Chronic Complications of Diabetes Mellitus

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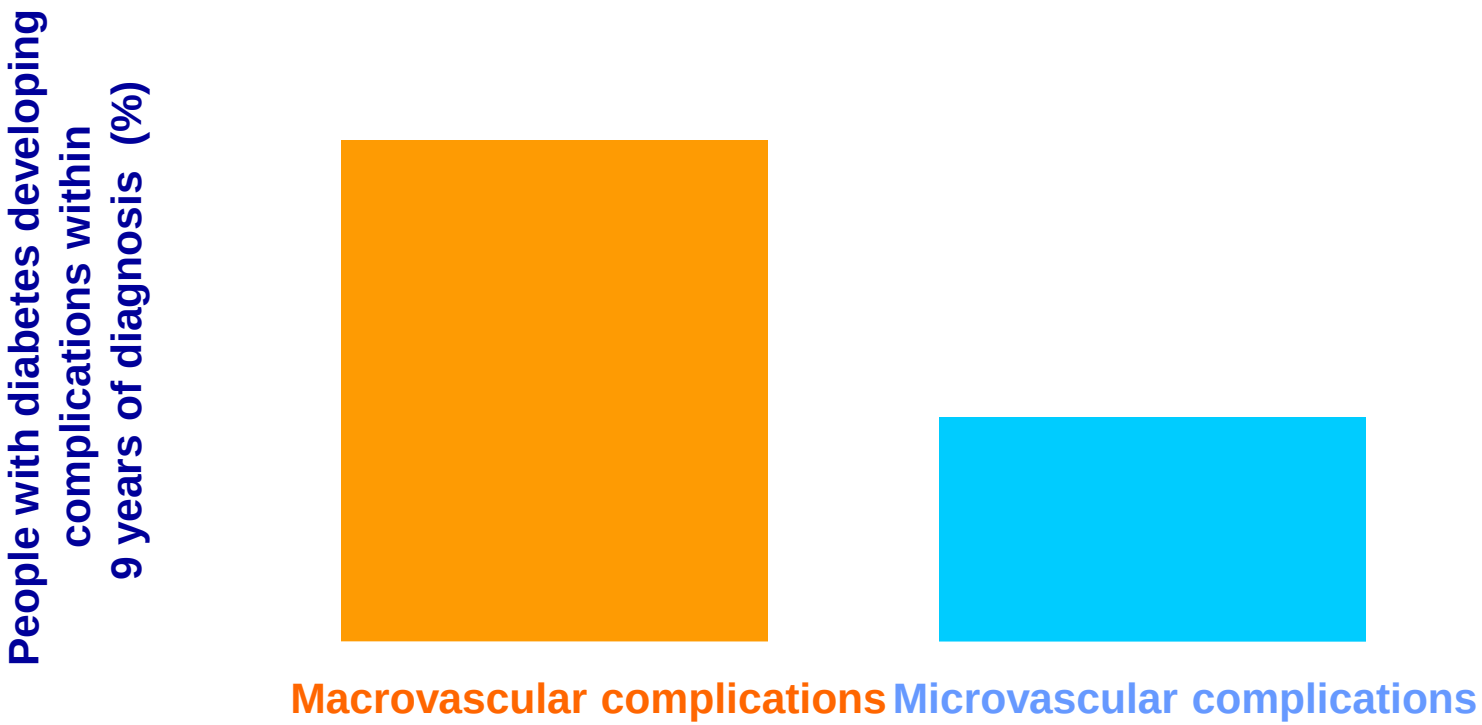
Chronic complications of Diabetes

- Macro Vascular
  - Coronary Heart Dis.
  - Stroke
  - Peripheral Arterial Dis.
- Micro and Macro
  - Diabetic Foot
- Micro Vascular
  - Neuropathy
  - Retinopathy
  - Nephropathy

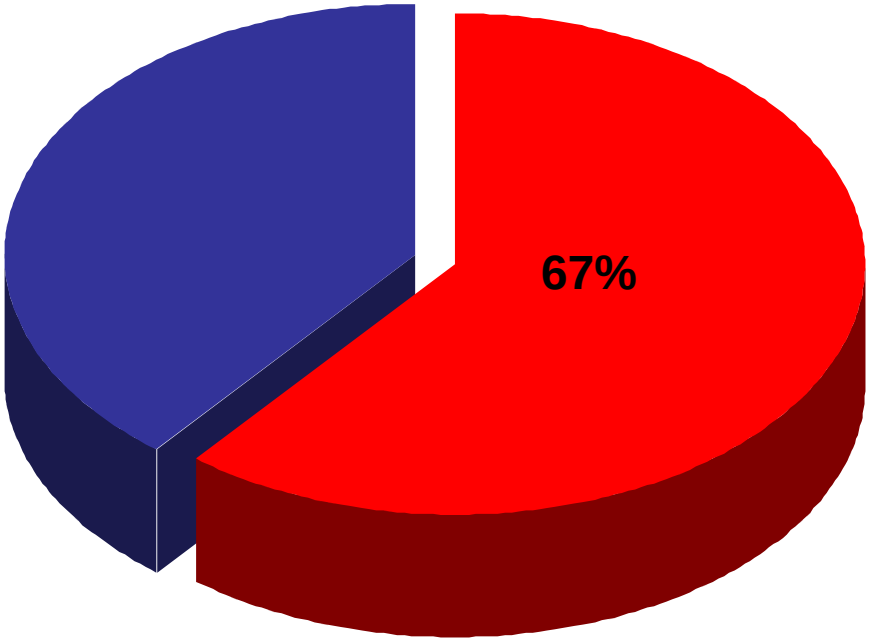
Macro vascular Complications

In People with Diabetes Macrovascular Complications Are Two Times Greater than Microvascular Complications



Adapted from Turner R et al *Ann Intern Med* 1996;124:136-145.

2/3 of People with Diabetes Die of Macrovascular Diseases



Adapted from Alexander CM, Antonello S *Pract Diabet* 2002;21:21-28.

Macro vascular complications

- **PAD**
- **CHD**
- **Stroke**

Macro vascular complications

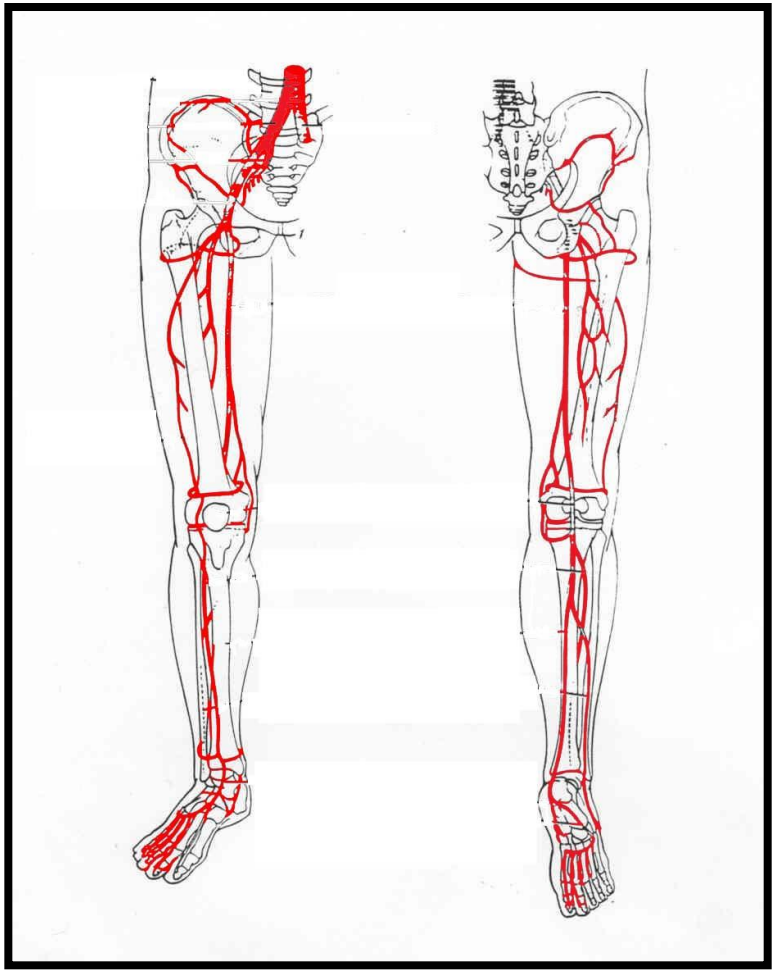
- **PAD**
- **CHD**
- **Stroke**

Does PAD differ in diabetic from nondiabetic Subjects ?

- **PAD is more common in Diabetes: 30% of diabetic subjects older than 50 yrs have PAD.**
- **Occurs at a younger age**
- **Loss of female protection: A roughly equal male-to-female ratio**

Different anatomical distribution:

Predilection for the tibial and peroneal arteries between the knee and the foot.

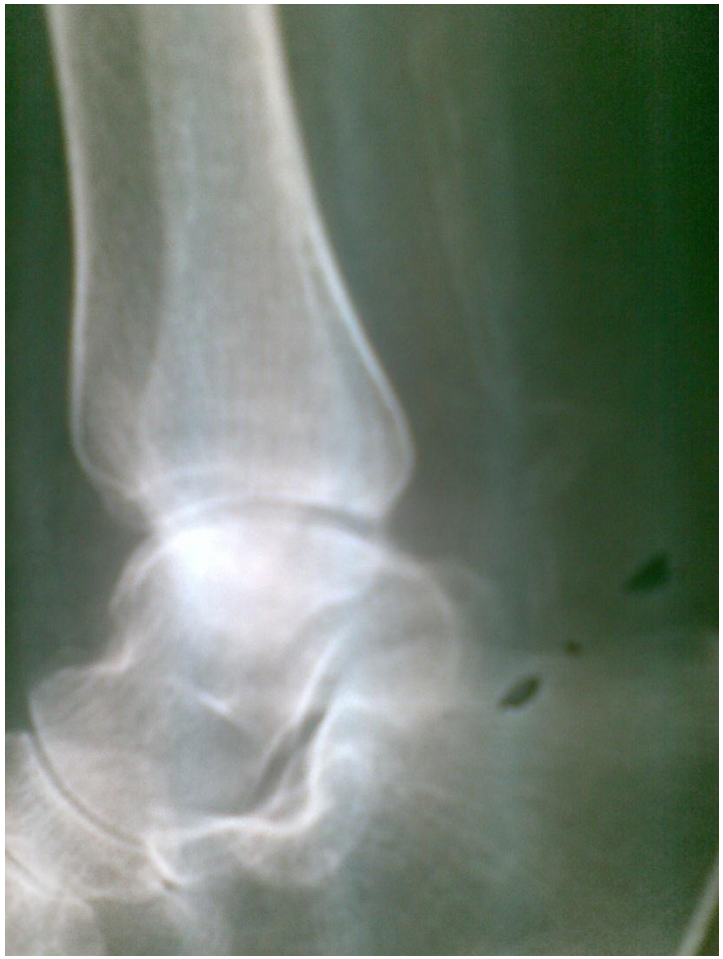


- **Diminished ability to establish collateral circulation, especially around the knee.**

- **Increased risk of progression from intermittent claudication to critical limb ischemia and gangrene.**

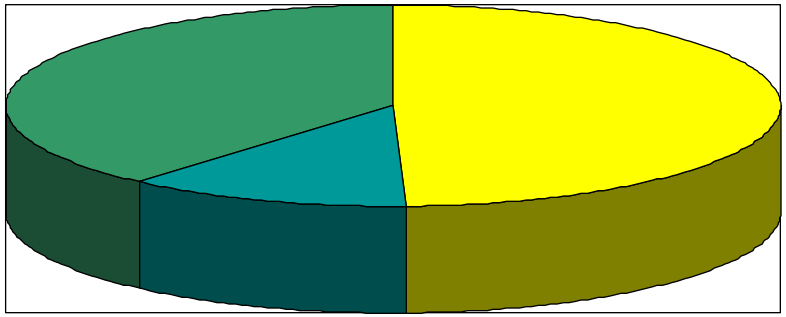
Medial calcinosis

- **Calcification involving the intimal plaque and media (medial calcinosis) frequently involves diabetic arteries at all levels.**



Presentation of PAD

- One-half are asymptomatic or have atypical symptoms,
- One-third have claudication,
- The remainder have more severe forms of the disease



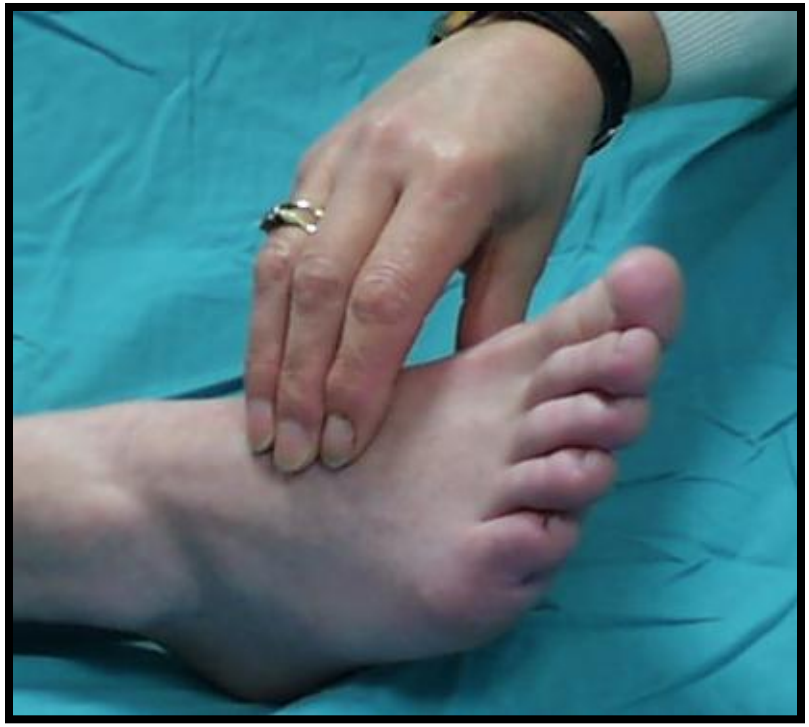
Intermittent Claudication

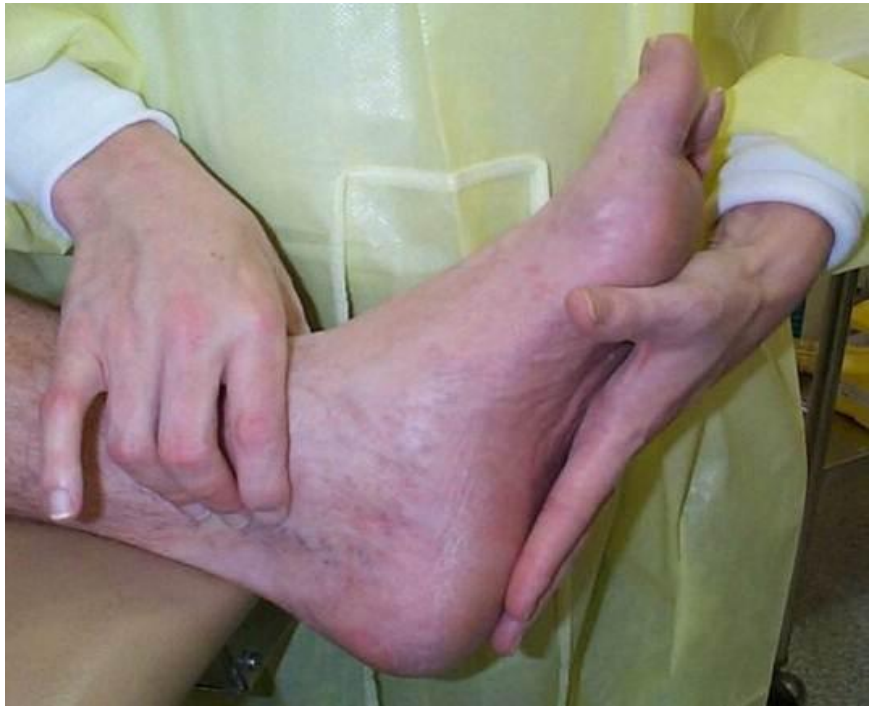
- **Intermittent claudication, defined as pain, cramping, or aching in the calves, thighs, or buttocks that appears reproducibly with walking exercise and is relieved by rest.**

- **The history of PAD is characteristic and consistently reproducible, and may alone be diagnostic for many individuals.**

Signs of PAD

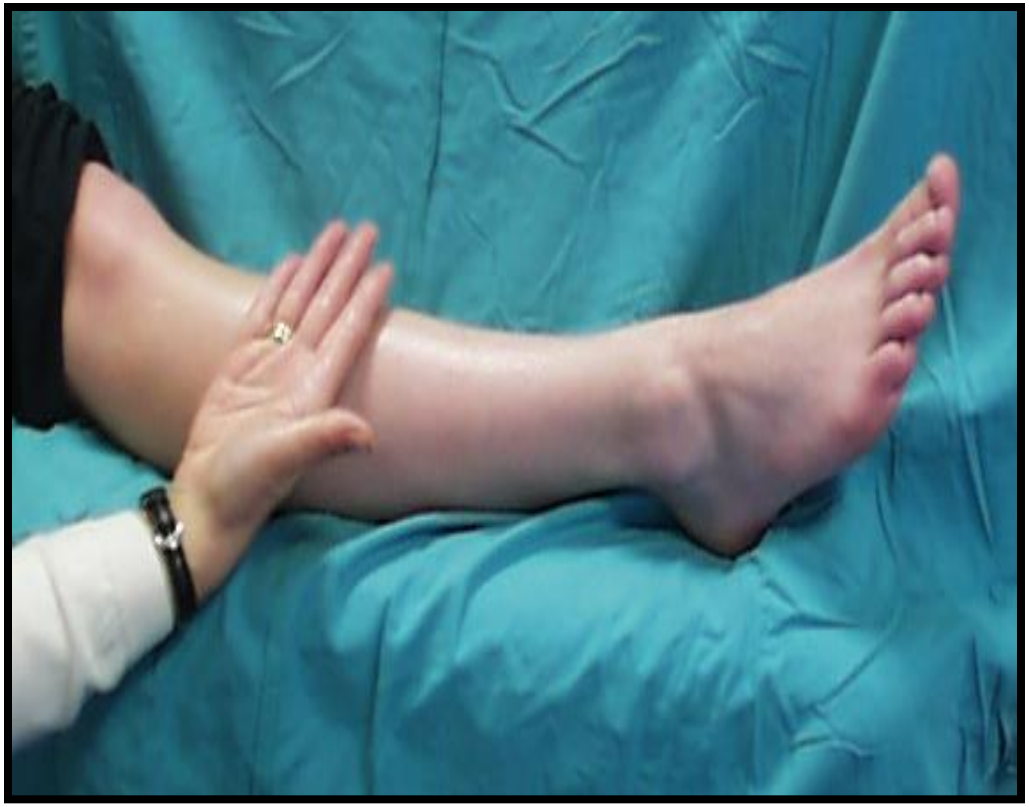
Unlike other forms of atherosclerotic disease, PAD is easily diagnosed in the outpatient clinic noninvasively.



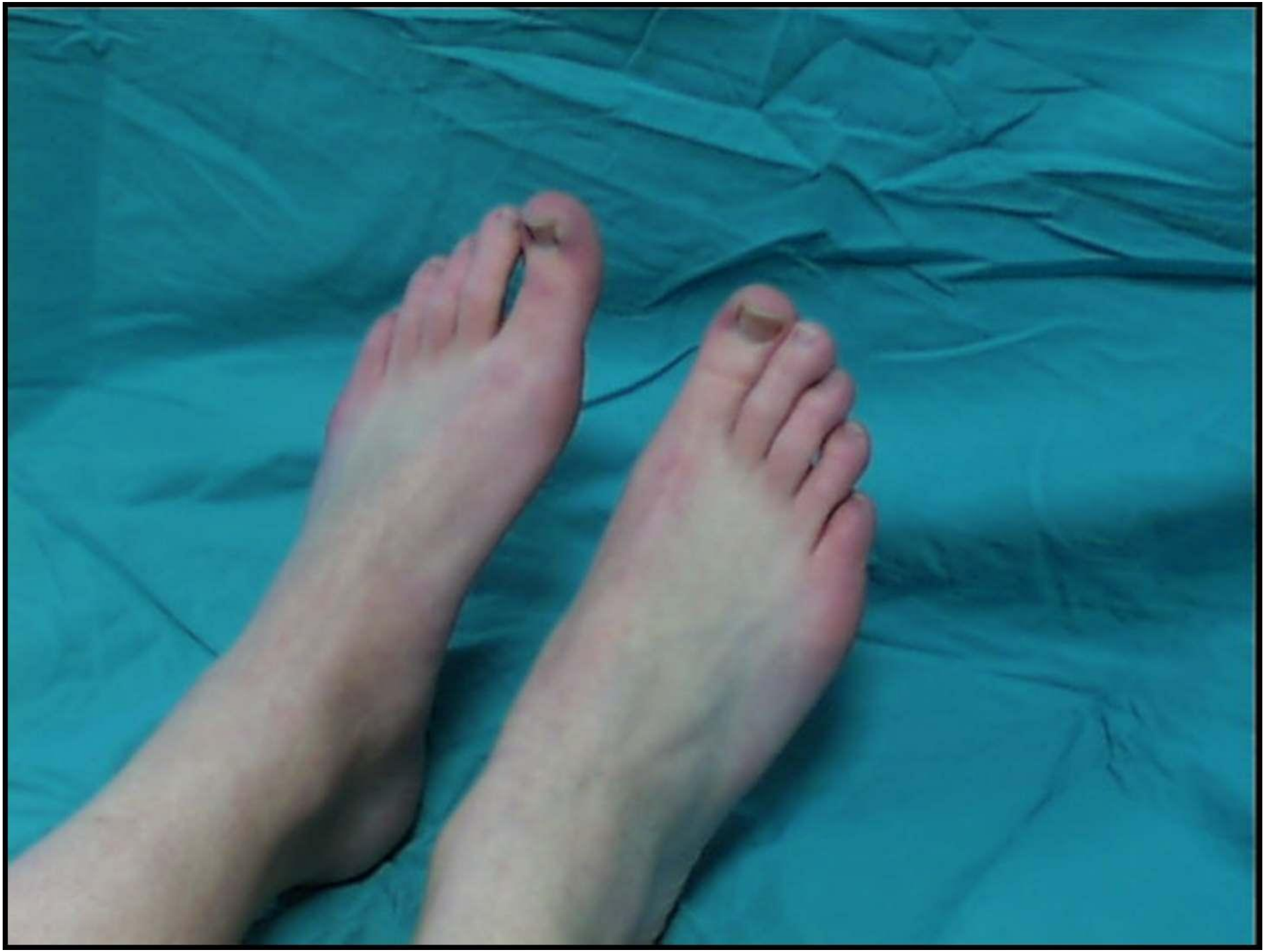


- **The dorsalis pedis pulse is reported to be absent in 8.1% of healthy individuals, and the posterior tibial pulse is absent in 2.0%.**

- **Nevertheless, the absence of both pedal pulses, when assessed by a person experienced in this technique, strongly suggests the presence of vascular disease**



- **Temperature differences can be reliably assessed only when limbs have been exposed to a constant room temperature for 10-20 minutes.**

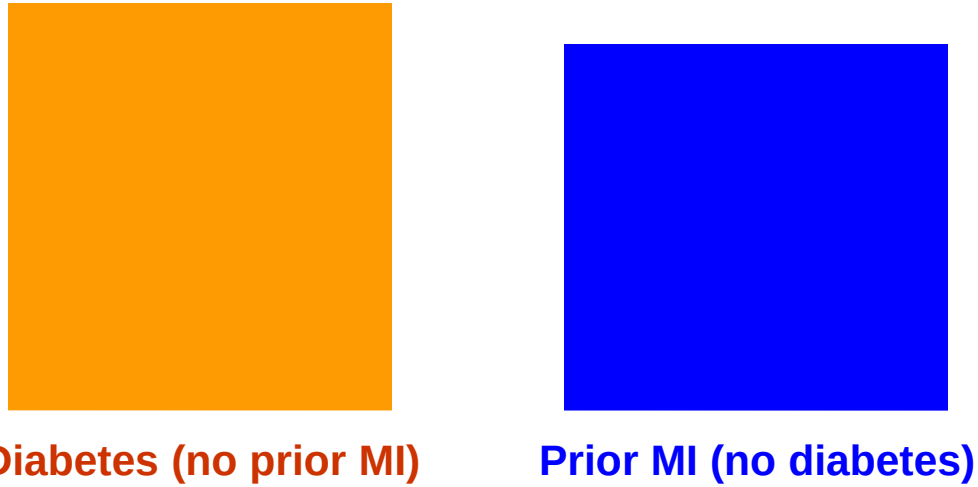


- **Absence of hair growth, thin and shiny skin, dystrophic toenails, and cool, dry, fissured skin are signs of vascular insufficiency and should be noted.**

Macro vascular complications

- PAD
- **CHD**
- Stroke

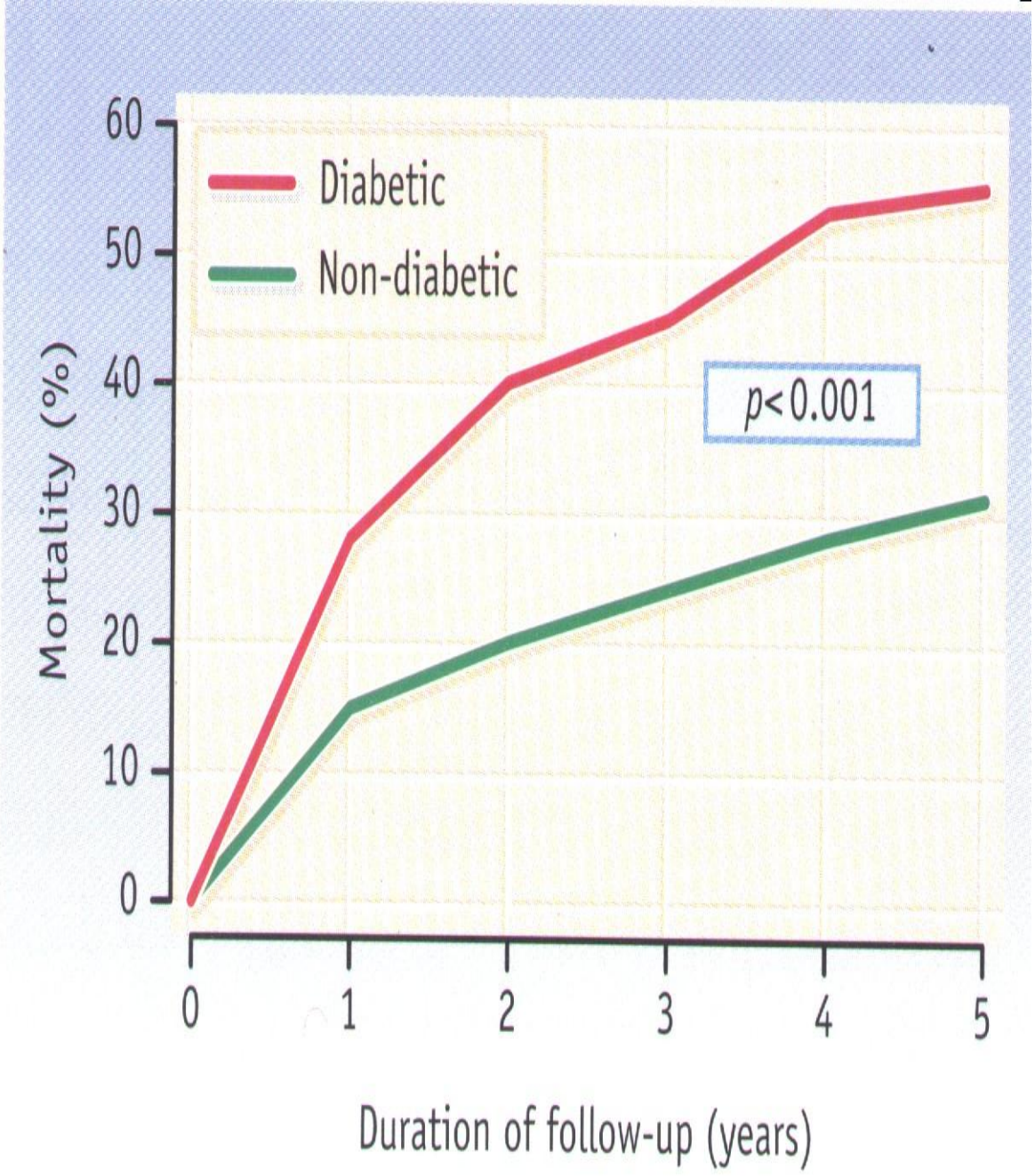
People with Diabetes Have MI Risk Levels Comparable to People with Prior MI



- **Patients with diabetes without previous MI have as high of a risk of MI as nondiabetic patients with previous MI.**
- **These data provide a rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in nondiabetic patients with prior MI.**

Poor prognosis following a CV event

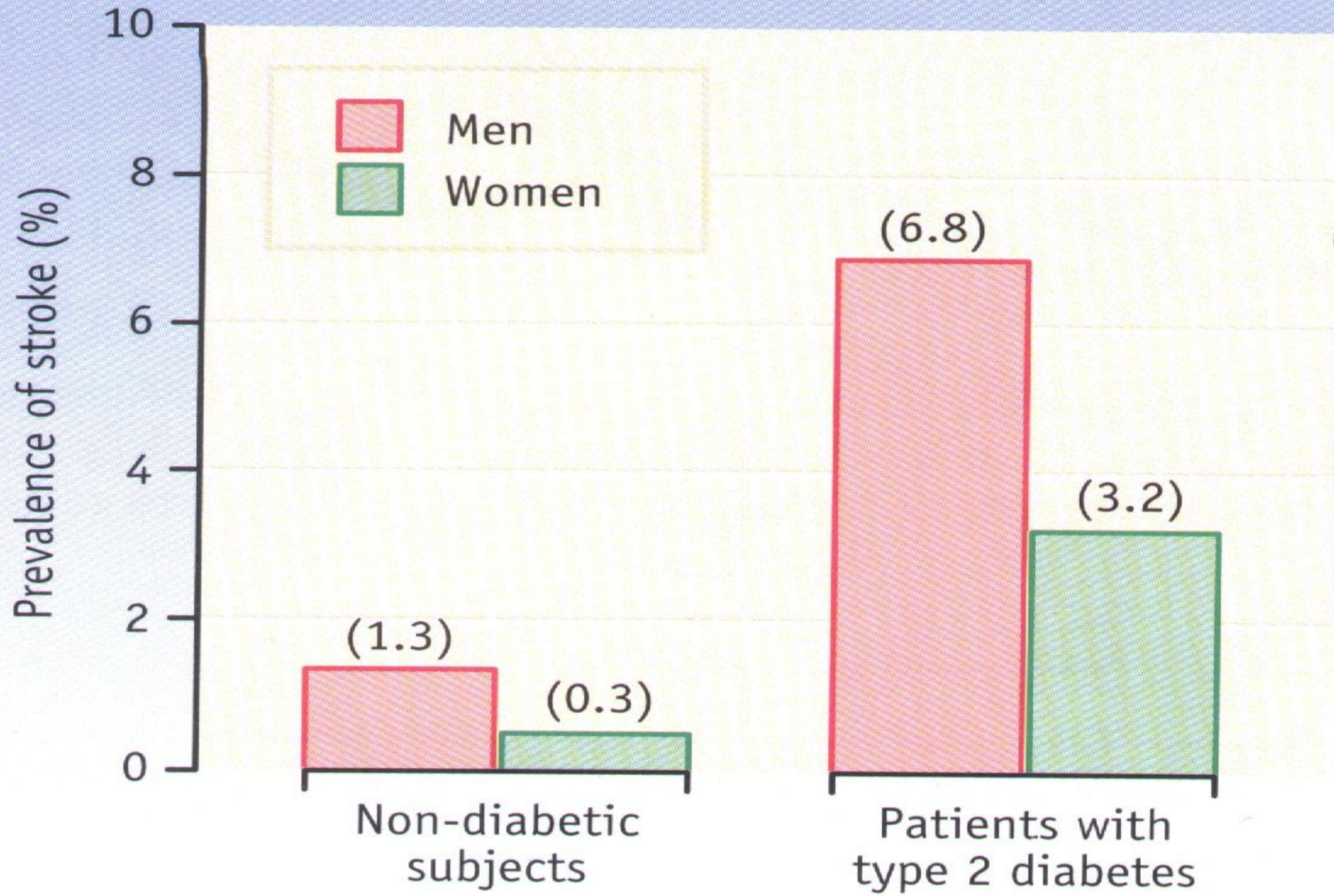
People with diabetes are up to two times more likely to die than those without diabetes after an MI.



Mortality from myocardial infarction is increased in diabetes largely due to increased risk of heart failure in diabetes.

Macro vascular complications

- PAD
- CHD
- **Stroke**



Increased prevalence of stoke in type 2 diabetes in comparison to the control.

Chronic complications of Diabetes

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  - Diabetic Foot
- Micro Vascular
  - Neuropathy
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Micro Vascular complications

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Micro vascular complications

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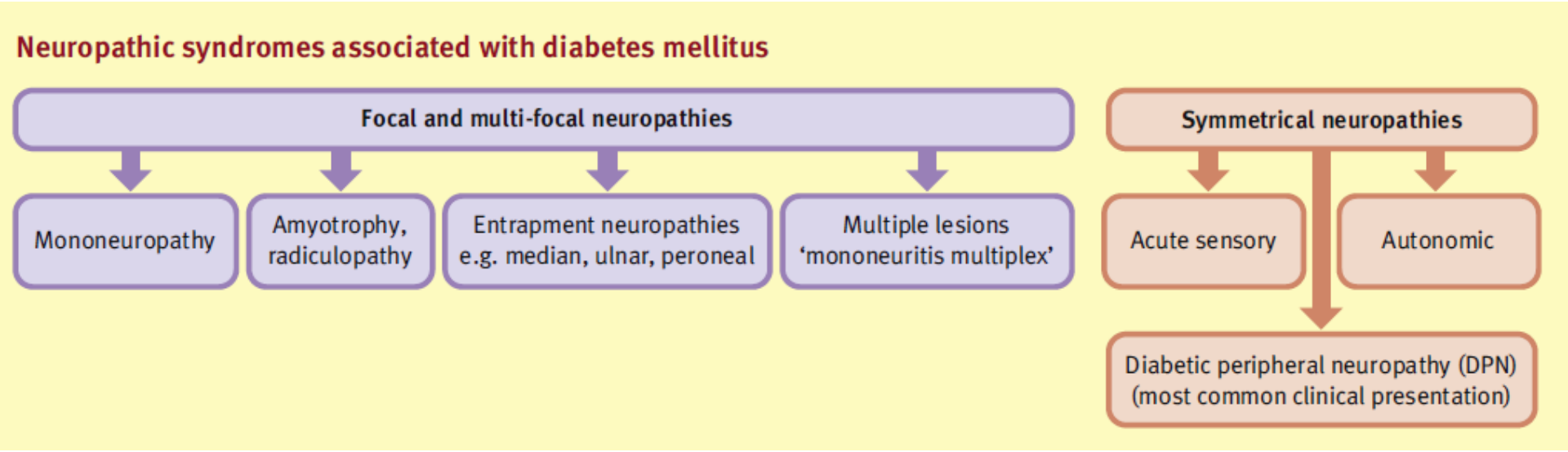
Definition

- The presence of ***symptoms*** and/or ***signs*** of peripheral nerve dysfunction in people with diabetes after ***exclusion*** of other causes.

Classification



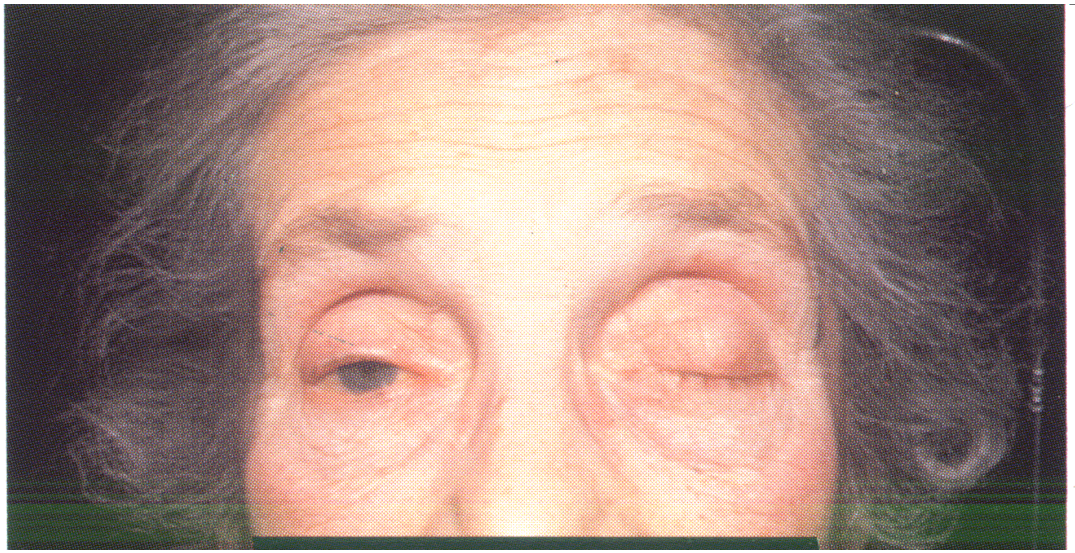
Mononeuropathies

- Affect peroneal, median or ulnar nerves,
- tend to occur at sites of entrapment or external compression.
- Peroneal nerve palsy is characterized by weakness or paralysis of foot and toe extension and foot eversion. Impaired sensation over the dorsum of the foot and the lower anterior aspect of the leg. The ankle reflex is preserved as is foot inversion.

Cranial nerve palsies

- often affect III, VI, IV and rarely VII nerves.
- III nerve palsy is characterized by
- 1. Acute onset
- 2. Painful: severe pain around the eye.
- 3. Intact papillary reactions: pupilloconstrictor fibres located peripherally so they are affected in lesions that produce compression e.g. aneurysm.

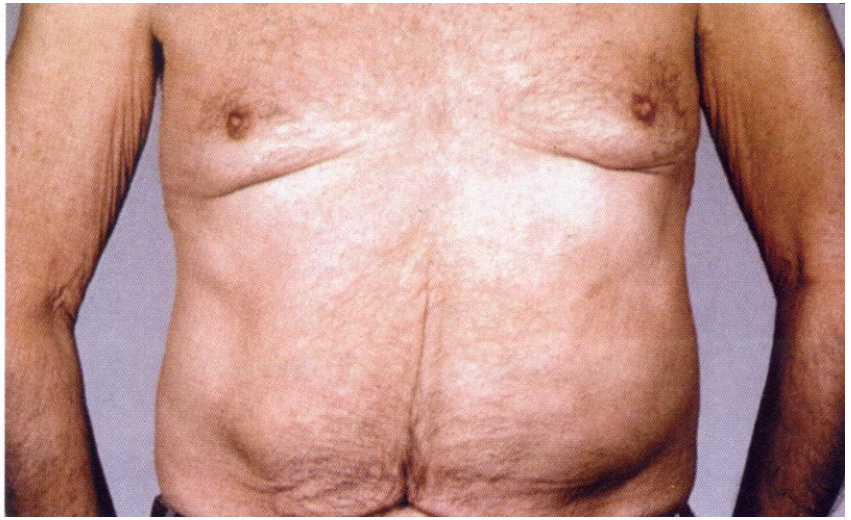
- 3rd nerve palsy : Left ptosis and diplopia.
- Intact pupillary reactions are characteristic features of 3rd nerve palsy in diabetes.



Radiculopathy

- truncal neuropathy may yield sensory manifestations (band like or constricting pain in thoracic root) or
- Motor manifestations (asymmetrical bulge in abdominal wall).

- Bulging of the left lower abdomenal wall due to truncal radiculopathy



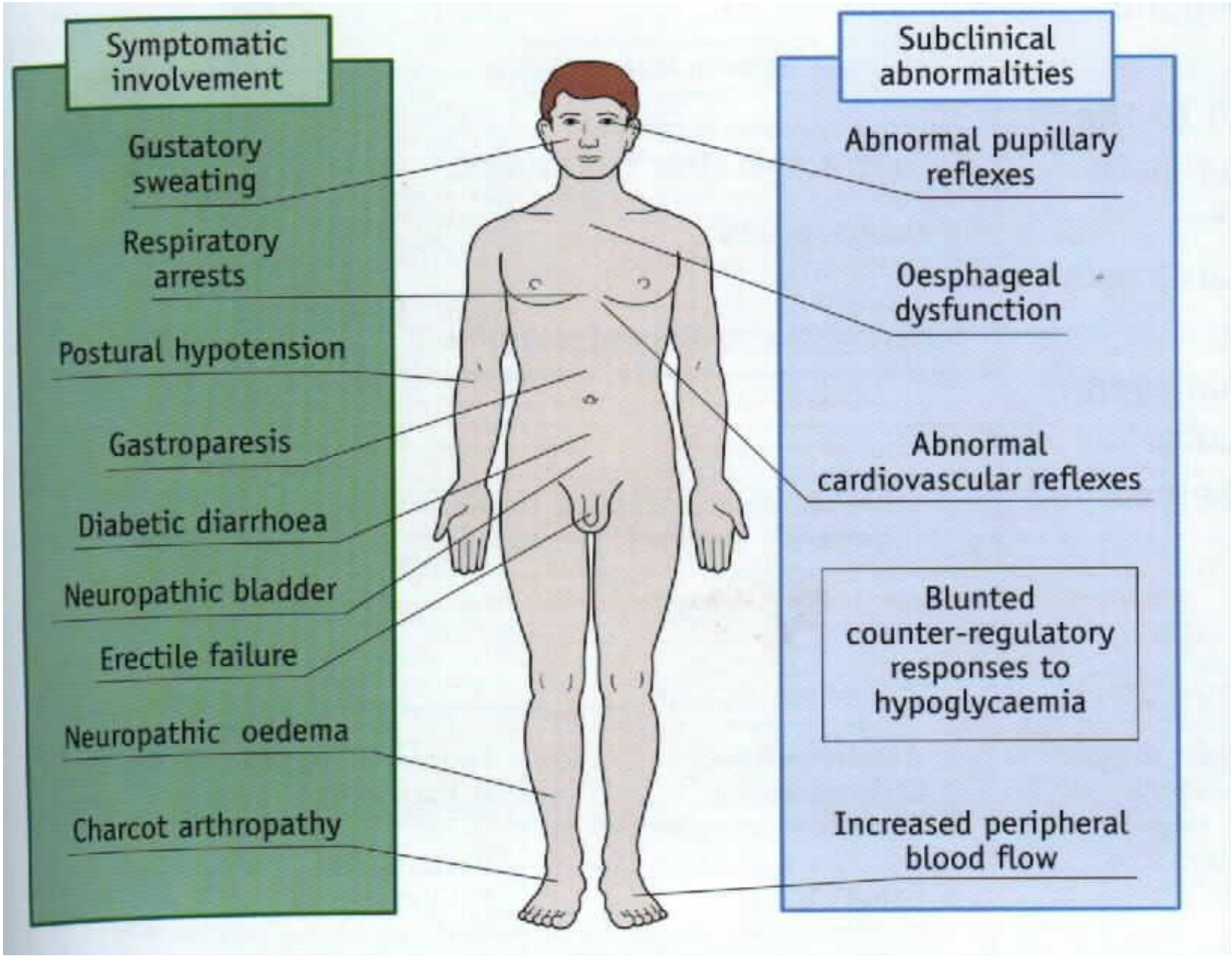
Proximal motor neuropathy (amyotrophy)

- More frequent in male type 2 diabetic
  - Unilateral or asymmetrical bilateral
- Pain, wasting and weakness in proximal muscles of the lower limbs.
- Often associated with polynuropathy and weight loss.
- DD: Internal malignancy, chronic inflammatory demyelinating polyneuropathy.

Entrapment Neuropathies

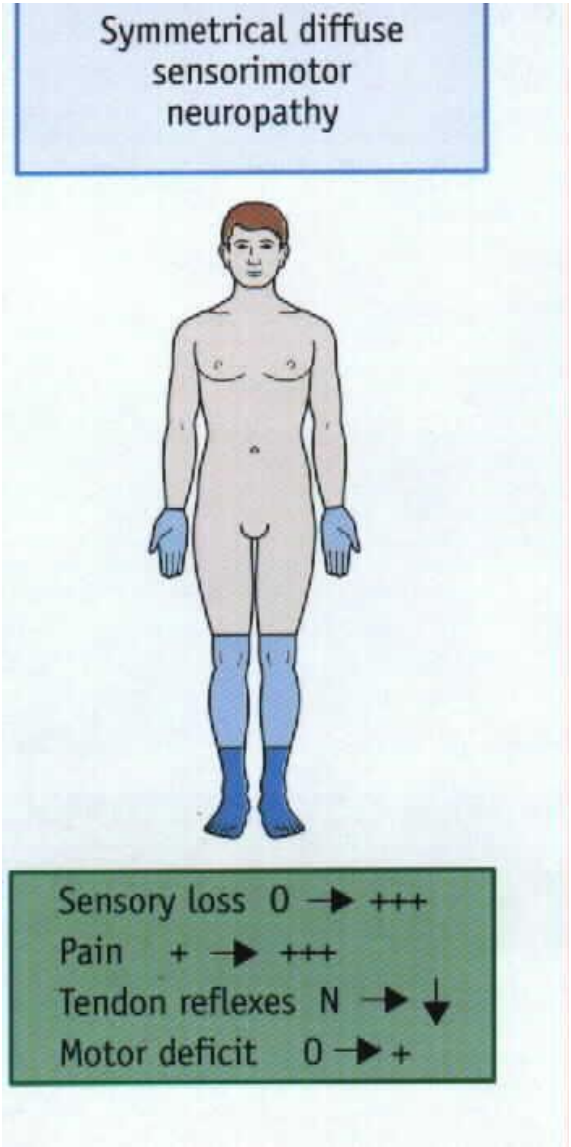
- 1-carpal tunnel syndrome: found in 5.8 % of diabetic patients. It has a less favorable outcome after surgical decompression, as diabetes slows nerve regeneration.
- 2- Ulnar neuropathy at the elbow affect 2.1% of diabetic patients
- 3- Peroneal neuropathy at the fibular head affect 1.4–13% of diabetic patients.
- 4- Lateral cutaneous nerve of the thigh (meralgia paresthetica) affect 0–1.0% of diabetic patients.

Autonomic neuropathy



Peripheral neuropathy

- Affect 25-35% of diabetic patients
- Gradual onset and progressive course.
- Predominant sensory manifestations .



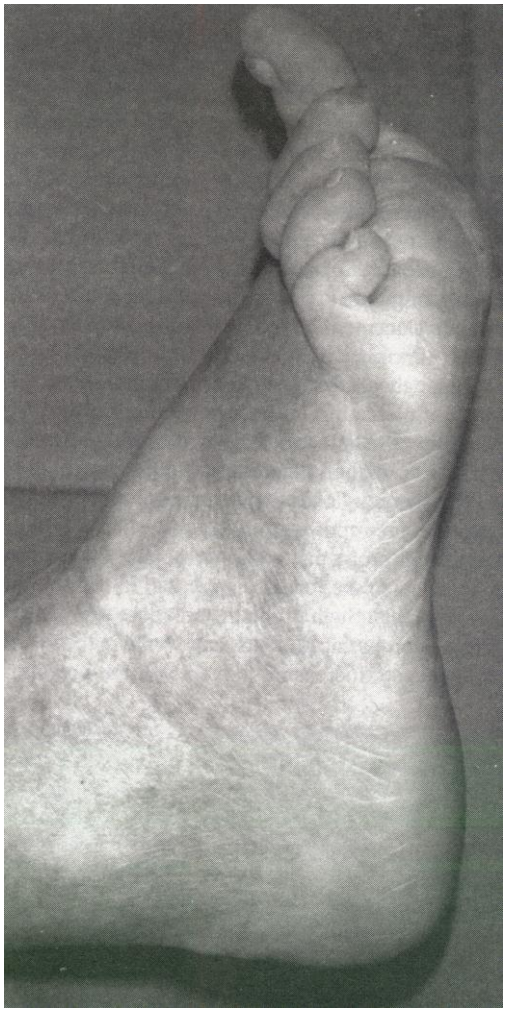
+ 'Positive' symptoms

- Persistent burning or dull pain
- Paroxysmal, 'electric shock' type or stabbing
- Dysaesthesias (painful paraesthesias)
- Evoked pain (hyperalgesia, allodynia)

– 'Negative' symptoms (deficits)

- Numbness ('dead feeling')
- Hypoalgesia, analgesia
- Hypoaesthesia, anaesthesia

- Motor fiber may be affected producing wasting of small muscles of hand and feet.



Signs of sensory impairment

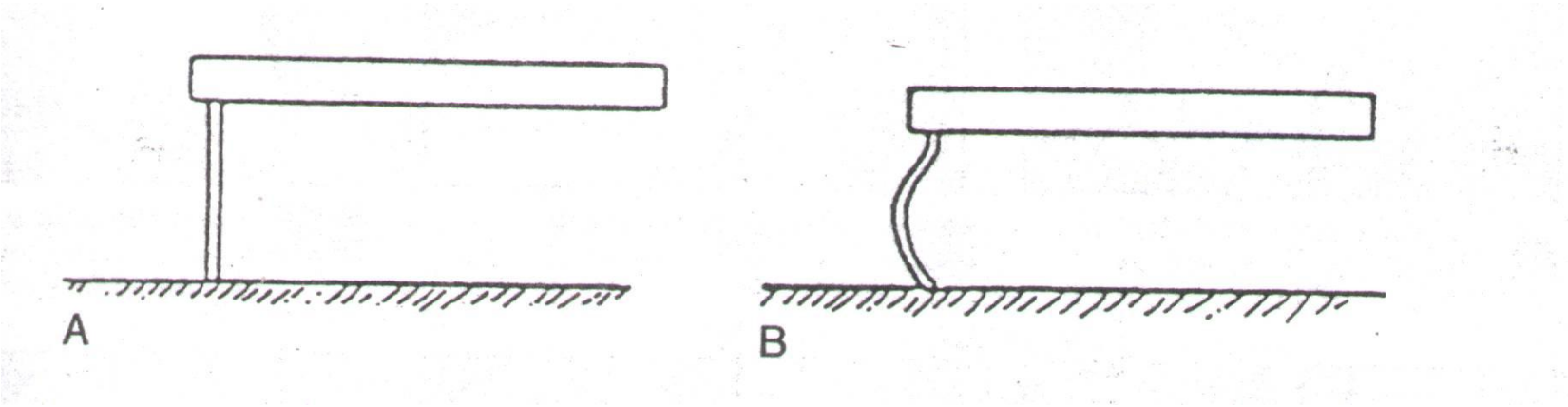
Pain and touch perception

- **Pain perception** is assessed by pin prick testing. Pinprick should be delivered once per second and not over the same point. More rapid delivery of pinprick produce summation of the effect and may obscure sensory loss.

- **Light touch** is assessed by cotton wool .

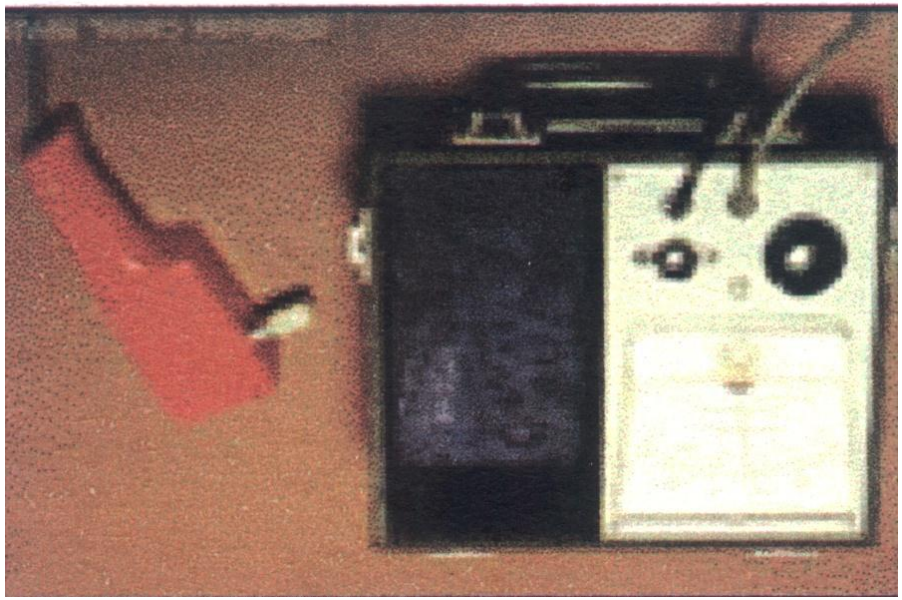
Pressure perception

- Pressure perception is assessed by 10 gm Semmes-Weinstein Monofilaments.



Vibration perception

- Vibration sense is assessed by tuning fork or Biothesiometer



Thermal perception

- **Percption of movement and position sense is tested in the fingers and toes .**
- **In more severe cases, with loss of proprioception, patients may demonstrate a positive Romberg's sign.**
- **Examination of muscle status, tone, power: wasting of small muscles of the hand and feet is common in neuropathy often with minimal weakness.**
- **Ankle reflex often lost (reduced or absent in elderly).**

Pathogenesis

3 main factors

Vascular

Metabolic

Autoimmune
auto AB
in some patients

Endoneurial
microangiopathy

Sorbitol accumulation

myoinistol depletion

Increased activity of
protein kinase C

Reduced Na-K
ATPase activity

Oxygen free
Radicals

decreased Nitric
oxide synthesis

AGEs

Management of DPN

1. **Primary prevention**
2. **Early detection and treatment**
3. **Disease modifying treatments**
4. **Symptomatic treatment of pain.**
5. **Protect a foot that lost its natural protective mechanisms.**

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- **The DCCT and the UKPDS demonstrated that the risk of neuropathy and other complications can be dramatically reduced or delayed by intensified glycemic control in patients with type 1 and 2 diabetes, respectively**

Management of DPN

1. Primary prevention
2. **Early detection and treatment**
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5. Protect a foot that lost its natural protective mechanisms.

- **The earlier the treatment of neuropathy the better will be the response to therapy.**

Management of DPN

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Tight blood glucose control

- **The stability rather than the actual level of glycemic control may be more important in relieving neuropathic pain especially in its early stages.**

Alpha Lipoic Acid

A meta analysis proved that treatment with alpha-lipoic acid (600 mg/day i.v.) over 3 weeks is safe.

It significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.

Ziegler et al Diabet Med. 2004 Feb;21(2):114-21

ALADIN III Study

Benfotiamine

- **A lipid-soluble derivative of thiamine.**
- **May reduce pain of PDN in a dose of 600 mg per day (Stracke et al 2008).**
- **Prevent the Accumulation of triosephosphates arising from high cytosolic glucose concentrations via the reductive pentosephosphate pathway.**

PKC inhibitors {Ruboxistaurin (LY333531)}

- **Therapy for diabetic macular oedema and other diabetic angiopathies including D retinopathy, D peripheral neuropathy and D nephropathy.**

- **A phase III trial of the protein kinase C β inhibitor ruboxistaurin has been disappointing after encouraging data from phase II studies were reported**

Aldose reductase inhibitors (Epalrestat and Ranirestat)

- **Sorbitol pathway is involved in pathogenesis of microvascular complications of diabetes.**
- **Aldose reductase inhibitors are effective in experimental animals (Matsumoto et al 2009).**
- **Safety!!!!**

Inhibitors of glycation (aminoguanidine)

- **Studies of aminoguanidine have mainly focused on nephropathy.**

Management of DPN

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2. Early detection and treatment
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4. **Symptomatic treatment of pain.**
5. Protect a foot that lost its natural protective mechanisms.

NSAID	Short courses may be used
Opioid analgesics	Should be avoided. But tramadol can be used for up to 6 months
SSRI	Debate about their effectiveness.
Carbamazepine	More effective in lancinating pain but it is a Toxic drug

Oxycarbazine	More safe Derivative of carbamazepine? Rapid titration of the dose…. serious adverse events.
Mexiletine	May induce serious arrhythmia
Capsaicin cream	Helpful for superficial and localized pain and in allodynia
Physiotherapeutic modalities	Acupuncture, TENS, PENS, Static magnetic field therapy, low-intensive laser therapy, monochromatic infrared light

Tricyclic antidepressants	1st line treatment, however, side effects are frequent. The tricyclic antidepressants have anticholinergic side effects.
Gabapentin	Effective and safe drug in a dose of 1800 mg /day (gradual increase of the dose every 3days)
Pregabalin	Analog of gamma aminobutyric acid, has anticonvulsant, analgesic, and anxiolytic properties . The greatest effect was observed in patients treated with 600 mg/day (Freeman et al 2008)
SNRI (Dual selective serotonin noradrenaline reuptake inhibitor)	It relieves pain by increasing the synaptic availability of 5-HT and noradrenaline in the descending pathways that inhibit pain impulses.

Management of DPN

1. Primary prevention
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4. Symptomatic treatment of pain.
5. **Protect a foot that lost its natural protective mechanisms.**

The neuropathic foot does not ulcerate spontaneously

It is the combination of neuropathy with either:

- **Extrinsic factors (e.g., ill-fitting shoe gear or foreign body in shoe)**

- **Intrinsic factors (e.g., high foot pressures or plantar callus) that results in ulceration.**

Micro vascular complications

- Neuropathy
- Retinopathy
- Nephropathy

- Diabetic retinopathy is the commonest cause of blindness worldwide.
- Diabetic retinopathy increases with the duration of diabetes.
- Progression of retinopathy often accelerated with poor control of diabetes and blood pressure.
- Asymptomatic until become advanced, so fundus examination should be routinely done at least annually.

Background diabetic retinopathy

- The first sign is the development of microaneurysms (small red dots).
- Superficial haemorrhages
- Cotton wool spots are micro-infarcts within the retina.
- Hard exudates (exudation of plasma rich in lipids and protein)

Proliferative retinopathy

- Proliferative retinopathy is preceded by the widespread development of capillary non-perfusion. This ischaemia induces new blood vessels to grow.
- New vessels do not give rise to any symptoms.
- New vessels are prone to bleed, particularly if there is vitreous traction.

- Small haemorrhages give rise to the preretinal haemorrhage with further bleeding or traction, the blood seeps into the vitreous with the consequent loss of vision.
- Once new vessels have developed this is an indication for laser therapy.

Diabetic eye diseases

1. Diabetic retinopathy
2. Cataract which develops earlier in diabetes than in the general population.
3. Error of refraction due to fluctuations in blood sugar leading to osmotic changes within the lens.
4. Ocular Nerve palsies: The sixth and the third nerve are the most commonly affected. These nerve palsies usually recover spontaneously within a period of 3–6 months

Micro vascular complications

- Neuropathy
- Retinopathy
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Renal affection in Diabetes

Increased risk of:

- **Renal atherosclerosis**
- **Urinary tract infections, papillary necrosis**
- **Glomerular lesions, e.g. from basement membrane thickening and glomerulosclerosis**.

Diabetic nephropathy

- Approximately 40% of patients with type 1 and 20% with type 2 diabetes develop nephropathy.
- Some centres have reported a falling incidence rate of diabetic nephropathy in type 1 diabetes. This may reflect good-quality local care for diabetes

- Diabetic nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease in the United States.

Pathophysiology

- The earliest functional abnormality in the diabetic kidney is renal hypertrophy associated with a raised glomerular filtration rate.
- As the kidney becomes damaged by diabetes, the afferent arteriole becomes vasodilated to a greater extent than the efferent glomerular arteriole. This increases the intraglomerular filtration pressure.

- This increased intraglomerular pressure leads to increased shearing forces locally which are thought to contribute to mesangial cell hypertrophy and increased secretion of extracellular mesangial matrix material.
- This process eventually leads to glomerular sclerosis.

- The initial structural lesion in the glomerulus is thickening of the basement membrane.
- Associated changes result in disruption of the protein cross-linkages which normally make the membrane an effective filter. In consequence, there is a progressive leak of large molecules (particularly protein) into the urine.

Stages of Diabetic nephropathy

1. Elevated glomerular filtration rate with enlarged kidneys
2. Intermittent Microalbuminuria
3. Microalbuminuria
4. Proteinuria and Nephrotic syndrome.
5. ESRD

Early Detection of Diabetic Nephropathy

- Clinical features are usually absent until advanced chronic kidney disease develops.
- Therefore, we should evaluate urinary albumin excretion (microalbuminuria) annually in all subjects with diabetes.

Definitions

- In healthy individuals, urinary albumin excretion is less than 30 mg per day.
- Microalbuminuria is defined as urinary albumin excretion 30 -300mg/day or albumin:creatinine ratio (ACR) greater than 2.5 mg/mmol (men) or 3.5 mg/mmol (women).
- Macroalbuminuria is defined as urinary albumin excretion >300mg/day

DD

Other renal disease should be suspected:

- In the absence of progressive retinopathy
- If proteinuria develops suddenly
- If significant haematuria is present

Management

- **Primary prevention**
- Optimal control of blood glucose and blood pressure.
  - The Diabetes Control and Complications Trial (DCCT) found that a reduction in mean HbA1c from 9.0% to 7.3% in people with type 1 diabetes was associated with a 39% reduction in microalbuminuria and 54% reduction in proteinuria over 6.5 years.
  - The United Kingdom Prospective Diabetes Study (UKPDS) also showed that a reduction in blood pressure from 154/87 to 144/82 mm Hg was associated with an absolute risk reduction of developing microalbuminuria of 8% over 6 years in patients with type 2 diabetes

Microalbuminuria and proteinuria

- Ensure good blood glucose control (HbA1c below 6.5-7.5%, according to the individual's target).
- ACE inhibitors should be started and titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes.
- If ACE inhibitors are not tolerated, angiotensin ll receptor antagonists should be substituted but combination therapy with both ACE inhibitors and angiotensin ll receptor antagonists is not recommended at present.
- ACE inhibitor and angiotensin ll receptor antagonists should be used with caution in those with:
  - Peripheral vascular disease or known renovascular disease
  - Raised serum creatinine

- Measure, assess and manage Cardiovascular risk factors aggressively (smoking, glucose, raised lipids, high blood pressure).
- Blood pressure should be maintained below 130/80 mm Hg by addition of other antihypertensive drugs if necessary.

- Avoid high protein intake.

- Avoid taking Contrast agents containing Iodine and NSAIDs.

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- Micro Vascular
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  - Retinopathy
  - Nephropathy

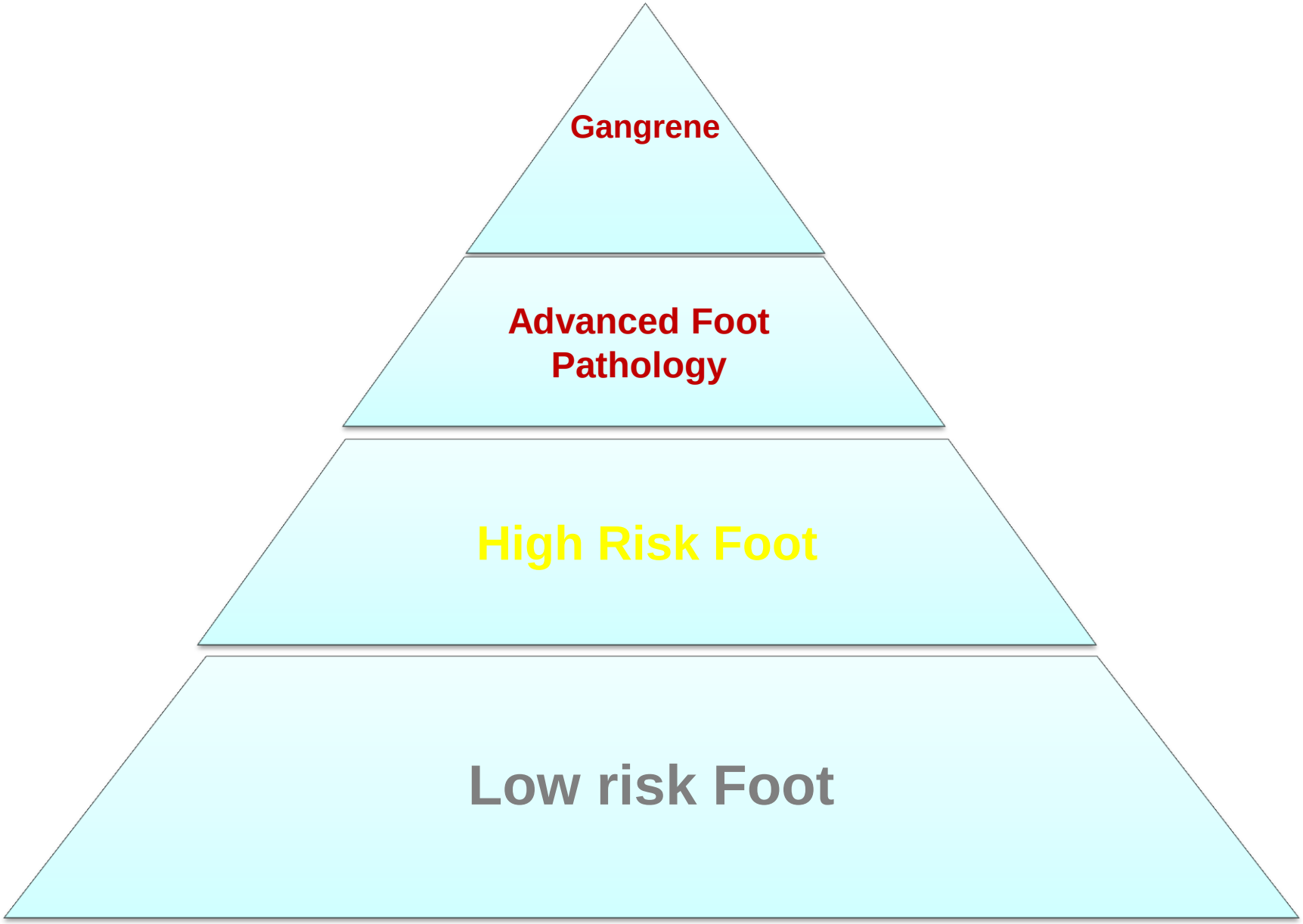
Diabetic Foot

The term diabetic foot indicate any foot pathology that results directly from diabetes or its long-term complications

The WHO definition of the diabetic foot

- **The foot of a diabetic patient that has the potential risk of pathologic consequences including infection, ulceration and or destruction of deep tissues associated with neurologic abnormalities, various degrees of peripheral vascular disease and/or metabolic complications of diabetes in the lower limb**

- Diabetic gangrene doesn’t occur suddenly but is preceded by several stages


Gangrene
Advanced Foot Pathology
High Risk Foot
Low risk Foot

Advanced foot Pathology

- Diabetic Foot ulcers (Neuropathic, Neurischemic or Uschemic)
- Diabetic foot Infections
- Charcot foot

The high risk foot

The high risk foot is the foot that has developed one or more of the following risk factors for ulceration:

- **Neuropathy**
- **Ischaemia**
- **Deformity**
- **Trauma**
- **Callus.**
- **Nail pathology**

The low risk foot

The National Institute of Health and Clinical Excellence defines low-risk patients as those with normal sensation and palpable pulses

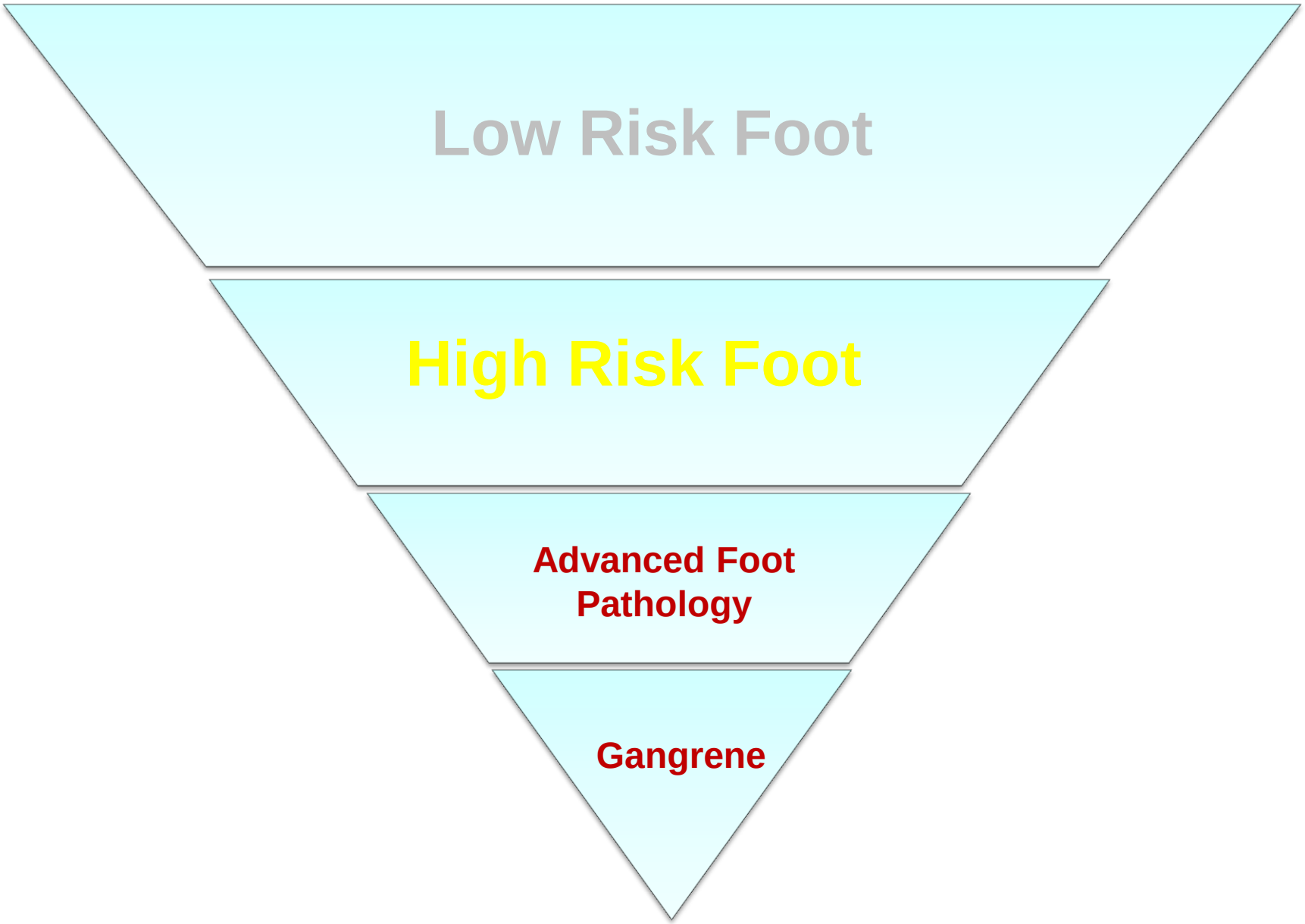
key educational elements for diabetic patients at low risk of complication

Foot care education in patients with diabetes at low risk of complications: a consensus statement. Diabet. Med. 28, 162–167 (2011)

CARE

- **C**ontrol: control blood glucose levels
- **A**nnual: attend your annual foot screening examination.
- **R**eport: report any changes in your feet immediately to your healthcare professional.
- **E**ngage: engage in a simple daily foot care routine by washing and drying between your toes,moisturizing and checking for abnormalities.

- In order to prevent amputation, we should diagnose and treat any mild foot pathology before its progression into advanced foot pathology.


Low Risk Foot
High Risk Foot
Advanced Foot Pathology
Gangrene

What can be done to prevent the development of advanced foot pathology?

- **Regular inspection and examination of the foot.**
- **Identification of the foot at risk.**
- **Education of patient, family and healthcare providers.**
- **Appropriate footwear.**
- **Treatment of non ulcerative pathology**