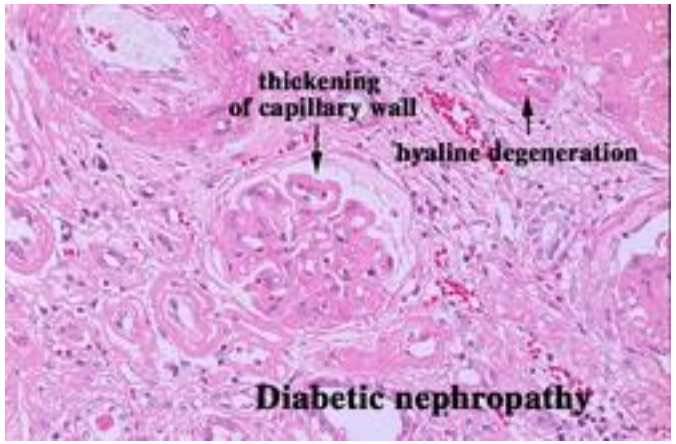


- Poor glycemic control
- Long duration of diabetes
- Presence of other microvascular complication
- Ethnicity (Asians, Pima Indians)
- Male gender
- Cigarette smoking
- Pre-existing hypertension
- Cardiovascular disease.

Diabetic nephropathy

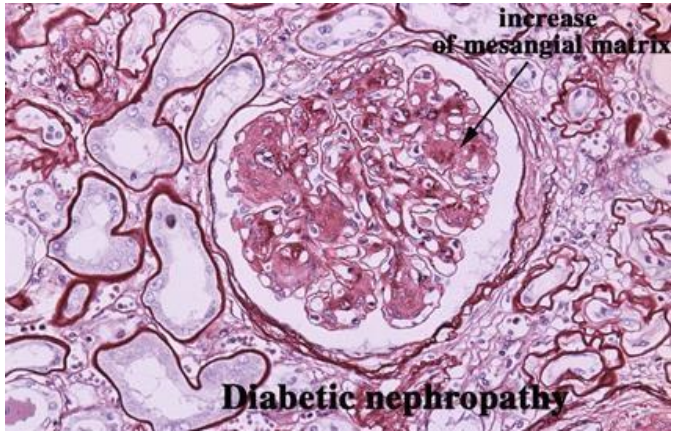


Diabetic nephropathy (DN) is microvascular complication of the kidneys **induced by diabetes mellitus** and is characterized by **albuminuria and progressive loss of kidney function.**



Classic glomerulosclerosis is characterized:

- increased glomerular basement membrane,
- diffuse mesangial sclerosis,
- hyalinosis,
- microaneurysm,
- hyaline arteriosclerosis
- tubular and interstitial changes.



Pathogenesis

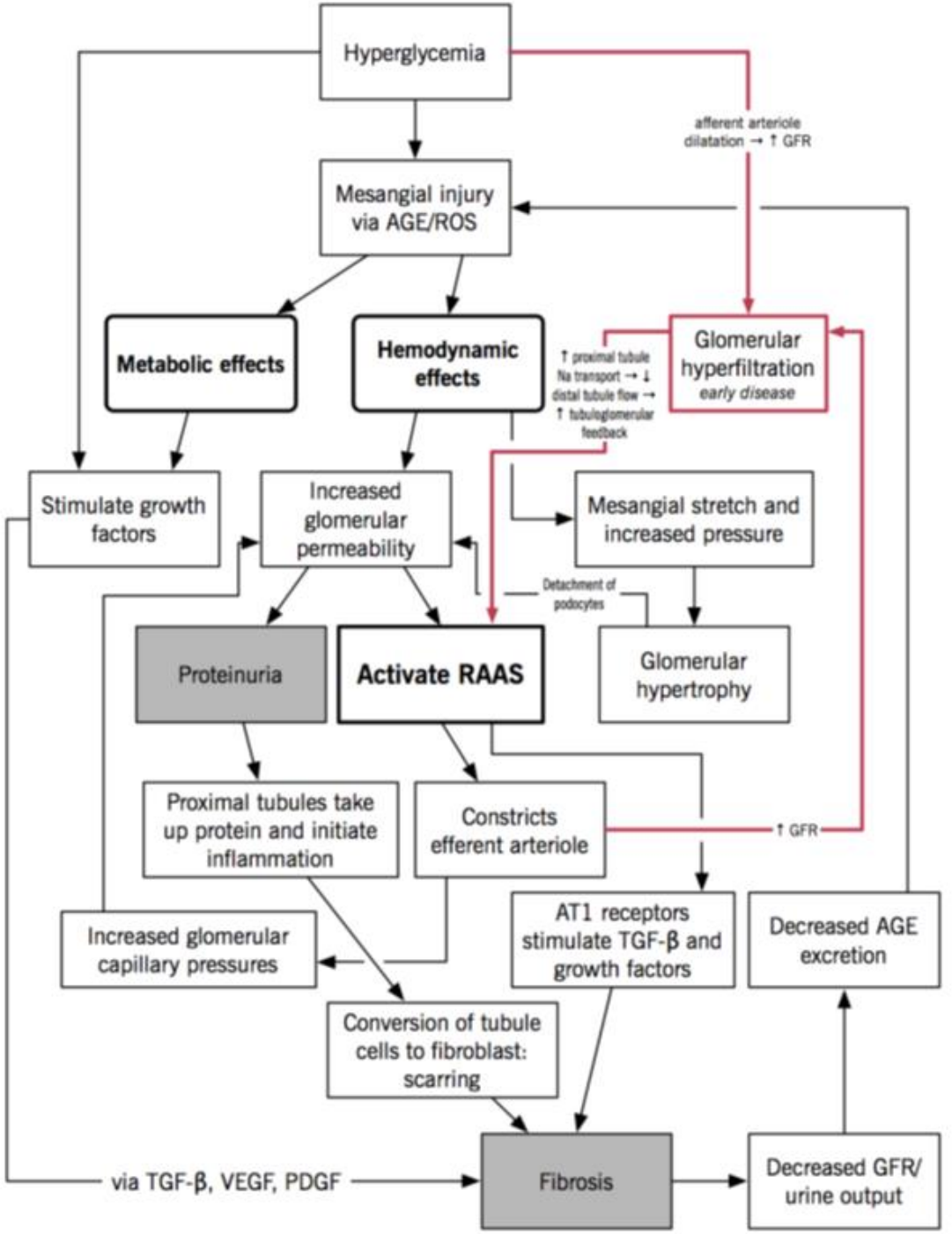
Chronic hyperglycemiais - the primary cause of DN.
This effect is mediated via a number of mechanisms including: 1)glomerular hyperfiltration, 2) direct effects of hyperglycemia, and 3) advanced glycosylation end products (AGE), and (iv) cytokine secretion.

Glomerular hyperfiltration is mediated mainly via dilatation the afferent arteriole leading to a rise in the GFR and the renal blood flow.

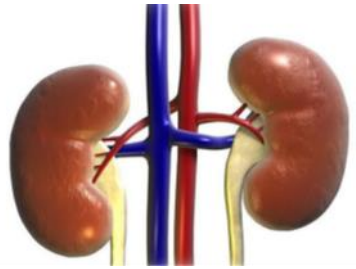
Hyperfiltration of glucose leads to augmented sodium-glucose transport in the proximal convoluted tubule causing enhanced sodium transport- to a rise in GFR- reduced distal fluid delivery which activates the tubuloglomerular feedback with the renin-angiotensin system which works to raise the GFR as well.

Hyperglycemia and AGE directly induce mesangial matrix production, cellular expansion and apoptosis, increase basement membrane permeability to albumin.

Elevations in vascular endothelial growth factor (VEGF), transforming growth factor beta (TFG-β), and profibrotic proteins increase damage to the nephrons at different levels; specific mechanisms are unclear.



CKD stages



Diabetes Care Volume 43, Supplement 1, January 2020

11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2020*

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GFR categories (mL/min/1.73m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
Glomerular filtration rate	G1	Normal to high	≥90	1 If CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 If CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

The numbers in the boxes are a guide to the frequency of visits (number of times per year).

Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually;

Yellow requires caution and measurements at least once per year;

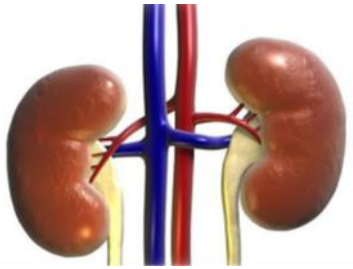
Orange requires measurements twice per year;

Red requires measurements three times per year;

Dark red requires measurements four times per year.

https://care.diabetesjournals.org/content/44/Supplement_1/S151

Chronic Diabetic Kidney Disease - screening



WHAT ?

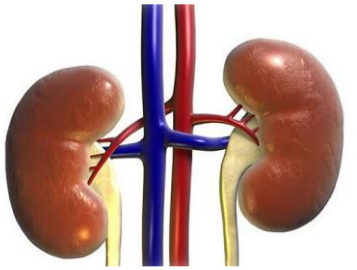
- **Assess**
- **urinary albumin (e.g., spot urinary albumin-to creatinine ratio) - UACR**
- **estimated glomerular filtration rate - eGFR**

HOW OFTEN?

- **At least once a year** - in patients:
- with type 1diabetes with duration >5years
- all patients with type 2 diabetes regardless of treatment.

- **twice annually in patients:**
- with urinary albumin > 30 mg/g creatinine
- and/or an eGFR<60mL/min/1.73m2

Chronic Kidney Disease - Nutrition

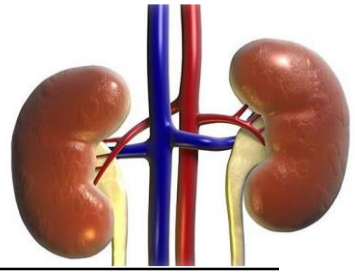


- **Protein intake**
  - For people with non-dialysis - dependent CKD, dietary protein intake ~ 0.8 g/kg/day
  - For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients.

- **Restriction of dietary sodium** (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk,

- **Restriction of dietary potassium** may be necessary to control serum potassium concentration.

Chronic Diabetic Kidney Disease - Treatment

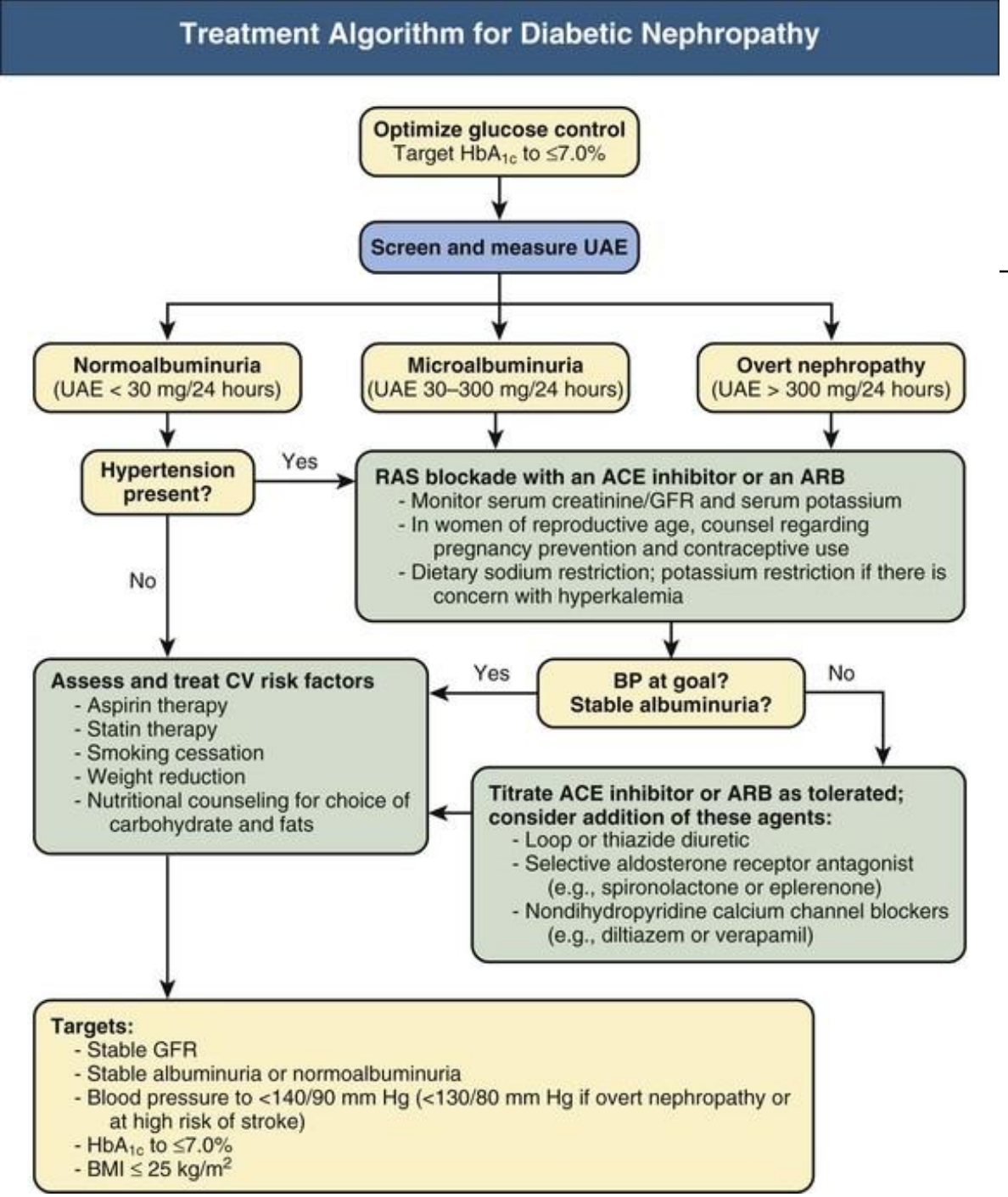


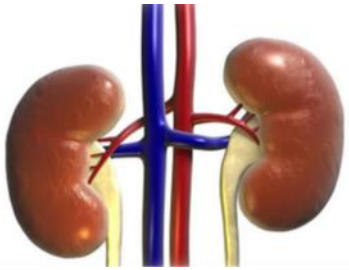
Nutritional intervention

Glycemic targets

- **HbA1c < 7.0%,** avoid hypoglycemia
- **DM 2 + CDKD** (eGFR ≥30 mL/min/1.73 m^2 and urinary albumin >30 mg/g creatinine,) **use SGLT2 inhibitor** - to reduce risk of chronic kidney disease (CKD) progression, cardiovascular events, or both.
- **DM2 + CKD + increased risk for cardiovascular events** - **use GLP1receptor agonist** may reduce risk of progression of albuminuria, cardiovascular events, or both.

Optimize blood pressure control to reduce the risk or slow the progression of chronic kidney disease.





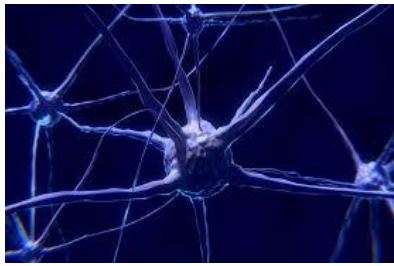
ACE inhibitors or ARBs are the preferred first-line agent:
- DM + hypertension with
- eGFR <60 mL/min/1.73 m2,
- UACR ≥300 mg/g Cr - benefits for prevention of CKD progression.

An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CDKD
- DM + normal blood pressure,
- normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine),
- normal eGFR.

Periodically monitor serum creatinine and potassium levels.

https://abdominalkey.com/prevention-and-treatment-of-diabetic-nephropathy/

Diabetic neuropathy



" Presence of symptoms and / or signs of peripheral nerve dysfunction in patients with diabetes, after excluding other causes" – *group NEURODIAB of EASD*

Diabetic neuropathy (2)

- The most common chronic complication
- It affects 60 - 70% of patients with T1DM and T2DM
- Affect 50-90% of patients with diabetes, of those 15-30% having painful diabetic neuropathy
- Prevalence –duration of diabetes & degree of metabolic control
- Diabetic neuropathy is a diagnosis of exclusion:
    - Involves various damage to the nervous system
    - Presents various clinical manifestations
    - More than 50% may be asymptomatic

Risk factors

- Damage to blood vessels
- Mechanical injury to nerves
- Autoimmune factors
- Genetic susceptibility
- Lifestyle factors
- Smoking
- Diet

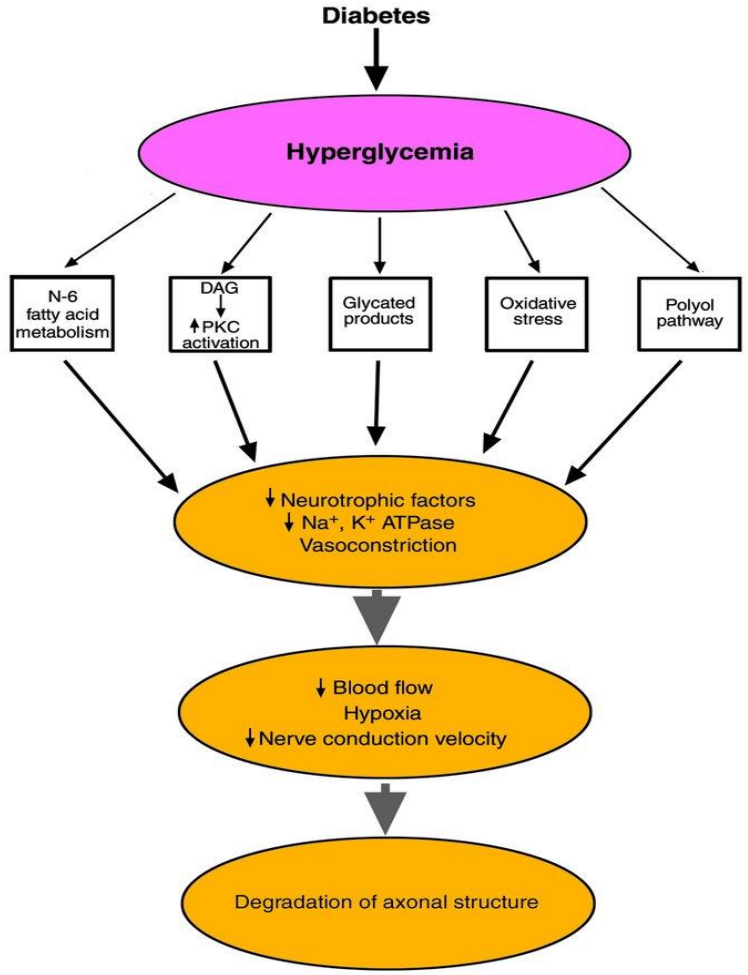
Pathogenesis of Diabetic Neuropathy

I. Metabolic factors

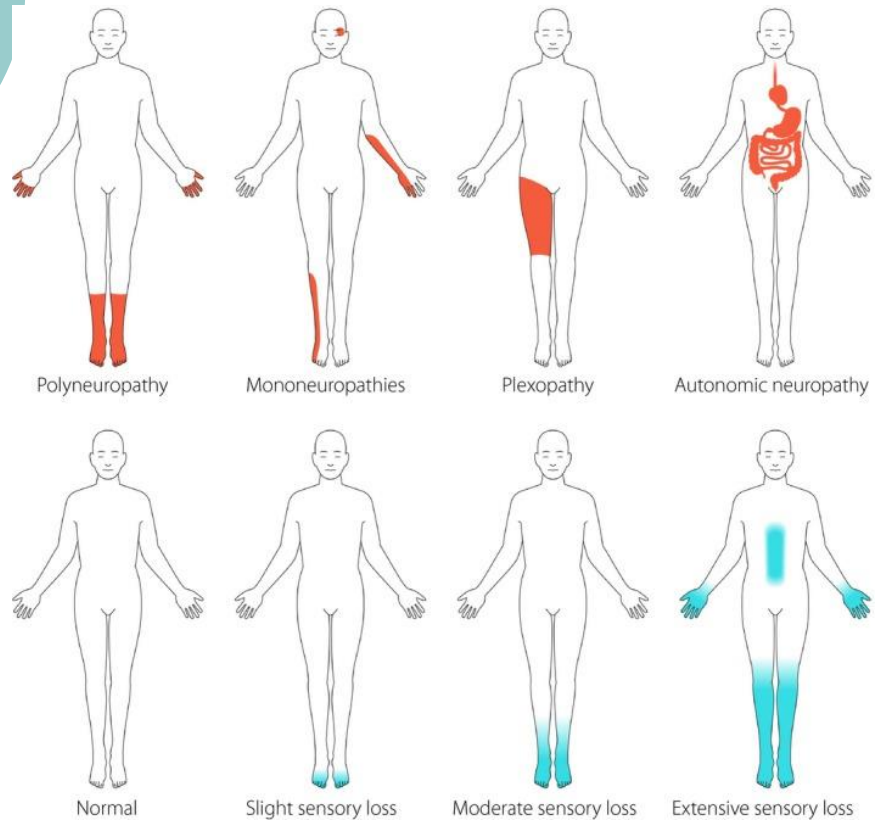
- High blood glucose
- Advanced glycation end products
- Sorbitol
- Abnormal blood fat levels

II. Ischemia

III. Nerve fiber repair mechanisms



Classification of diabetic neuropathies



https://care.diabetesjournals.org/content/diacare/40/1/136.full.pdf

Table 1—Classification for diabetic neuropathies

Diabetic neuropathies

A. Diffuse neuropathy

DSPN
- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most common)

Autonomic

Cardiovascular
- Reduced HRV
- Resting tachycardia
- Orthostatic hypotension
- Sudden death (malignant arrhythmia)

Gastrointestinal
- Diabetic gastroparesis (gastropathy)
- Diabetic enteropathy (diarrhea)
- Colonic hypomotility (constipation)

Urogenital
- Diabetic cystopathy (neurogenic bladder)
- Erectile dysfunction
- Female sexual dysfunction

Sudomotor dysfunction
- Distal hypohydrosis/anhidrosis,
- Gustatory sweating

Hypoglycemia unawareness

Abnormal pupillary function

B. Mononeuropathy (mononeuritis multiplex) (atypical forms)

Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)

Mononeuritis multiplex (if confluent may resemble polyneuropathy)

C. Radiculopathy or polyradiculopathy (atypical forms)

Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)

Thoracic radiculopathy

Distal sensory or sensorimotor polyneuropathy

- Small fiber neuropathy
- Location: distal portion of leg (1/2 leg, foot)
- Progressive clinical signs
- Predominant sensory disorders compared to motor ones
- Symmetrical symptoms: paresthesias, ascending evolution (in the sock), burns (nocturnal, especially)
- Frequent spontaneous reversibility

Symmetrical sensory polyneuropathy – Clinical features

Asymtomatic

- Mc signs :

– diminished perception of vibration sensation distally

– Gloves & stocking impairment

– Loss of tendon reflexes in feet

- A diffuse small fibre neuropathy altered perception of pain & temperature, a/w symptomatic autonomic neuropathy → foot ulcers & Charcot neuroarthropathy

Symtomatic

- Sensory abnormalities predominant
- Paraesthesiae in the feet
- Pain in the feet
- Burning sensation in the soles of feet
- Cutaneous hyperaesthesiae
- Abnormal gait- wide based
- a/w numbness in the feet
- Callus skin at pressure point
- Electrophysiological test-slow conduction both motor & sensory
- Test vibration & thermal thresholds-abnormal

Asymmetrical motor diabetic neuropathy

- Called as diabetic amyothrophy
- Progressive weakness & wasting of proximal muscles
- Severe pain – hyperaesthesiae & paraaesthesiae
- Loss of weight (neuropathic cachexia)
- Tendon reflexes –absent
- Extensor plantar responses +++
- Management-mainly supportive
- Recovery within 12 month, some deficit may permanent.

Mononeuropathy

- Motor or sensory function affected within a single peripheral or cranial nerve
- Severe & rapid in onset, but eventually recover
- Most common CN affected : 3rd& 6th (diplopia)
- Nerves compression palsies most commonly occur→ median nerve (carpal tunnel syndrome), less common→ ulnar nerves
- Lateral popliteal nerves compression→ foot drop.

Autonomic neuropathy

Cardiovascular	• Postural hypotension • Resting tachycardia • Fixed heart rate
Gastrointestinal	• Dysphagia • Abdominal fullness, nausea , vomiting • Nocturnal diarrhea + fecal incontinence • constipation
Genitourinary	• Difficulty in micturition, urinary incontinence, recurrent infection • Erectile dysfunction & retrograde ejaculation
sudomotor	• Nocturnal sweat w/o hypoglycemia • Gustatory sweating • anhydrosis
vasomotor	• Feet feel cold • Dependent edema • Bullous formation
Pupillary	• Decreased pupil size • Resistance to mydriatics • Delayed/ absent reflexes to light

Distal Symmetric Polyneuropathy – diagnosis

Patients experience:

- burning,
  "electrical" pain - it may be worse at night,
- tingling,
- sometimes simple numbness.

The following clinical tests may be used:

1.Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception and 10-g monofilament
3.Protective sensation: 10-g monofilament

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms§	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination (clinically diagnostic)**	Ankle reflexes: reduced/absent Vibration perception: reduced/absent 10-g monofilament: reduced/absent Proprioception: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent** Pinprick sensation: reduced/absent**

§To document the presence of symptoms for diagnosis; **Documented in symmetrical, distal to proximal pattern.

Distal Symmetric Polyneuropathy – treatment

Clinical diagnosis of DSP +/- neuropathic symptoms

Lifestyle modification, control of CVD/other risk **factors**

Assessment of comorbidities, potential for drug interactions

Asymptomatic DSP	Symptomatic non-painful DSP	Painful DSP
alfa-lipoic acids	alfa-lipoic acids Benfotiamin Actovegin	Analgesic treatment Duloxetine Pregabalin

Autonomic neuropathy – clinical manifestation

Cardiac Autonomic Neuropathy

- **CAN** is associated with mortality independently of other cardiovascular risk factors.

- **Early stages** - CAN may be asymptomatic, can be detected - by decreased heart rate variability with deep breathing.

- **Advanced disease** - associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg,

- **CAN treatment** is generally focused on symptoms.

Gastrointestinal Neuropathies

- May involve any portion of the gastrointestinal tract.

- **Clinical manifestations:** esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence.

- **Gastroparesis** - suspected in erratic glycemic control or with upper gastrointestinal symptoms without another identified cause.

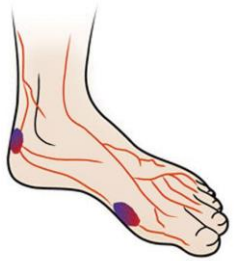
- **Gold standard for diagnosis** is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake.

Genitourinary Disturbances

- ***sexual dysfunction***
- **In men**, - erectile dysfunction and/or retrograde ejaculation .
- **Female** - decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication.

- ***bladder dysfunction.***
- urinary incontinence
- bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream).

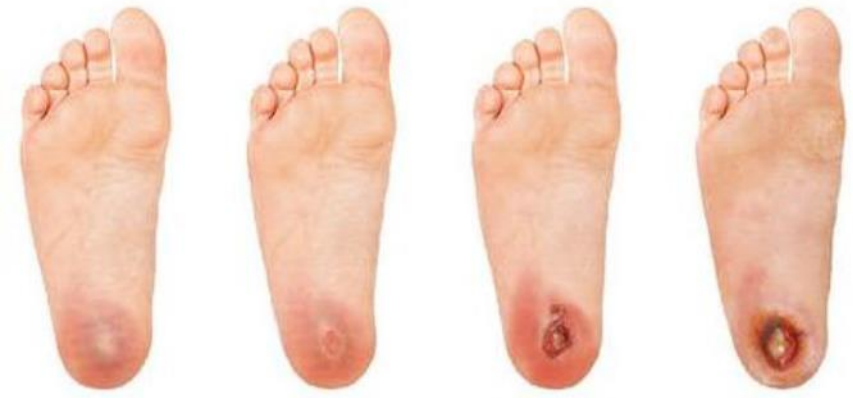
- Evaluation of bladder function - individuals who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.



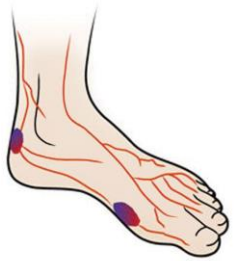
Diabetic foot

- Consequences of diabetic neuropathy and/or peripheral arterial disease (PAD)
  - which lead to foot ulcers and amputation.

- Infection, ulceration, or destruction of tissues of the foot of a person with currently or previously diagnosed diabetes mellitus, usually accompanied by neuropathy and/or PAD in the lower extremity.

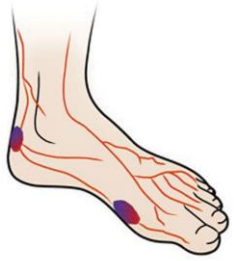


Diabetic foot (2)



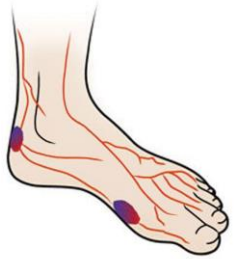
- Approximately 15% of all people with diabetes will be affected by foot ulcer during their lifetime;
- 85% of diabetes-related amputations are preceded by foot ulcers (International Diabetes Federation) ;
- Up to 70% of amputations are performed on people with Diabetes;
- “Someone, somewhere, loses a leg because of diabetes every 30 seconds of everyday…”

Lancet. 2005;366:1674



Risk Factors for Diabetic Foot Ulcers

General / Systemic contributions	Local issues
Uncontrolled hyperglycemia	Peripheral neuropathy
Duration of diabetes > 10 years	Structural foot deformity
Peripheral vascular disease	Trauma / ill fitted shoes
Blindness or visual loss	Callus
Chronic renal disease	History of prior ulcer / amputation
Older age	Prolonged elevated pressures
High body mass index	Limited joint mobility

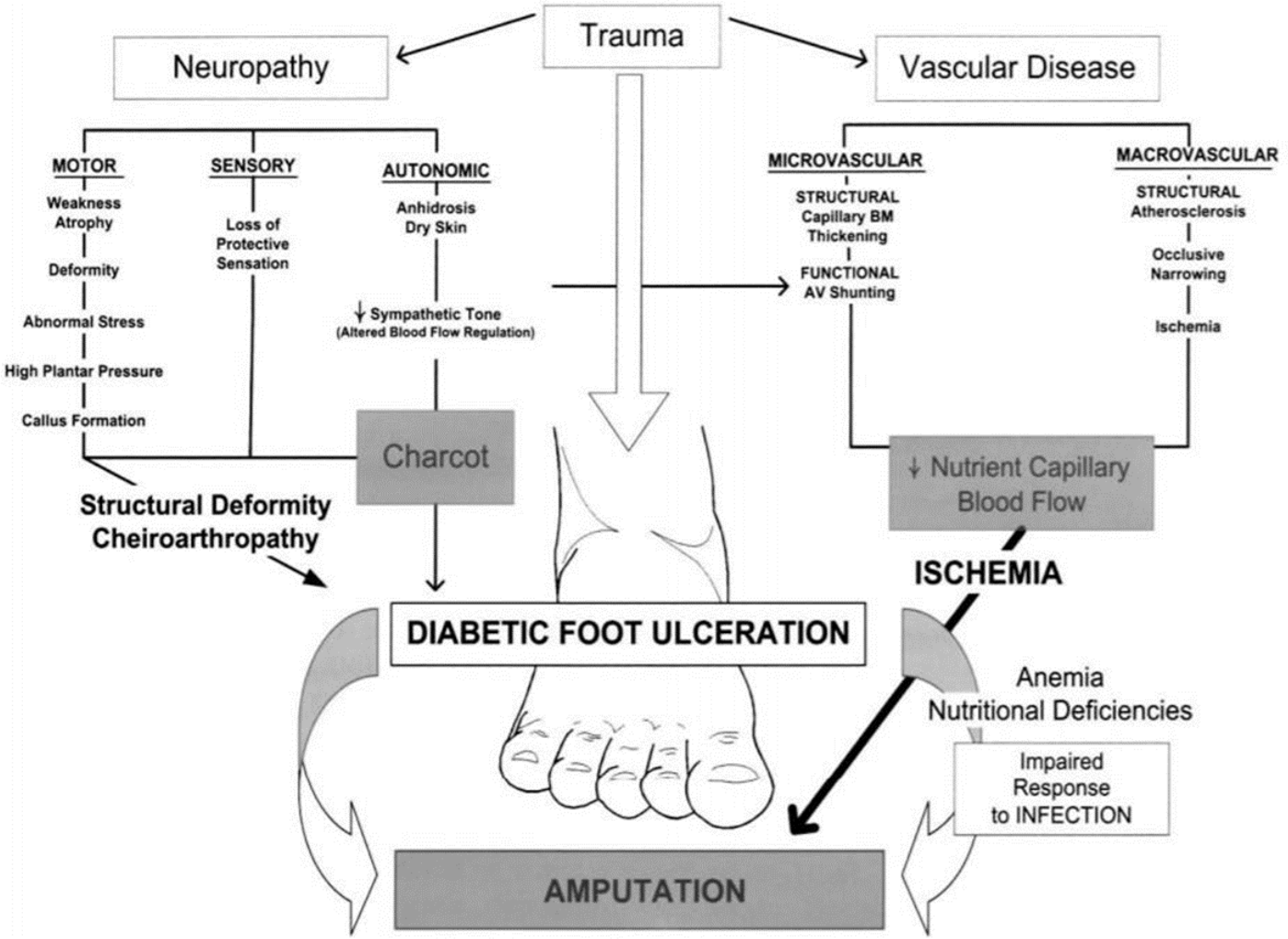


Pathogenesis

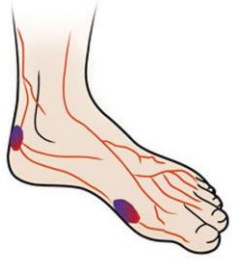
Multi-factorial & Complex:

1. Neuropathy
2. Vasculopathy
3. Immune dysfunction

Prolonged Hyperglycemia contributes to all the above factors through different mechanisms



Diabetic callus formation



Loss of protective sensation, foot deformities, and limited joint mobility can result in **abnormal biomechanical loading of the foot**.

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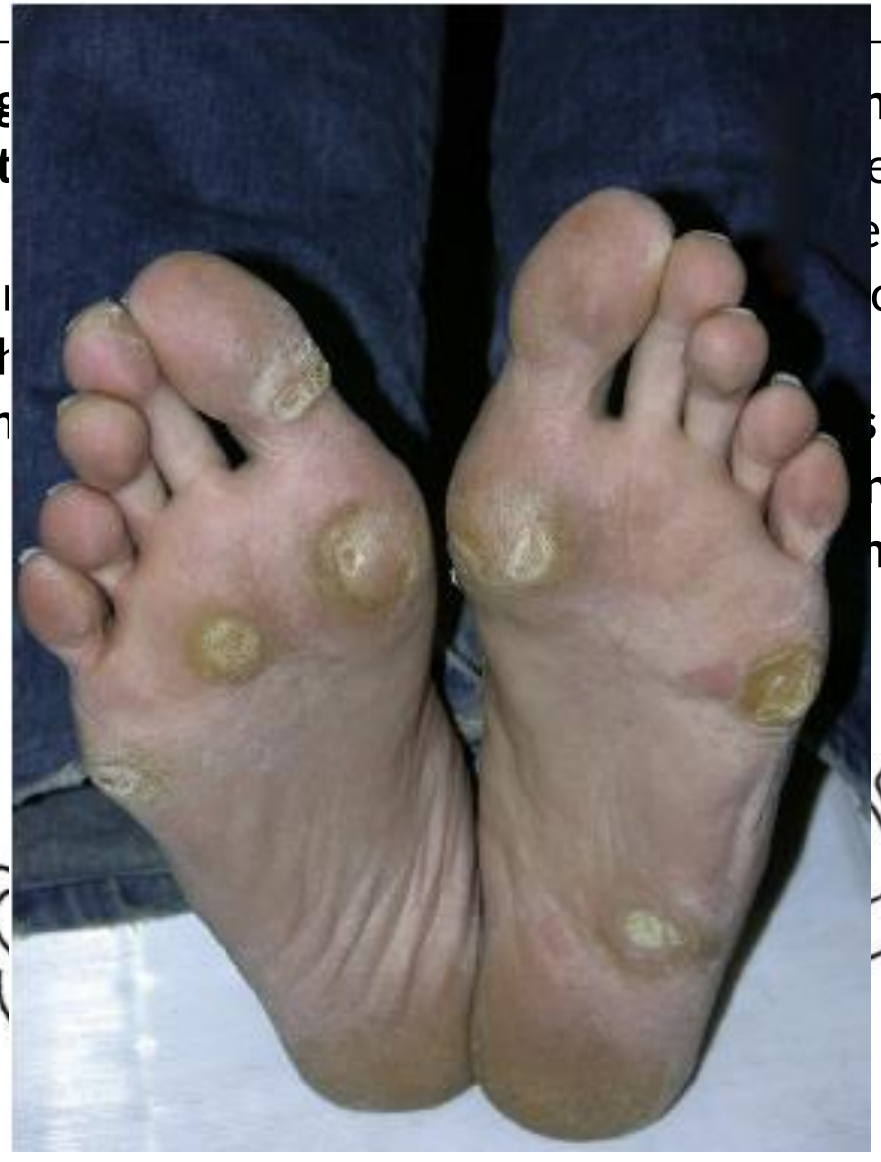
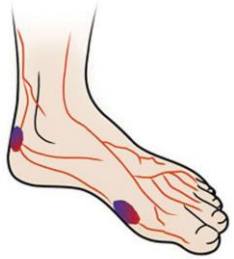


Whatever the primary cause of ulceration, continued walking on the insensitive foot **impairs healing of the ulcer.**

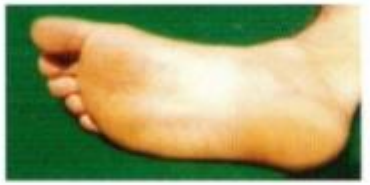
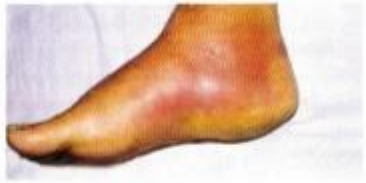
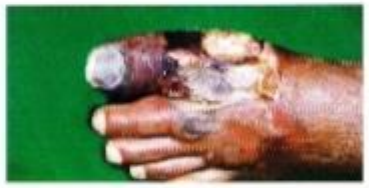
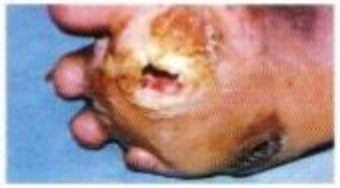
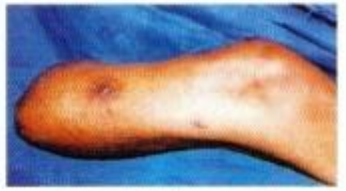


Classification & Staging

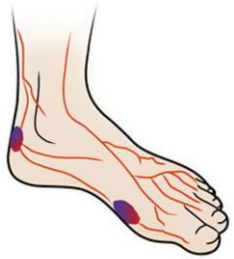
On the basis of etiology:

- Neuropathic foot (neuropathy is dominant)
  - a. with infection
  - b. without infection
- Ischemic foot (vascular disease is dominant)
  - a. with infection
  - b. without infection
- Mixt

According to natural history (ME Edmond & AV Foster)

Stage	Clinical Condition	Stage	Clinical Condition
1.	 Fig. 7.9: Normal	4.	 Fig. 7.12: Cellulitic
2.	 Fig. 7.10: High-risk	5.	 Fig. 7.13: Necrotic
3.	 Fig. 7.11: Ulcerated	6.	 Fig. 7.14: Major amputation

Neuropathic foot

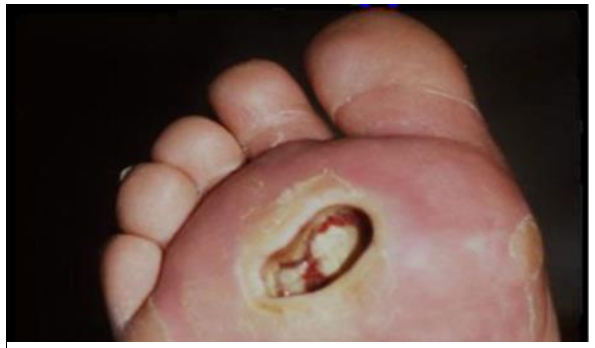


- The foot has diminished sensation
- It invariably warm, with intact, often bounding pulses.
- Ulcers

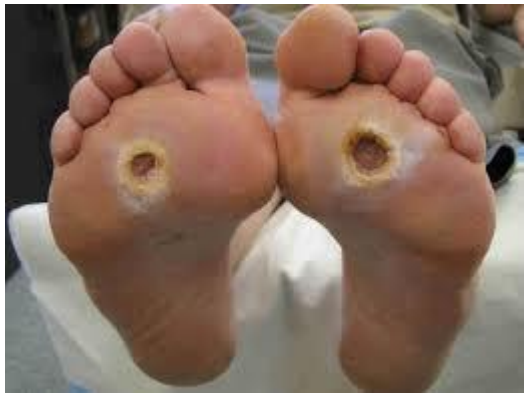
Pressure points on planter surface

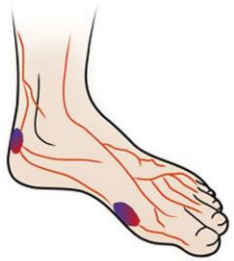
Stress areas on dorsal surface

- Ulcer often preceded by callus formation
- Ulcers can be secondarily infected
- Quickly lead to cellulitis, abscess formation, and osteomyelitis
- Sepsis may complicate, resulting in gangrene.



Neuropathic ulcer

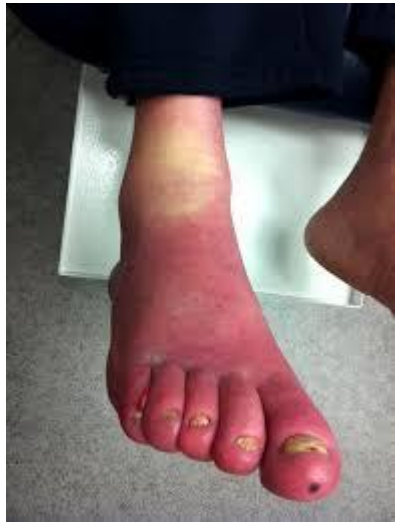


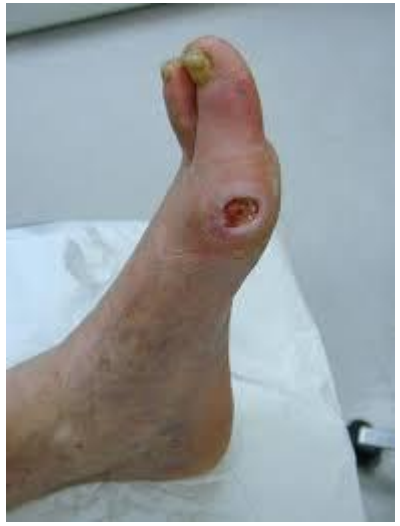


Diabetic Ischaemia

- Micro-vascular and Macro-vascular
- Pathology identical to non-diabetics
- Earlier onset
- Complications of high blood pressure, high cholesterol and smoking are all amplified by diabetes
- 1 Cigarette reduces peripheral blood flow by 30% for 1 hour.

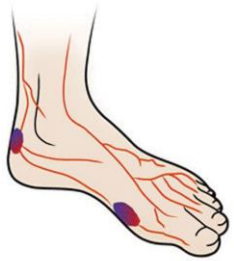
- Foot pulses are absent indicating ischaemia
- Foot is not warm
- Lesions on the margins of the foot & tip of the toes
- Absence of callus is characteristic features. Ischaemic ulcer





- Gangrene may be present.
- It is essential to identify critical ischaemia:
  - characteristic pink
  - painful
  - pulseless
  - cold foot

Differential Diagnosis



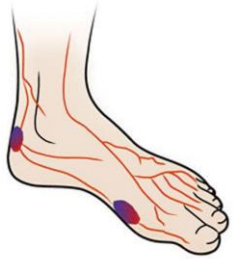
Neuropathic

- Warm
- Normal colour
- Palpable pulses
- Skin well nourished
- Callus at pressure points
- Ulceration plantar

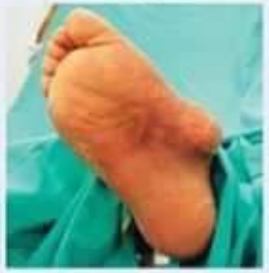
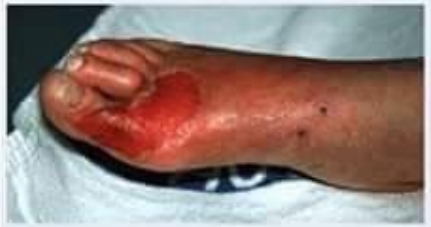
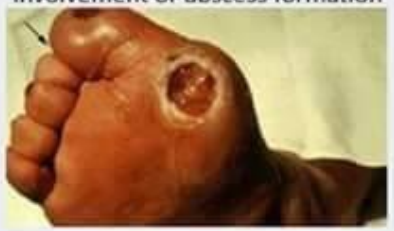
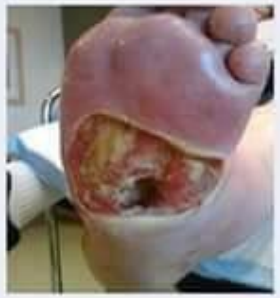
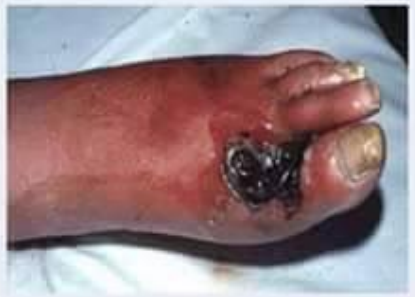
Neuroischaemic

- Cool
- Pale
- Pulses diminished/ absent
- Skin thin shiny no hair
- No callus fissuring at bony prominences
- Ulcers peripheral

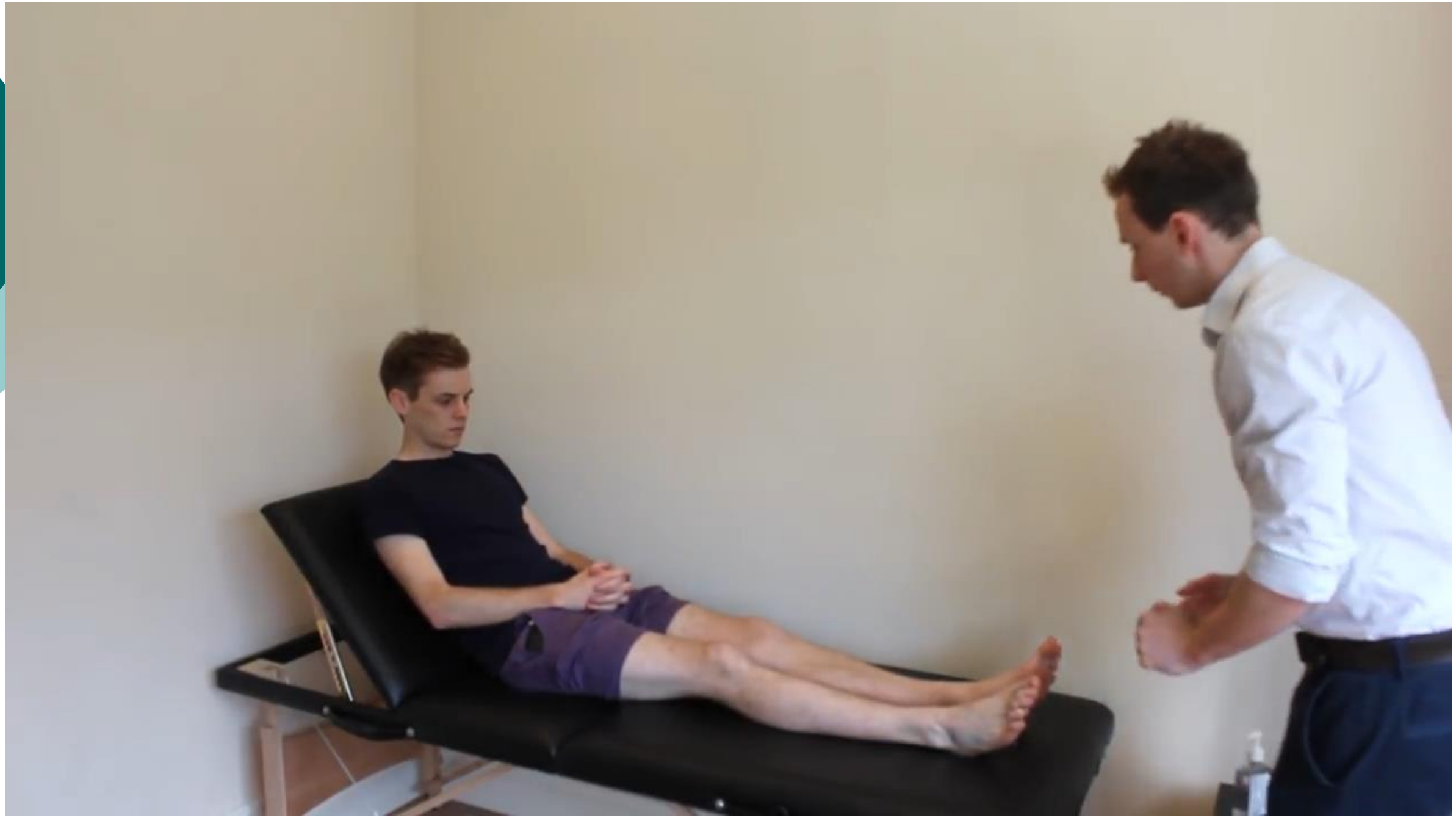
Wagner classification



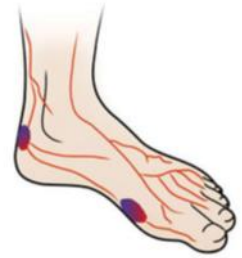
Wagner classification of diabetic foot ulcers

Grade 0	Grade 1	Grade 2
No ulcer in a high-risk foot 	Superficial ulcer involving the full skin thickness but not underlying tissues 	Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation 
Grade 3	**Grade 4**	**Grade 5**
Deep ulcer with cellulitis or abscess formation, often with osteomyelitis 	Localized gangrene 	Extensive gangrene involving the whole foot 

https://ro.scribd.com/document/378925048/Diabetic-foot-wagner-docx

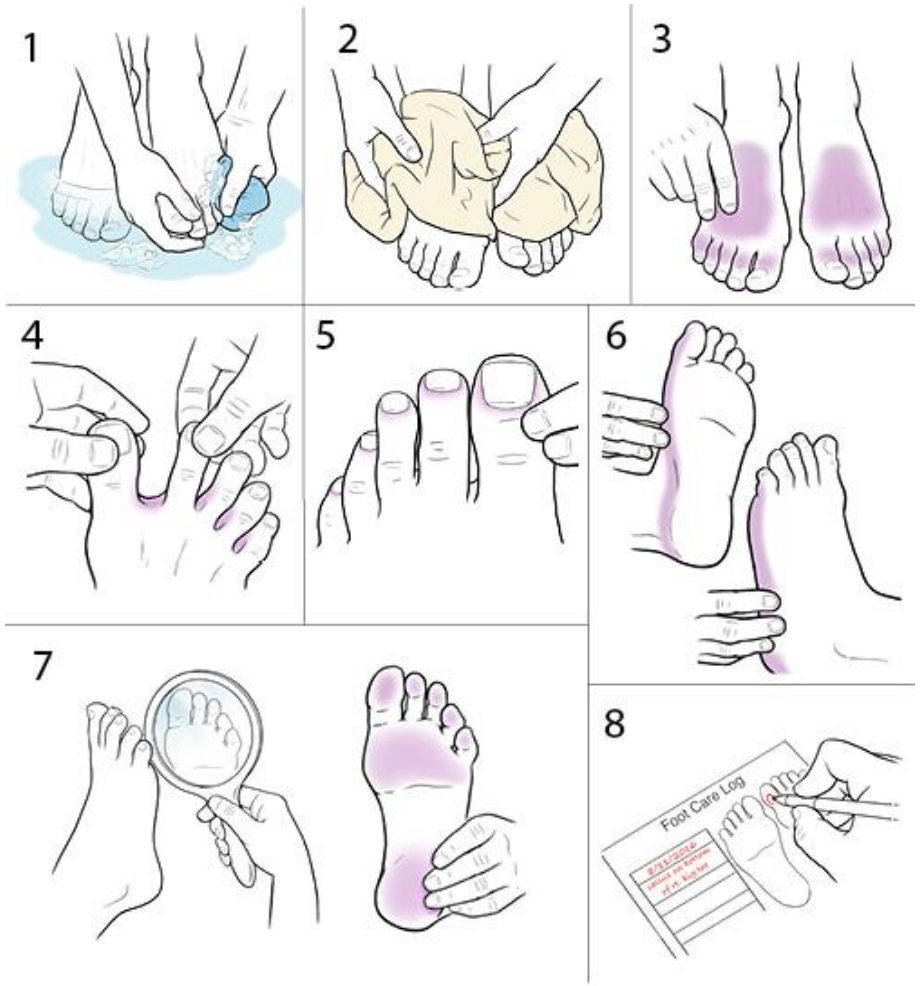


Diabetic Foot Care

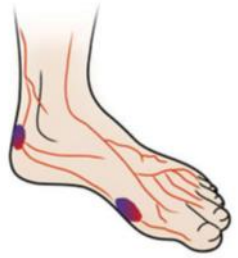


Patient should check feet daily

- Wash feet daily
- Keep toe nails short
- Protect feet
- Always wear shoes
- Look inside shoes before putting them on
- Always wear socks
- Break in new shoes gradually

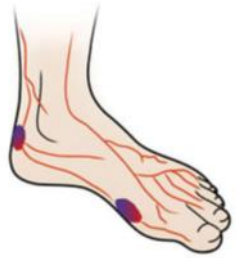


Diabetic foot – principles of ulcer treatment



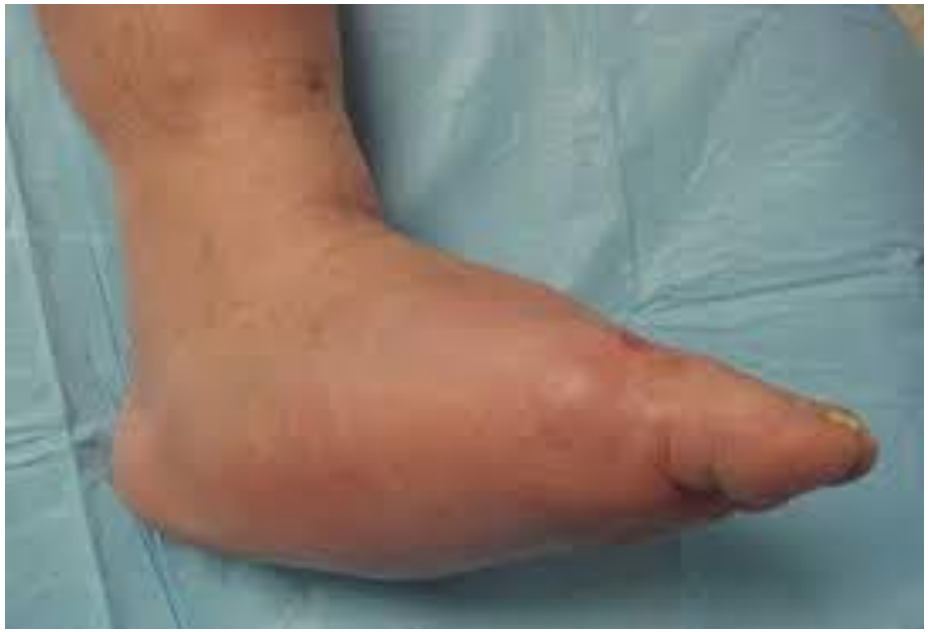
- Pressure offloading and ulcer protection
- Restoration of tissue perfusion
- Treatment of infection
- Metabolic control and treatment of co-morbidities
- Local ulcer care
- Education for patient and relatives

Charcot foot



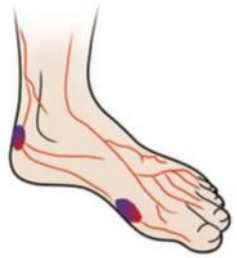
Charcot neuropathic osteoarthropathy (CN), commonly referred to as the Charcot foot, is a condition affecting the bones, joints, and soft tissues of the foot and ankle, characterized by inflammation in the earliest phase.

- The interaction of several component factors (diabetes, sensory-motor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone) results in an acute localized inflammatory condition that may lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity.



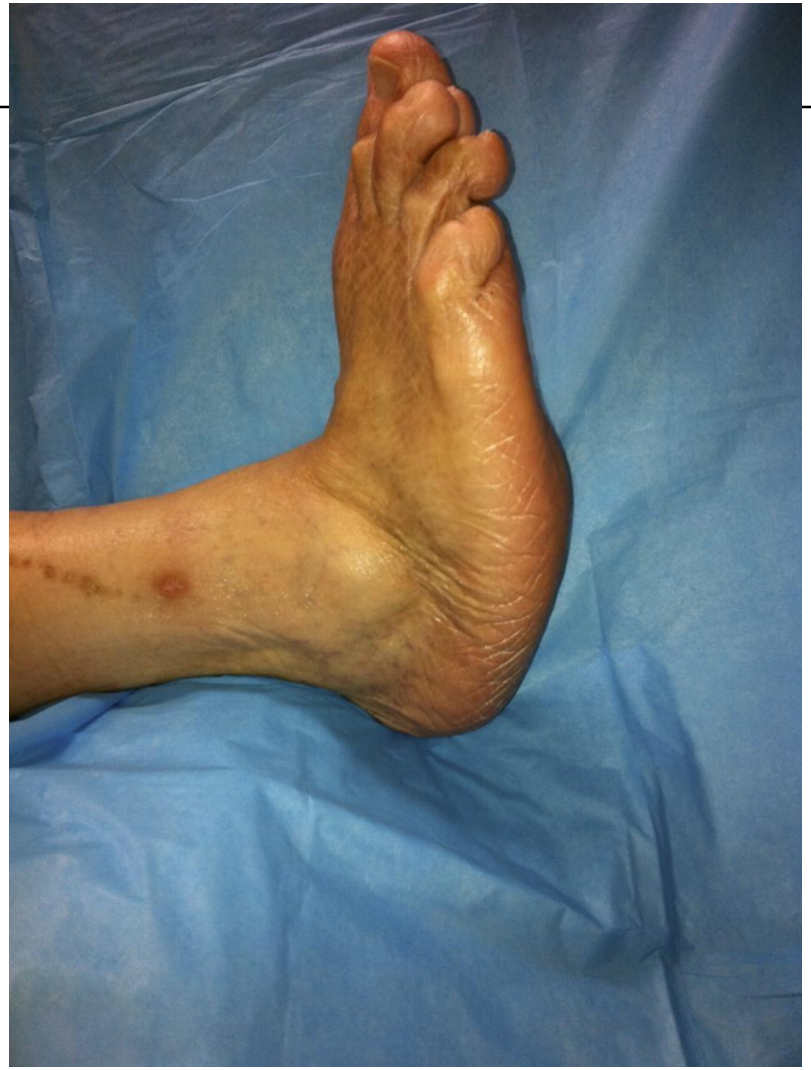
https://diabet-si-nutritie.ro/piciorul-charcot-in-diabet/

Charcot foot (2)



Acute phase

- Markedly swollen
- Warm - temperature differential between the two feet of several degrees
- Often erythematous foot
- Only mild to modest pain or discomfort

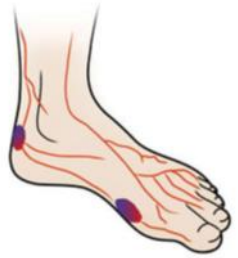


Chronic phase

- Midfoot collapse - “rocker-bottom” foot
- Foot becomes shorter and wider,
- Eversion, external rotation,
- With or without plantar ulceration.

Lee C. Rogers et al. Dia Care 2011;34:2123-2129

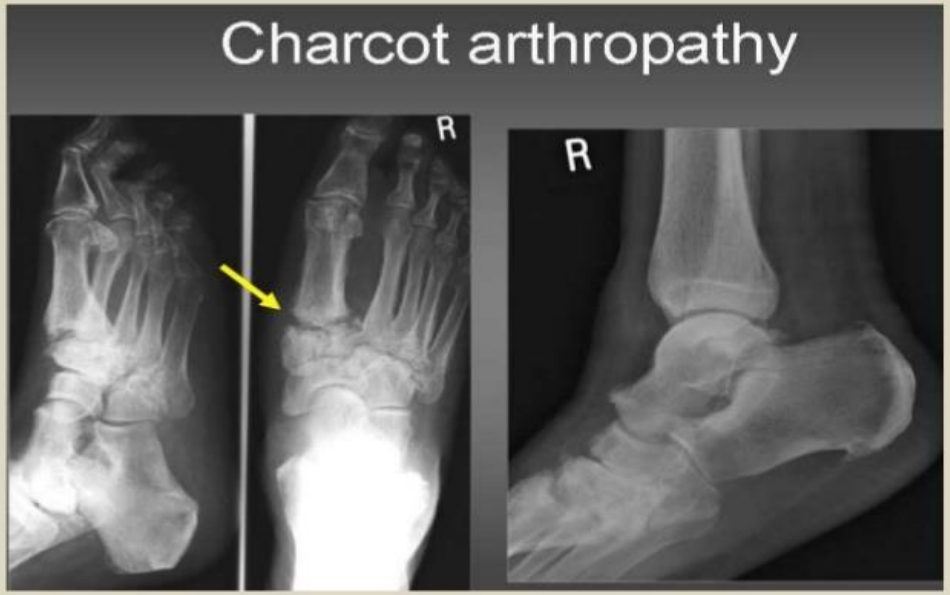
Charcot foot - diagnostic recommendations



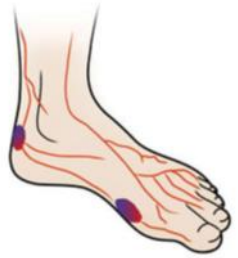
History and clinical findings but should be confirmed by imaging.

Inflammation plays a key role in the pathophysiology of the Charcot foot and is the earliest clinical finding.

- The occurrence of acute foot/ankle fractures or dislocations in neuropathic individuals is considered active CN because of the inflammatory process of bone healing, even in the absence of deformity.
- **X-rays** should be the initial imaging performed, and one should look for subtle fractures or subluxations if no obvious pathology is visible.
- **MRI or nuclear imaging** can confirm clinical suspicions in the presence of normal- appearing radiographs.



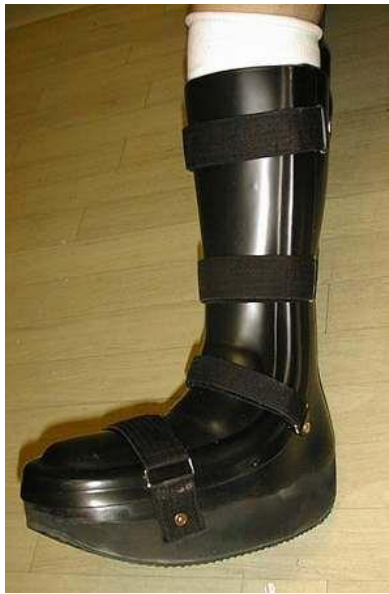
Chronic Charcot arthropathy at Lisfranc joint and Charcot joint. Note loss of normal alignment and bone loss.



Charcot foot - Management

Initial

- Rest, ideally bed rest or use of non-weight bearing crutches (until the oedema and local warmth have resolved)
- Alternatively, the foot can be immobilised in a well moulded total contact plaster which is initially non-weight bearing
- Immobilisation is continued until bony repair is complete, usually in two to three months
- The use of bisphosphonates in preventing bone damage in Charcot foot is promising.



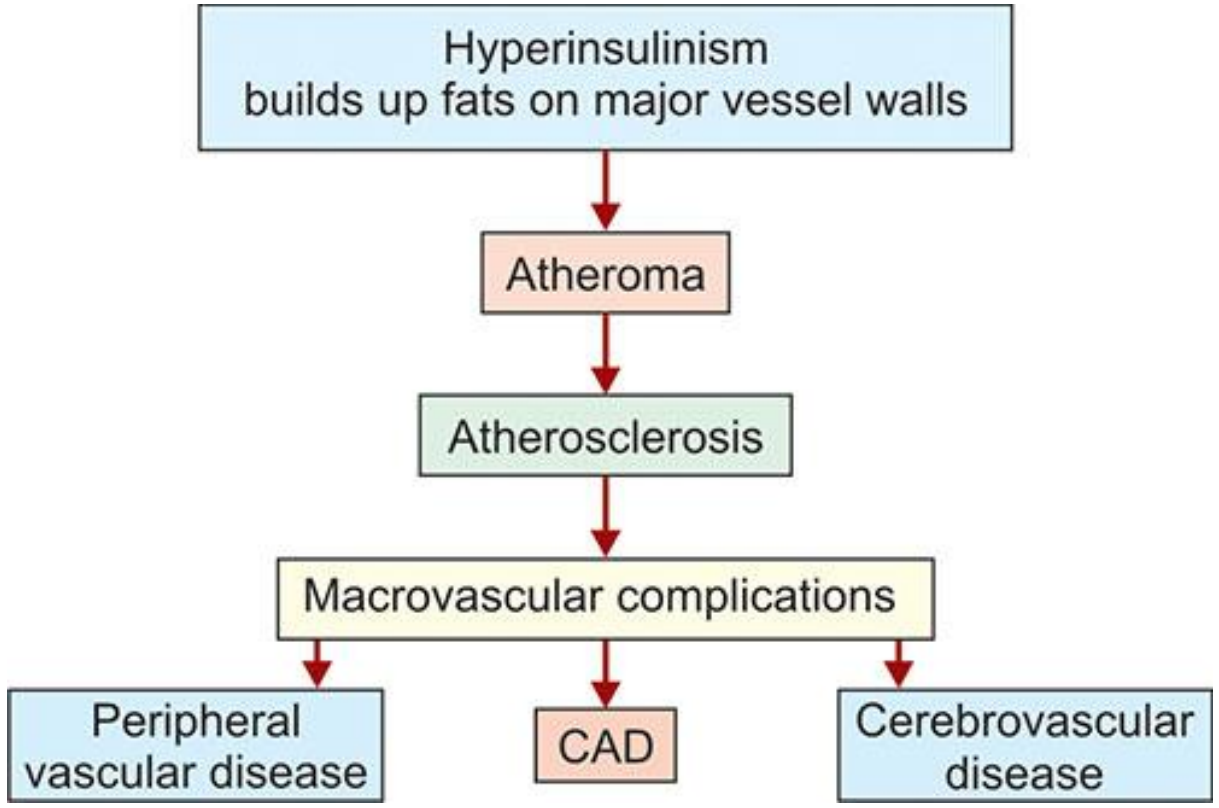
Long-term management

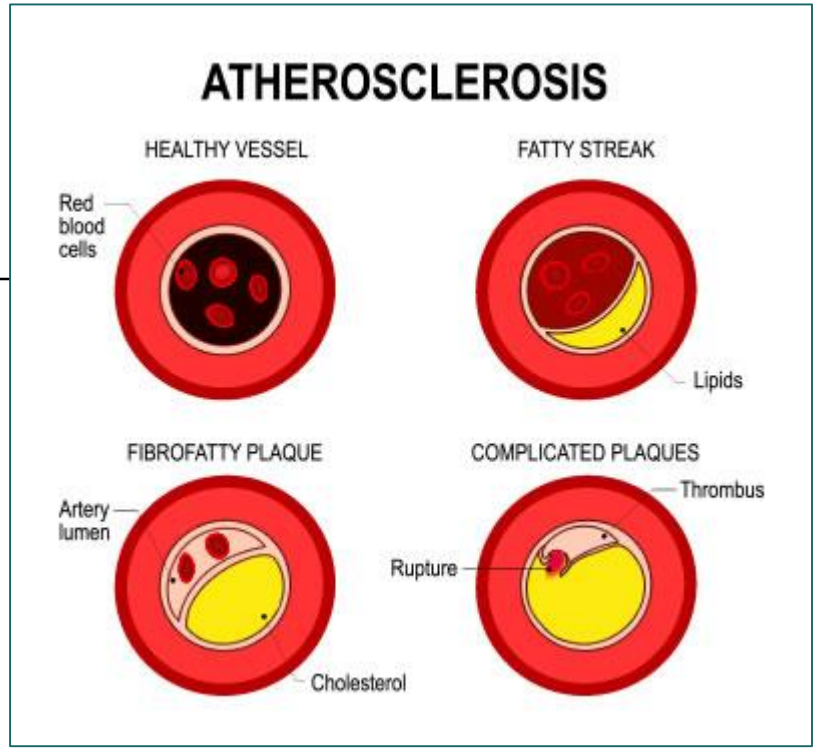
- Special shoes and insoles should be fitted to accommodate deformity and prevent ulceration (major hazard of the Charcot foot).

Macrovascular complications

- Diseases of the large and medium-size blood vessels
- Occur with greater frequency and earlier onset in people with diabetes
- More common
- Earlier (10 years)
- More severe
- Equal for both sexes
- Predominates in T2DM
- It is the leading cause of morbidity and mortality for people with DM.

Macrovascular Changes

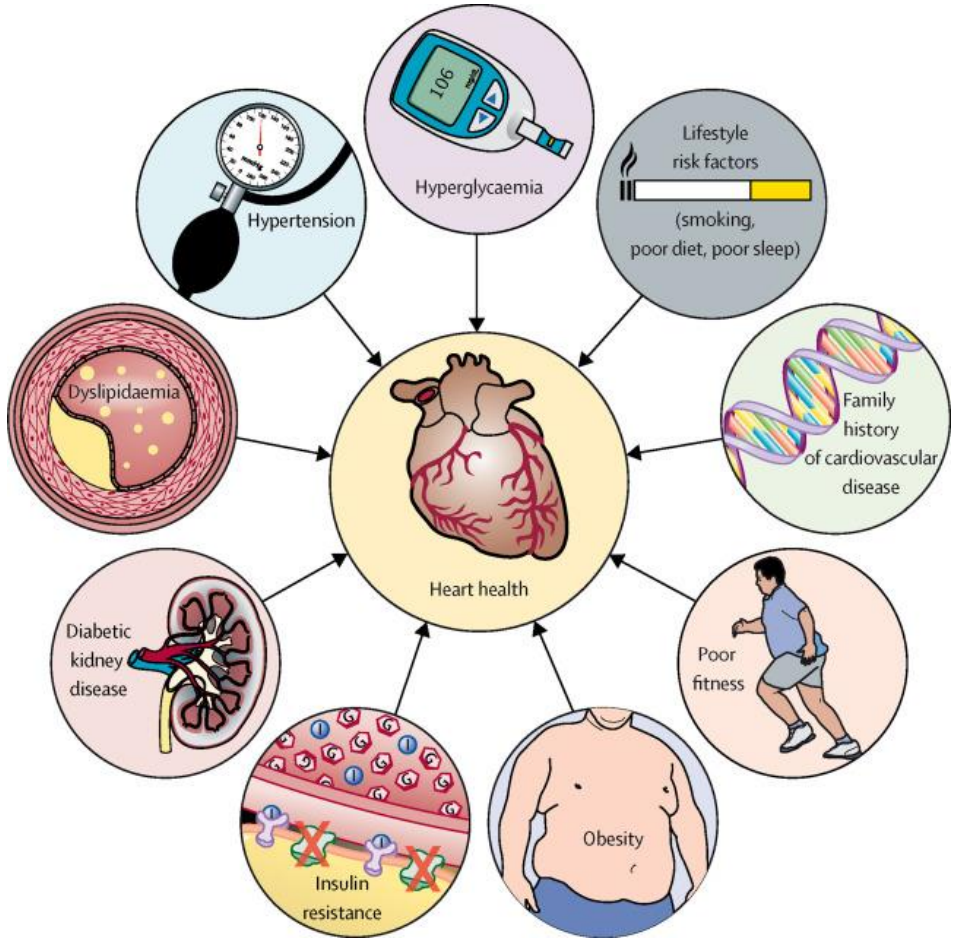




- Atherosclerotic changes
  - Blood vessels thicken, sclerose & become thickened by plaque→ adheres to vessel wall
  - Eventual blockage of blood vessel
  - Changes occur at an earlier age and more often in the diabetic

Macroangiopathy-Coronary artery disease (CAD)

- MI- 2x as common in men & 3x as common in women with diabetes
- Diabetic patients have more complications of MI (arrhythmias, cardiogenic shock and others) than nondiabetic ones.
- Ischemic symptoms may be absent
  - May be secondary to autonomic neuropathy
  - Silent MI common in DM



Macroangiopathy-Occlusive Peripheral Arterial Diseases

- Occurs 2-3x more frequently in diabetics
- Signs & symptoms
  - Decreased pulses
  - Intermittent claudication (pain in buttock, thigh or calf when walking)
  - Gangrene & amputation – result from severe form of arterial occlusion

- More common
- Affects younger individuals
- Multi-segmental and bilateral
- More distal
- More medial calcification
- Impaired collateral formation
- Faster progress with higher risk of amputation

Reduction of risk factors for Macroangiopathies

- Medical nutrition therapy & exercise
  - Reduces obesity, HTN & hyperlipidemia
  - Obesity increases insulin resistance
  - BP control – meds and lifestyle changes
  - ↓triglyceride concentrations
  - ↓complications

- **No smoking!!!**

Diabetes-related skin conditions

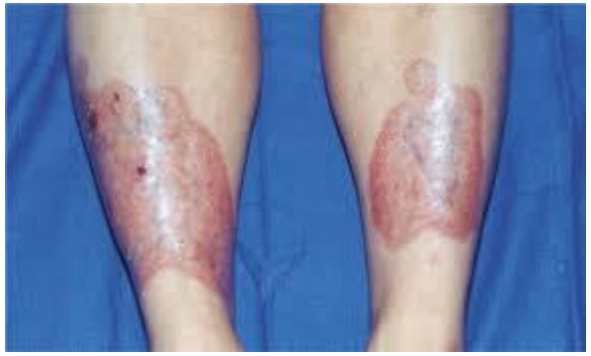
- Diabetic dermopathy;
- Acanthozis nigricans;
- Necrobiosis lipoidica diabeticorum;
- Diabetic blisters (bullosis diabeticorum);
- Eruptive xanthomatosis;
- Digital sclerosis.

Diabetic dermopathy

- Diabetes can cause changes in the small blood vessels, that can cause diabetic dermopathy.
- Dermopathy often looks like light brown, scaly patches. These patches may be oval or circular. Some people mistake them for age spots. This disorder most often occurs on the front of both legs. But the legs may not be affected to the same degree. The patches do not hurt, open up, or itch.
- Dermopathy is harmless and doesn't need to be treated.

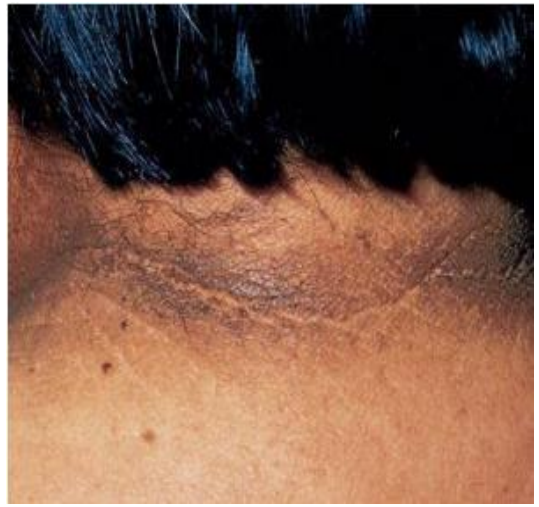
Necrobiosis lipoidica diabeticorum (NLD)

- NLD is a rare condition. Adult women are the most likely to get it.
- More in T1DM;
- NLD causes spots similar to diabetic dermopathy, but they are fewer, larger, and deeper.
- NLD often starts as a dull, red, raised area. After a while, it looks like a shiny scar with a violet border. The blood vessels under the skin may become easier to see.
- Sometimes NLD is itchy and painful. Sometimes the spots crack open.



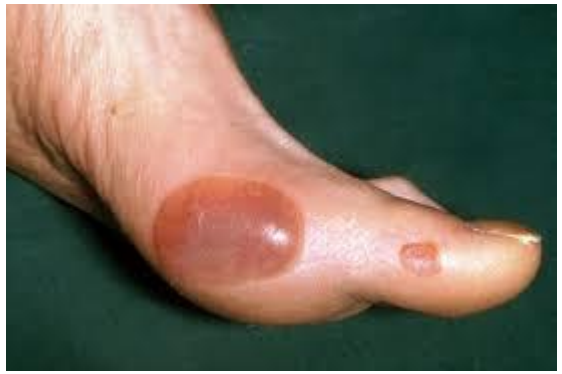
Acanthosis nigricans

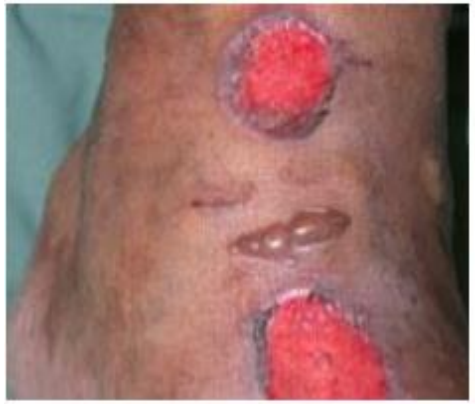
- Marker of insulin resistance;
- Tan or brown raised areas appear on the sides of the neck, armpits and groin. Sometimes they also occur on the hands, elbows and knees.
- Acanthosis nigricans usually strikes people who are very overweight.
- The best treatment is to lose weight. Some creams can help the spots look better.



Diabetic blisters

- Rarely, people with diabetes erupt in blisters.
- Diabetic blisters can occur on the backs of fingers, hands, toes, feet and sometimes on legs or forearms.
- These sores look like burn blisters and often occur in people who have diabetic neuropathy. They are sometimes large, but they are painless and have no redness around them.
- They heal by themselves, usually without scars, in about three weeks.
- The only treatment is to bring blood sugar levels under control.





Acute DM complications

Diabetic ketoacidosis (DKA)

- DKA is the most serious complication of DM, representing the expression of absolute or relative insulin deficiency and the rapid and marked decrease in glucose utilization by body tissues.
- It usually occurs in patients with T1DM which has a serious, often unstable course.
- In 25% of patients with T1DM at the time of diagnosis of diabetes.
- In about 15% of cases it occurs in patients treated with diet and ADO.

Diabetic ketoacidosis (2)

DKA is an acute metabolic complication of diabetes and necessarily includes the triad:

- **hyperglycaemia**> 13.9 mmol / l (250 mg/dl) (often much higher),
- **ketosis** (increase in the production and concentration of ketone bodies in the blood > 5 mmol / l),
- **metabolic acidosis** (decreased pH and serum bicarbonate).

Diabetic ketoacidosis - precipitating cause

Infection – most common– 45%

New onset of diabetes

Drugs including glucocorticoids, excess diuretics, atypical antipsychotics

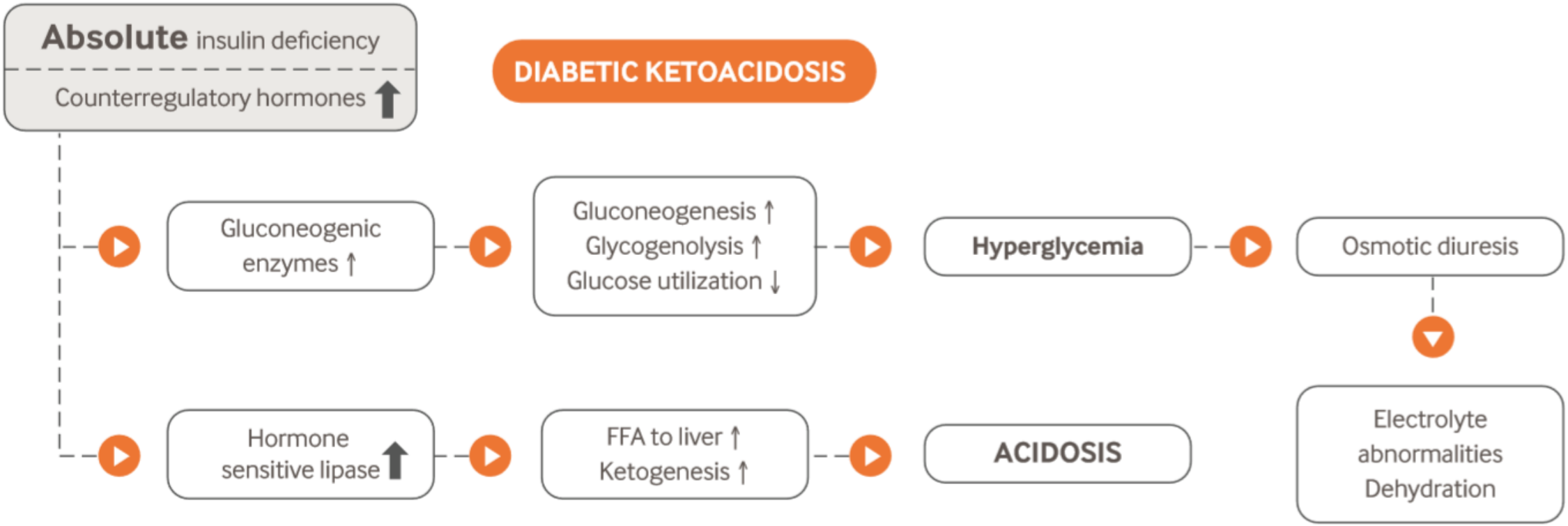
Inadequate insulin therapy – 20%

- Insulin omission –
  - eating disorders,
  - psychological distress,
  - fear of hypoglycemia,
  - fear of weight gain

Other metabolic stressors - pregnancy, decreased caloric intake, heavy alcohol use, and chronic liver disease

SGLT2 inhibitors have been identified as causal agents in several reported cases of euglycemic diabetic ketoacidosis

Pathogenesis



Diabetic ketoacidosis – clinical manifestations

Hyperglycemia

- Polyuria,
- Polydipsia
- Visual disturbance

Dehydration

- Tachycardia,
- severely volume depleted with orthostatic hypotension

Acidosis

- abdominal pain
- tachypnea,
- Kussmaul respirations,
- fruity odor to the breath

Electrolyte abnormalities

DKA– clinical manifestations (2)

- The symptoms of poorly controlled diabetes may be present for several days.
- History of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status change.
- Physical findings may include poor skin turgor, Kussmaul respirations (in DKA), tachycardia, and hypotension.
- Infection is a common precipitating factor for both DKA, patients can be normothermic or even hypothermic primarily because of peripheral vasodilation.

DKA - Diagnosis

Parameters	*Mild DKA*	*Moderate DKA*	*Severe DKA*
Sr. Glucose (mg/dL)	> 250	> 250	> 250
Arterial pH	7.25–7.30	7.00–7.24	< 7.00
NaHCO3 (mEq/L)	15–18	10– < 15	< 10
Urine ketones	Positive	Positive	Positive
Serum Ketones	Positive	Positive	Positive
Sr Osmolality (mOsmol/kg)	Variable	Variable	Variable
Anion gap	> 10	> 12	> 12
Mental status	Alert	Alert/drowsy	Stupor/coma

(DKA: Diabetic ketoacidosis).
Source: Adapted from Kitabchi AE, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2006;29.

Hyperosmolar hyperglycemic state (HHS)

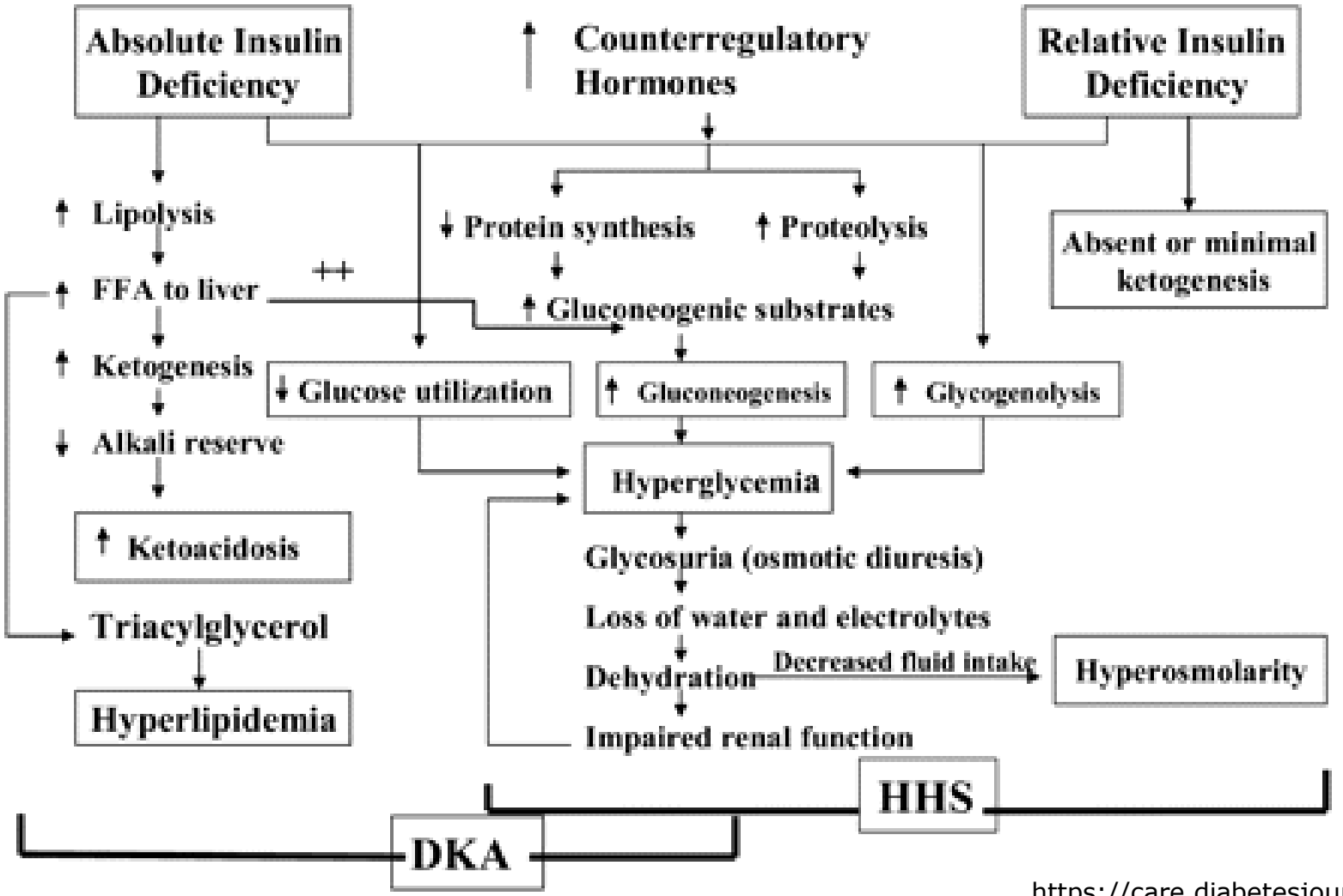
HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.

- 10 times rarer than DKA, more common in women.
- HHS is rare, about 10% of diabetics, but with an increased mortality, 5-20%.
- Hyperosmolar coma is a serious complication of diabetes, especially T2DM, which occurs most frequently in elderly patients.

Precipitating cause

- Intercurrent infections in 40–60% of patients, with the most common precipitating infections being pneumonia (40–60%) and urinary tract infection (5–16%);
- Omission of insulin injection;
- Insulin pump failure;
- Consumption of alcohol or drugs;
- Conditions lead to dehydration of the body and worsening of insulin deficiency (burns, trauma, bleeding, vomiting and diarrhea, etc.).

Pathogenesis



https://care.diabetesjournals.org/content/32/7/1335.figures-only

HHS– clinical manifestations

Hyperglycemia

- Polyuria,
- Polydipsia
- Visual disturbance

Dehydration

- tachycardia,
- severely volume depleted with orthostatic hypotension

Hyperosmolarity

- altered level of consciousness
- risk for thrombosis

Electrolyte abnormalities

HHS – Diagnostic criteria

Diagnostic criteria of HHS first reported by Arieff and Carroll and current ADA criteria

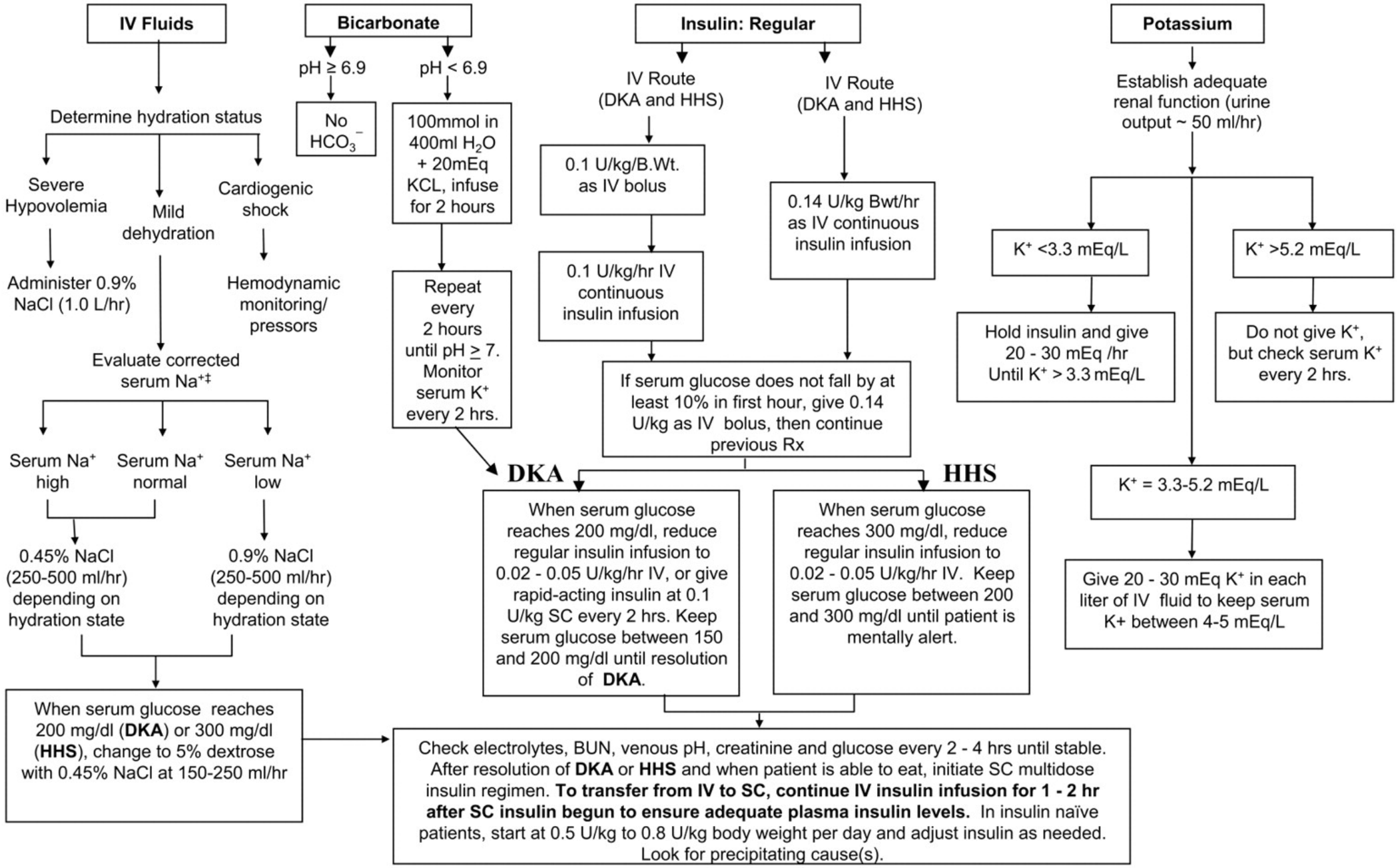
	Arieff and Carroll (56)	ADA (4)
Plasma glucose, mg/dL	>600	>600
Arterial pH	N/A	>7.30
Serum bicarbonate, mEq/L	N/A	>18
Urine or serum ketones by nitroprussiate test (acetoacetate)	0 to 2 pluses	Negative or small
Serum β-hydroxybutyrate, mmol/L	N/A	<3 mmol/L
Total serum osmolality, mOsm/kg*	>350	N/A
Effective serum osmolality, mOsm/L**	N/A	>320
Anion gap, mEq/L	N/A	Variable
Mental status	N/A	Variable; most patients present with stupor, coma

*Total serum osmolality formula = 2(Na) + 18/glucose + BUN/2.

**Effective serum osmolality formula = 2(Na) + 18/glucose.

American Diabetes Association.

Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†



Criteria for resolution

- Blood glucose < 200 mg/dl and two of the following:
- Serum bicarbonate level > 15 mEq/l, a venous pH > 7.3, and a calculated anion gap < 12 mEq/l.
- After, subcutaneous insulin therapy can be started.
- Allow an overlap of 1 - 2 h between the discontinuation of intravenous insulin and the administration of subcutaneous insulin.

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crisis in adult patients with diabetes. Diabetes Care. 2009 July; 32 (7): 1335 - 1343

Lactic acidosis (LA)

- DEFINITION

LA consists of elevation of lactic acid above 5.0 mEq/L with acidosis (pH <7.3) and without ketoacidosis.

It is a rare, but important, adverse event in patients with diabetes.

The usual precipitating factors for LA are conditions of impaired oxygenation, such as hypoxemia, shock, sepsis, carbon monoxide poisoning, and some medications, including phenformin and metformin, particularly when used in patients with renal failure.
Phenformin,a biguanide, increases the risk of life-threatening LA

LA symptoms

- Extreme fatigue
- muscle cramps or pain
- body weakness
- overall feelings of physical discomfort
- abdominal pain or discomfort
- diarrhea
- decrease in appetite
- headache
- rapid heart rate

Essentials of diagnosis

- Severe metabolic acidosis with compensatory hyperventilation.
- Blood pH < 7.30.
- Serum bicarbonate less than 15 mEq/L.
- Anion gap greater than 15 mEq/L.
- Absent serum ketones.
- Serum lactate greater than 5 mmol/L.

Hypoglycemia

Hypoglycemia: All episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm.

Alert value: Plasma glucose < 3.9 mmol/L with no symptoms

(Note!: 3.5 mmol/L is the lower limit of the alert range)

Epidemiology

- Hypoglycemia is common in type 1 diabetes, especially in patients receiving intensive therapy, in whom the risk of severe hypoglycemia is increased more than threefold.
- Incidence :
  - 3.14% in the intensive treatment group
  - 1.03% in the standard group

Risk factors

Medical-related factors

- Strict glycemic control
- Previous history of severe hypoglycemia
- Long duration of type 1 diabetes
- Duration of insulin therapy in type 2 diabetes
- Lipohypertrophy at injection sites
- Impaired awareness of hypoglycemia
- Severe hepatic dysfunction
- Impaired renal function (including those patients requiring renal replacement therapy)
- Sepsis
- Inadequate treatment of previous hypoglycemia
- Terminal illness
- Cognitive dysfunction/dementia

Lifestyle-related factors

- Increased exercise (relative to usual)
- Irregular lifestyle
- Alcohol
- Increasing age
- Early pregnancy
- Breast feeding
- No or inadequate blood glucose monitoring

Reduced carbohydrate intake/absorption

- Food malabsorption, e.g., gastroenteritis, coeliac disease
- Bariatric surgery involving bowel resection

Other factors:

- Hypoglycemia unawareness
- Number of years since diabetes diagnosis
- Time since insulin initiated

Symptoms and signs of hypoglicemia

Autonomic symptoms	**Neuroglycopenic symptoms**
Sweating Tingling Trembling Feeling shaky Feeling hungry Palpitations Anxiety	Blurred vision Difficulty speaking Feeling faint Difficulty thinking Confusion Dizziness Feeling drowsy Irritability
Autonomic signs	**Neuroglycopenic signs**
Tachycardia Increased systolic blood pressure Pallor Diaphoresis Mydriasis	Transient Focal Neurological Deficit occasionally

Classification

Classification	Blood Glucose Level (mg/dL)	Typical Signs and Symptoms
Mild hypoglycemia	~50-70	• Neurogenic: palpitations, tremor, hunger, sweating, anxiety, paresthesia
Moderate hypoglycemia	~50-70	• Neuroglycopenic: behavioral changes, emotional lability, difficulty thinking, confusion
Severe hypoglycemia	<50*	• Severe confusion, unconsciousness, seizure, coma, death • Requires help from another individual

*Severe hypoglycemia symptoms should be treated regardless of blood glucose level.

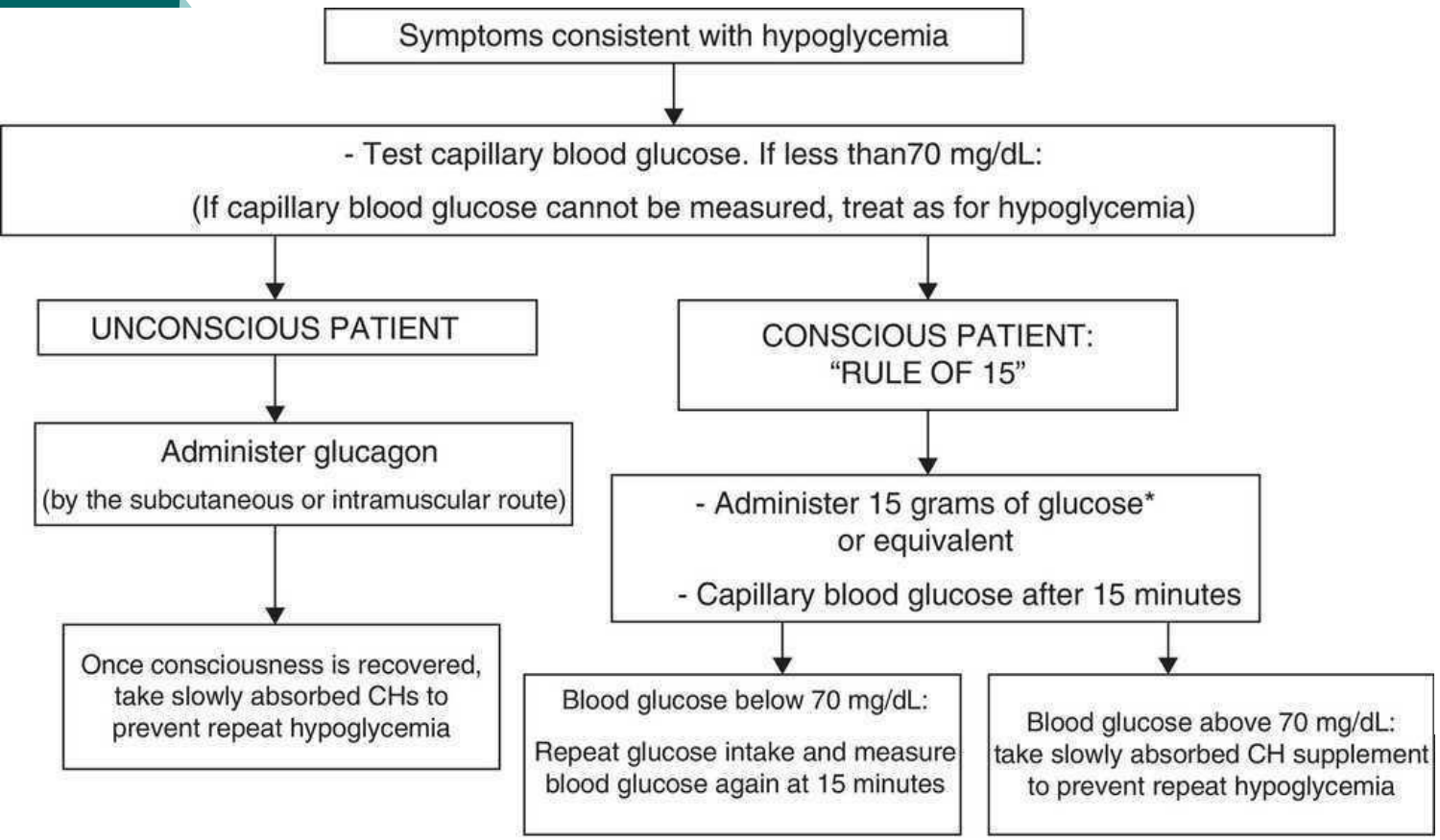
ADA Workgroup on Hypoglycemia Diabetes Care 2005, 28, 1245-1249

Consequences of Hypoglycemia

- Cognitive, psychological changes (eg, confusion, irritability)
- Accidents
- Falls
- Recurrent hypoglycemia and hypoglycemia unawareness
- Refractory diabetes
- Dementia (elderly)
- CV events
    - Cardiac autonomic neuropathy
    - Cardiac ischemia
    - Angina
    - Fatal arrhythmia

Handelsman YH, et al. Endocr Pract. 2015;21(suppl 1):1-87.

Treatment of Hypoglycaemia



*This option should be preferred to all others because of its faster effect on blood glucose and symptom correction

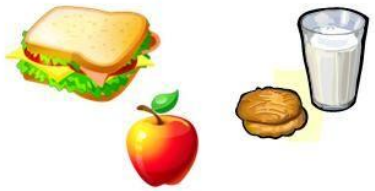
Treatment of Hypoglycaemia

Take quickly absorbed carbohydrates such as:

- half a glass of juice (a little carton or small bottle of fruit juice)
- 5-7 jellybeans
- 3 teaspoons of honey or sugar
- glucose that contains 15 grams of carbohydrate (see package labels)

THEN follow up with more slowly absorbed carbohydrate such as:

- a sandwich
- biscuits
- a glass of milk
- a piece of fruit



Re-test the blood glucose level after 15 minutes

Endocrinol Nutr. 2013;60:517.e1–517.e18

"THANK YOU FOR YOUR ATTENTION"