# DM complications

# Chronic Complications of DM

❖Vascular

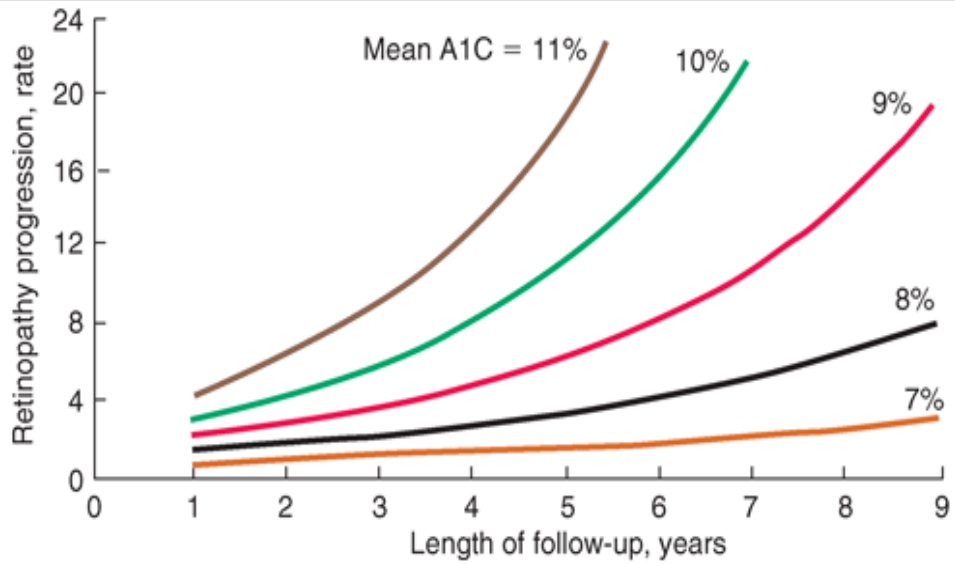
❖Nonvascular

- Duration and degree of hyperglycemia:
  - Usually in the **second decade** of hyperglycemia.

| Table 344-7 Chronic Complications of Diabetes Mellitus |
| --- |
| Microvascular |
| Eye disease |
| Retinopathy (nonproliferative/proliferative) |
| Macular edema |
| Neuropathy |
| Sensory and motor (mono- and polyneuropathy) |
| Autonomic |
| Nephropathy |
| Macrovascular |
| Coronary heart disease |
| Peripheral arterial disease |
| Cerebrovascular disease |
| Other |
| Gastrointestinal (gastroparesis, diarrhea) |
| Genitourinary (uropathy/sexual dysfunction) |
| Dermatologic |
| Infectious |
| Cataracts |
| Glaucoma |
| Periodontal disease |
| Hearing loss |

- Microvascular complications of both type 1 and type 2 DM:
  - Chronic hyperglycemia
  - Genetic susceptibility
- Macrovascular complications:
  - Role for chronic hyperglycemia is less conclusive.
  - Other factors (dyslipidemia and hypertension)

## Figure 344-8




Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



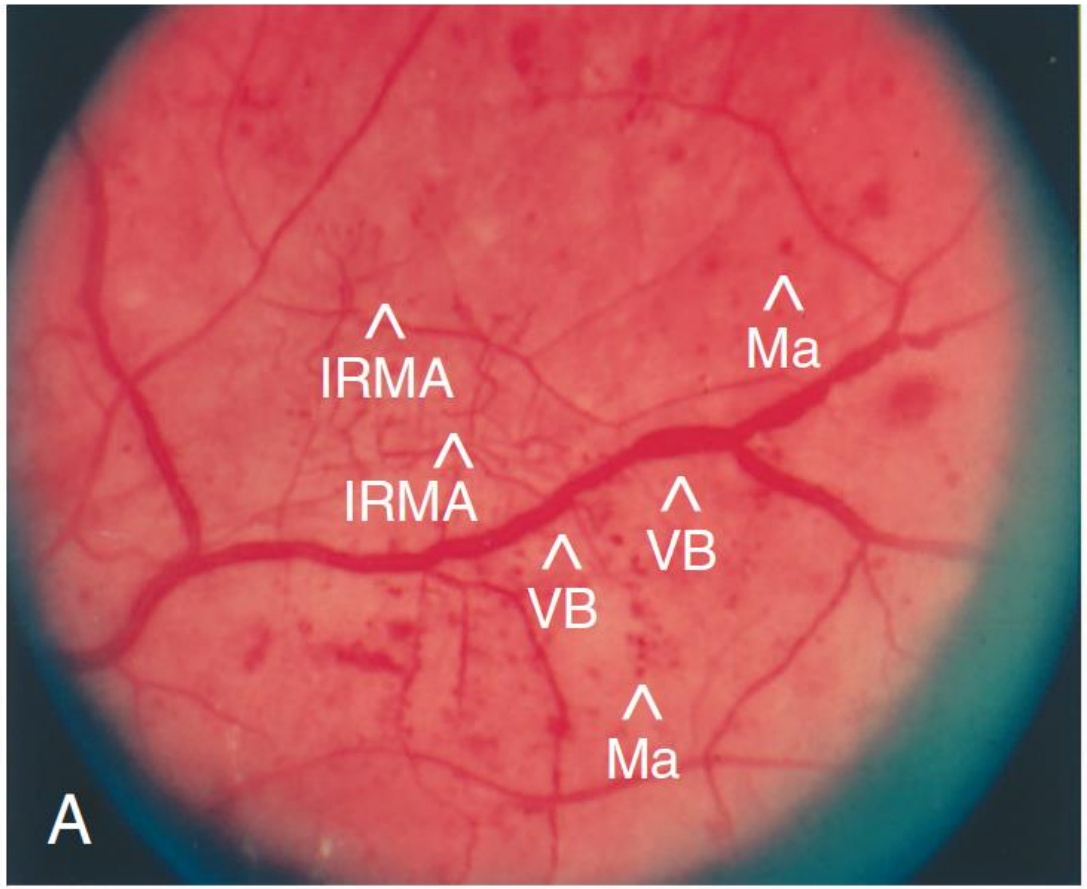
**Relationship of glycemic control and diabetes duration to diabetic retinopathy.** The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different $A_{1C}$ values. *(Adapted from The Diabetes Control and Complications Trial Research Group: Diabetes 44:968, 1995.)*

# Ophthalmologic Complications

- DM is the leading cause of blindness between the ages of 20 and 74 in the United States.
- **25 times more likely** to become legally blind
- Blindness is primarily the result of:
  - Progressive diabetic retinopathy
  - Clinically significant macular edema

# Nonproliferative diabetic retinopathy:

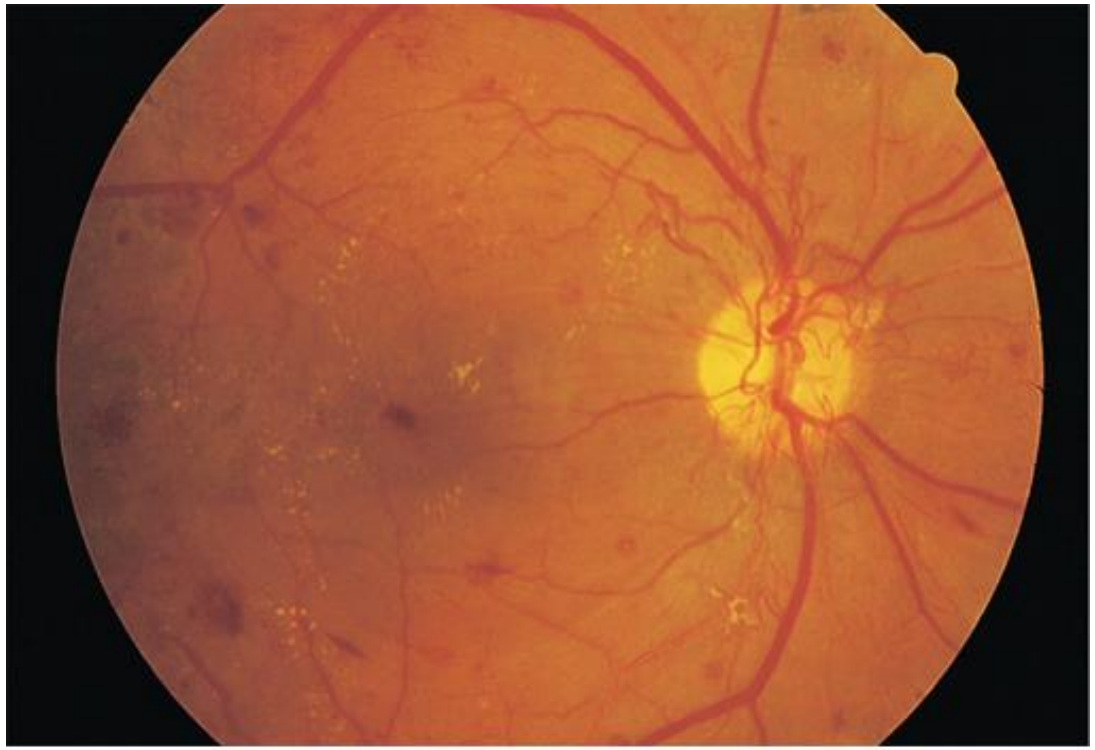
- Usually **appears late in the first decade** or **early in the second decade** of the disease:
  1. **Retinal vascular microaneurysms:** (saccular outpouchings of the capillary walls that can leak fluid and result in intraretinal edema and hemorrhages)
  2. **Blot hemorrhages**
  3. **Cotton-wool spots** :caused by microinfarcts in the nerve fiber layer of the retina.




microaneurysms (Ma), venous beading (VB), and intraretinal microvascular abnormalities (IRMA).

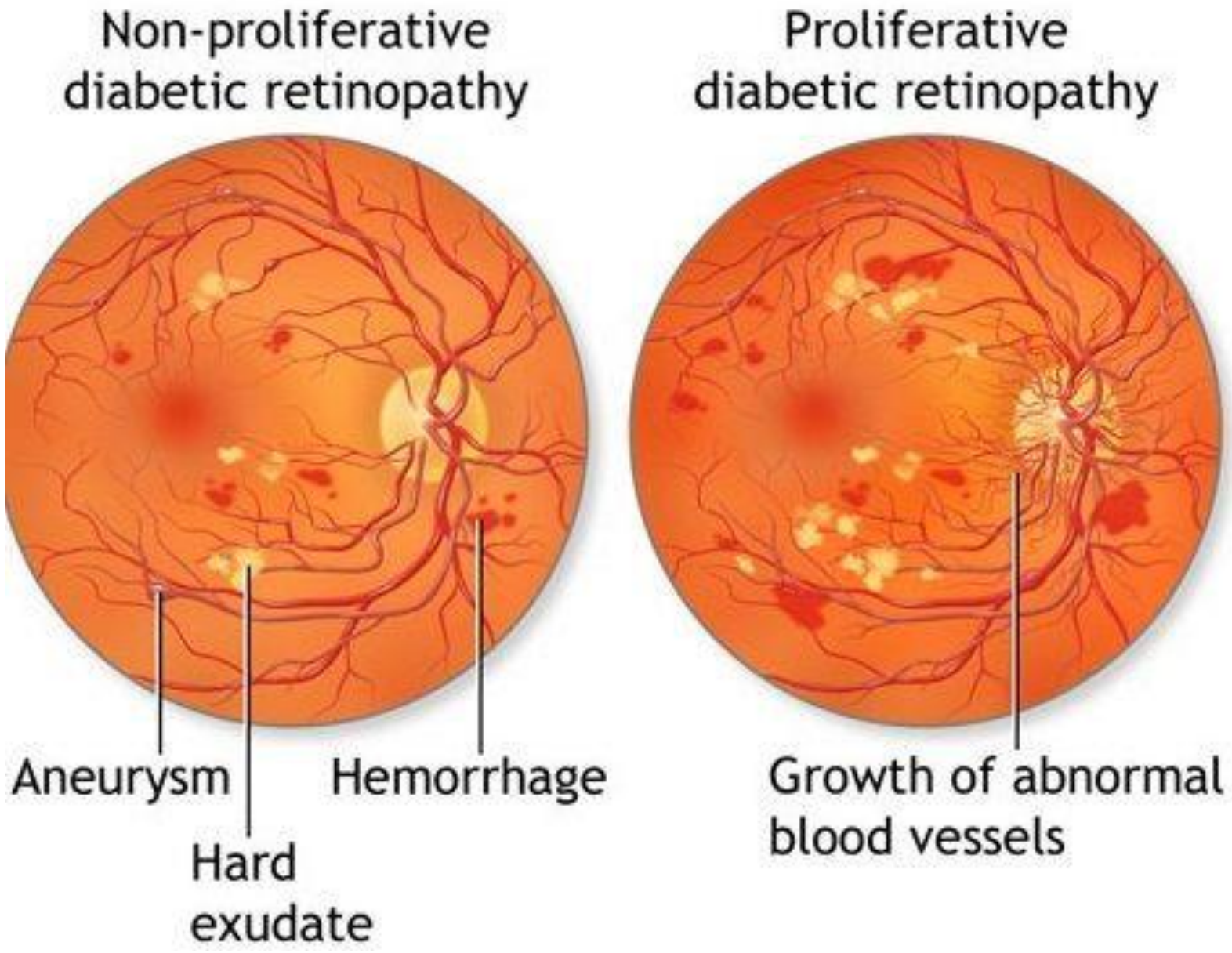
# Proliferative diabetic retinopathy

- The appearance of ***neovascularization*** in response to retinal hypoxemia is the hallmark





**scattered hemorrhages, yellow exudates, and neovascularization**


Non-proliferative
diabetic retinopathy
Proliferative
diabetic retinopathy
Aneurysm
Hard
exudate
Hemorrhage
Growth of abnormal
blood vessels

- These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to:
  - Vitreous hemorrhage
  - Fibrosis
  - Ultimately retinal detachment
- Not all individuals with nonproliferative retinopathy develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years.

- **Clinically significant macular edema:**
- Can occur when only nonproliferative retinopathy is present.
- DX:
  - Fluorescein angiography is useful to detect macular edema.
- 25% chance of moderate visual loss over the next 3 years.

- Predictors of the development of retinopathy:
  - Duration of DM and degree of glycemic control
  - Hypertension
  - Genetic susceptibility for retinopathy (less influence)
- Nonproliferative retinopathy is found in many individuals who have had DM for >20 years:
  - 25% incidence with 5 years
  - 80% incidence with 15 years of type 1 DM

# Treatment: Diabetic Retinopathy

- Prevention
- Intensive glycemic and blood pressure control
  - Paradoxically, during the first 6–12 months of improved glycemic control, established diabetic retinopathy may transiently worsen.
  - Candidates for prophylactic photocoagulation when initiating intensive therapy.
- Proliferative retinopathy :
  - Panretinal laser photocoagulation
- Macular edema
  - Focal laser photocoagulation.

# Renal Complications

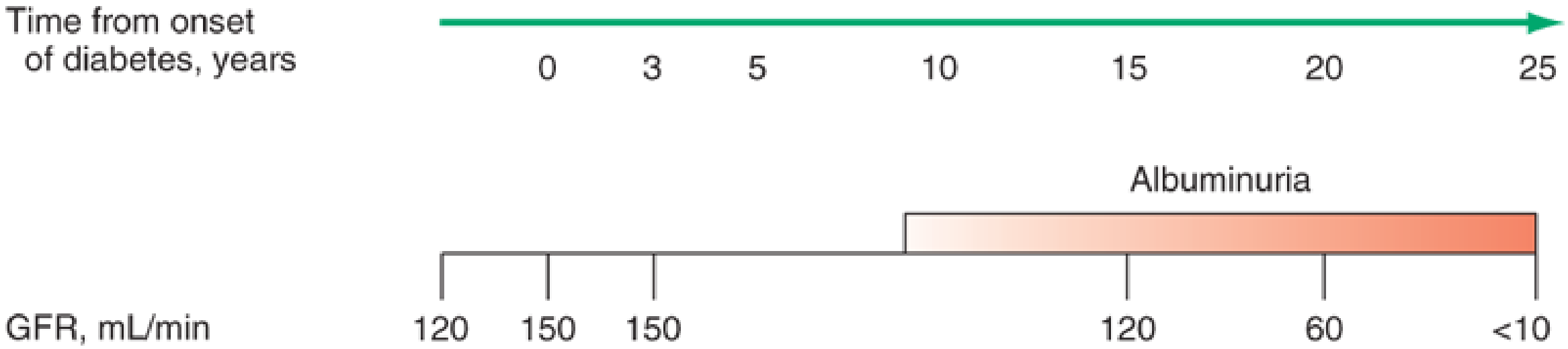
- Diabetic nephropathy is the leading cause of ESRD in the United States and a leading cause of DM-related morbidity and mortality.

- Individuals with diabetic nephropathy commonly have diabetic retinopathy.

- Pathogenesis of diabetic nephropathy:
  - Chronic hyperglycemia
  - Because only **20–40%** of patients with diabetes develop diabetic nephropathy, additional susceptibility factors remain unidentified
  - Family history of diabetic nephropathy

- First years after the onset of DM:
  - Glomerular hyperperfusion and renal hypertrophy and are associated with an increase of the GFR.
- During the first 5 years of DM:
  - Thickening of the glomerular basement membrane
  - Glomerular hypertrophy
  - Mesangial volume expansion occur
  - GFR returns to normal
- After 5–10 years of type 1 DM:
  - 40% of individuals begin to excrete small amounts of albumin in the urine.

# Time course of development of diabetic nephropathy




Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

# Nephropathy in type 2 DM

1. Albuminuria may be present when type 2 DM is diagnosed reflecting its long asymptomatic period
2. Hypertension more commonly accompanies albuminuria
3. Albuminuria may be less predictive of diabetic kidney disease
4. Albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as:
   - Hypertension
   - Congestive heart failure (CHF)
   - Prostate disease
   - Infection

- **Screening for albuminuria** should be performed annually:

1. In patients with type 1 diabetes for ≥5 years
2. In patients with type 2 diabetes at the time of diagnosis
3. During pregnancy

# Radiocontrast-induced nephrotoxicity.

- Risk factors:
  - Preexisting nephropathy
  - Volume depletion
- Individuals should be well hydrated before and after dye exposure
- Serum creatinine should be monitored for 24–48 h following the procedure.
- Metformin should be held until postintervention confirmation of preserved kidney function.

# Treatment: Diabetic Nephropathy

- The optimal therapy: is prevention by control of glycemia.
- Interventions effective in **slowing progression** of albuminuria include:

1. Improved glycemic control
2. Strict blood pressure control
3. Administration of an ACE inhibitor or ARB.
4. Dyslipidemia should also be treated.

# Treatment

- During the later phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation.
- Some glucose-lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency.
- Many individuals with type 1 or type 2 DM develop hypertension.
- Blood pressure should be maintained at <140/90 mmHg in individuals with diabetes
- Possibly <130/80 in individuals at increased risk for CVD and CKD progression.

# Treatment

- Either ACE inhibitors or ARBs should be used to reduce the albuminuria and the associated decline in GFR that accompanies it in individuals with type 1 or type 2 DM.
- Two classes of drugs are equivalent in patient with diabetes.
- **ARBs** can be used as an alternative in patients who develop ACE inhibitor–associated cough or angioedema.
- After initiation of therapy, some increase the dose and monitor the urinary albumin.

# Treatment

- There is no benefit of intervention prior to onset of albuminuria or using a combination of an ACE inhibitor and an ARB.
- If use of either ACE inhibitors or ARBs is not possible or the blood pressure is not controlled, then:
  - Diuretics
  - Calcium channel blockers (nondihydropyridine class)
  - Beta blockers
- Protein intake of 0.8 mg/kg of body weight/day in individuals with diabetic kidney disease.

# Treatment

- Nephrology consultation should be considered when albuminuria appears and when the estimated GFR is <30 mL/min per 1.743 m .
- Referral for transplant evaluation: GFR approaches **20** mL/min per 1.743 m .
- Hemodialysis in patients with DM is associated with more frequent complications, such as:
  - Hypotension (due to autonomic neuropathy or loss of reflex tachycardia)
  - More difficult vascular access
  - Accelerated progression of retinopathy

# Neuropathy and Diabetes Mellitus

- Diabetic neuropathy, which occurs in **~50%** of individuals with long-standing type 1 and type 2 DM

❖Diffuse neuropathy (distal symmetrical polyneuropathy and/or autonomic neuropathy)

❖Mononeuropathy

❖Radiculopathy/polyradiculopathy

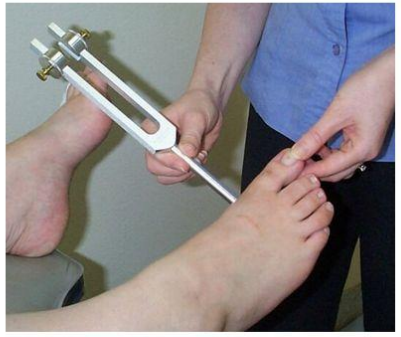
- Development of neuropathy correlates with:
  - Duration of diabetes
  - Glycemic control
  - Body mass index (BMI) (the greater the BMI, the greater the risk of neuropathy)
  - Smoking
  - The presence of **CVD**, elevated **triglycerides**, and **hypertension** is also associated with diabetic peripheral neuropathy.
- Diagnosis of diabetic neuropathy should be made only **after other possible etiologies are excluded**.

# Distal Symmetric Polyneuropathy (DSPN)

- DSPN, the **most common** form of diabetic neuropathy, most frequently presents with distal sensory loss and pain, but up to 50% of patients do not have symptoms of neuropathy.
- Symptoms :
  - Sensation of numbness, tingling, sharpness, or burning
  - Begins in the feet and spreads proximally.
  - Hyperesthesia, paresthesia, and dysesthesia also may occur.
- Pain typically involves the lower extremities, is usually present at rest, and worsens at night.

- Physical examination:
  - Sensory loss (to 10-g monofilament and/or vibration)
  - Loss of ankle deep-tendon reflexes
  - Abnormal position sense
  - Muscular atrophy or foot drop.


## Screening for Neuropathy



- 128 Hz tuning fork for testing of vibration perception
- 10g Semmers monofilament

The main reason is to identify patients at risk for development of diabetic foot(LOPS)

- Annual screening for DSPN should begin 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM and is aimed at detecting loss of protective sensation (LOPS).
- LOPS and DSPN are major risk factors for **foot ulceration** and **falls** due to small and large nerve fiber dysfunction.

# Autonomic Neuropathy

- Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic systems.
- DM-related autonomic neuropathy can involve multiple systems, including:
  - Cardiovascular
  - Gastrointestinal (GI)
  - Genitourinary
  - Sudomotor
  - Metabolic systems

- **Cardiovascular autonomic neuropathy**, reflected by:
  - Decreased heart rate variability
  - Resting tachycardia
  - Orthostatic hypotension
- Associated with an increase in CVD.
- Reports of sudden death in DM have also been attributed to cardiovascular autonomic neuropathy.

- Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM.
- Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction.
- Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of foot ulcers.

- Autonomic neuropathy may reduce counterregulatory hormone release (especially catecholamines)
- leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

# Mononeuropathy

- Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with:
  - **Pain and motor weakness** in the distribution of a single nerve.
- Mononeuropathies can occur at **entrapment sites** such as carpal tunnel or be **noncompressive**.

- Involvement of the **third cranial nerve is most common** and is heralded by diplopia.
- Physical examination reveals **ptosis** and **ophthalmoplegia** with **normal pupillary constriction to light**.
- Sometimes other cranial nerves, such as IV, VI, or VII (Bell's palsy), are affected.
- Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

# Radiculopathy/Polyradiculopathy

- Diabetic radiculopathy or polyradiculopathy is a syndrome characterized by **severe disabling pain** in the **distribution of one or more nerve roots**.
- It may be accompanied by motor weakness.
- Intercostal or truncal radiculopathy causes pain over the thorax or abdomen.
- Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy).
- Fortunately, diabetic polyradiculopathies are usually **self-limited** and **resolve over 6–12 months**.

55-Y Old woman with history of T2 DM for 13 years write the name of the complications in this patient in figures 1 & 2?

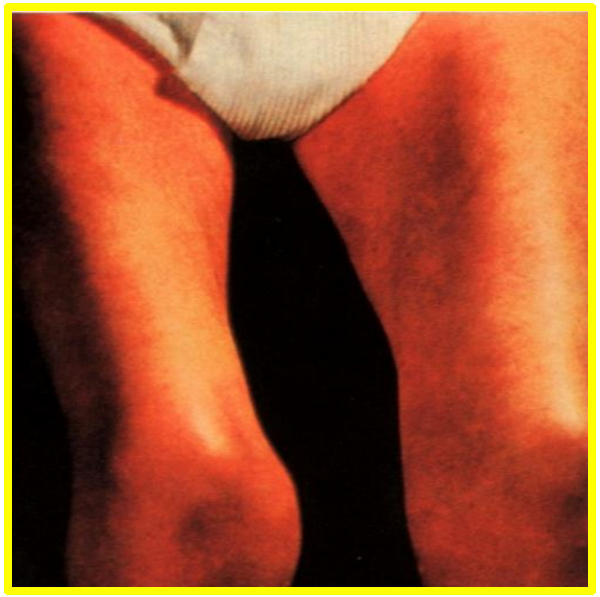


Figure 1

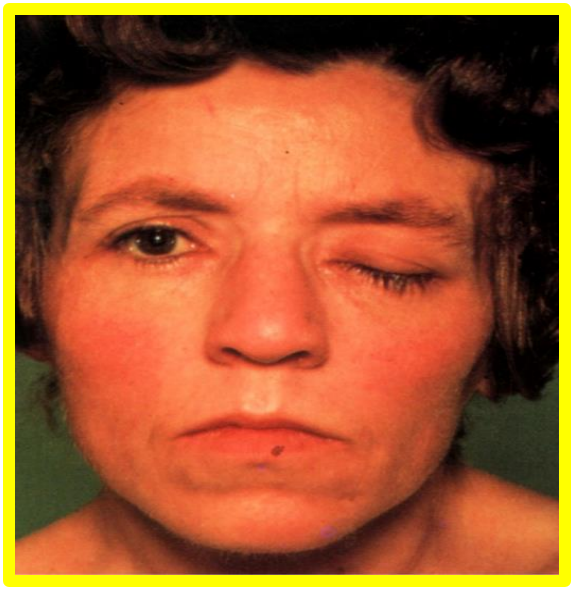


Figure 2

# TREATMENT

- Prevention through improved glycemic control.
- DSPN in type 2 DM:
  - Lifestyle modifications (exercise, diet)
  - Hypertension and hypertriglyceridemia should be treated.
- Avoidance of neurotoxins (alcohol) and smoking
- Supplementation with vitamins for possible deficiencies ($B_{12}$ , folate).
- Treatment of diabetic neuropathy is less than satisfactory (Duloxetine and pregabalin)

# Cardiovascular Morbidity and Mortality

- Cardiovascular disease is increased in individuals with type 1 or type 2 DM.
- DM is"CHD risk equivalent."
- Type 2 diabetes patients without a prior MI have a similar risk for coronary artery–related events as nondiabetic individuals who have had a prior MI.

- The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation should be considered in individuals undergoing major surgical procedures.
- The prognosis for individuals with diabetes who have CHD or MI is worse than for nondiabetics.
- CHD is more likely to involve multiple vessels in individuals with DM.

- Risk factors for macrovascular disease in diabetic individuals include:
  - Dyslipidemia
  - Hypertension
  - Obesity
  - Reduced physical activity
  - Cigarette smoking
  - Albuminuria
  - Elevation of serum creatinine
  - Abnormal platelet function
  - Insulin resistance

# Treatment: Cardiovascular Disease

- In general, the treatment of coronary disease is not different in the diabetic individual.
- Revascularization procedures for CHD, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual.
- Diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies.

- Glycemic control
- beta blockers (after MI).
- ACE inhibitors (or ARBs):
  - Type 2 DM and other risk factors (smoking, dyslipidemia, history of cardiovascular disease, microalbuminuria).
- Patients with atypical chest pain or an abnormal resting ECG should be considered for screening for CHD.

# Cardiovascular Risk Factors

- **Dyslipidemia**
- The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels.
- DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

- All individuals with diabetes: lifestyle modification, including:
  - Diet
  - weight loss
  - increased physical activity
- If individuals with diabetes have elevated triglyceride levels (>150 mg/dL) or low HDL cholesterol (<40 mg/dL) in men and (<50 mg/dL) in women, **lifestyle modification** and **improved glycemic control** should be further emphasized.
- If triglycerides remain >500 mg/dL, treatment with fish oil and fibrate drugs may reduce the risk of pancreatitis.

# Treatment

1. All patients with diabetes and atherosclerotic cardiovascular disease should receive high-intensity statin therapy;
2. in patients aged 40–75 years, consider using moderate-intensity statin therapy (without additional risk factors)
3. in patients <40 years and additional risk factors, consider moderate-intensity statin therapy.
4. Individuals with diabetes who are >75 years are similar to that for individuals aged 40–75 years.

# Hypertension

- Hypertension can accelerate other complications of DM, particularly CVD, nephropathy, and retinopathy.
- In targeting a goal of blood pressure of <140/90 mmHg:
  - Weight loss
  - Exercise
  - Stress management
  - Sodium restriction
- In some younger individuals or those with increased CV risk, the provider may target a blood pressure of <130/80 mmHg.

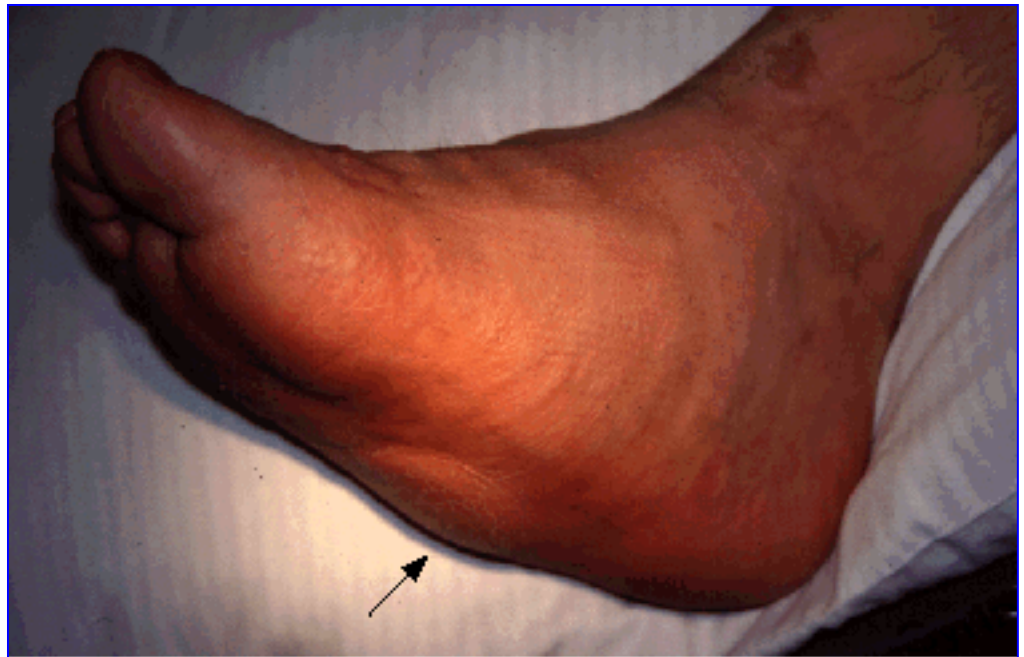
- All patients with diabetes and hypertension should be treated with an ACE inhibitor or an ARB initially. Subsequently, agents that reduce cardiovascular risk:
  - Beta blockers
  - Thiazide diuretics
  - Calcium channel blockers
- ACE inhibitors and ARBs should not be combined.
- Serum **potassium** and **renal function** should be monitored.

# Lower Extremity Complications

- DM is the leading cause of nontraumatic lower extremity amputation in the United States.
- The reasons:
  - Neuropathy
  - Abnormal foot biomechanics
  - PAD
  - Poor wound healing

- Many individuals with type 2 DM develop a foot ulcer (great toe or metatarsophalangeal areas are most common)
- A significant subset who develop an ulceration will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration).

- Risk factors for foot ulcers or amputation include:
  - male sex
  - diabetes >10 years' duration
  - peripheral neuropathy
  - abnormal structure of foot (bony abnormalities, callus, thickened nails)
  - peripheral arterial disease
  - Smoking
  - history of previous ulcer or amputation
  - visual impairment
  - poor glycemic control
  - diabetic nephropathy, especially dialysis



**Charcot arthropathy** Diabetic patient with Charcot arthropathy characterized by collapse of the arch of the midfoot which is replaced by a bony prominence (arrow). Several factors contribute to this painless condition, including small muscle wasting, decreased sensation, and maldistribution of weight bearing. Courtesy of David McCulloch, MD.

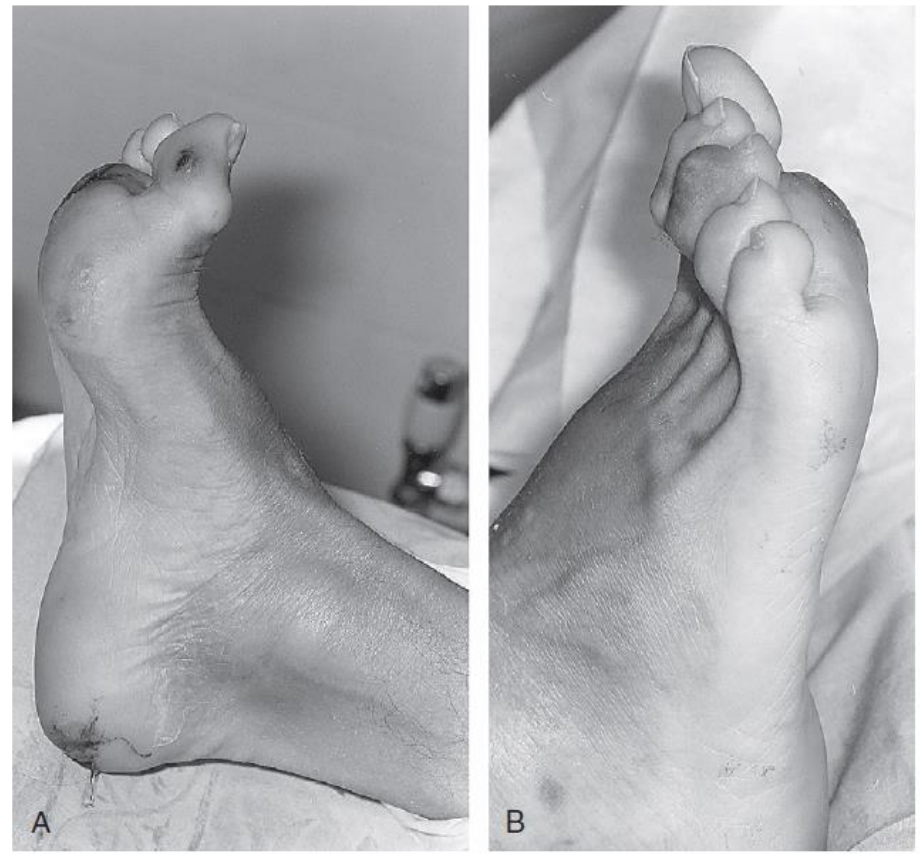
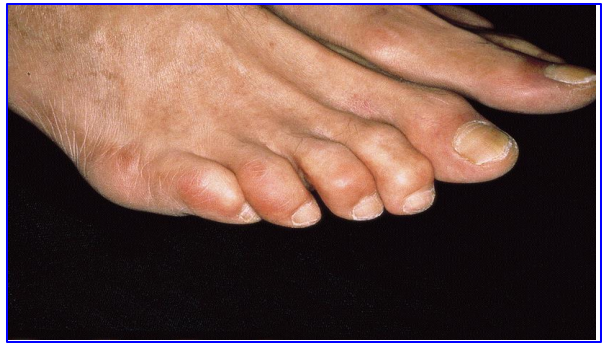
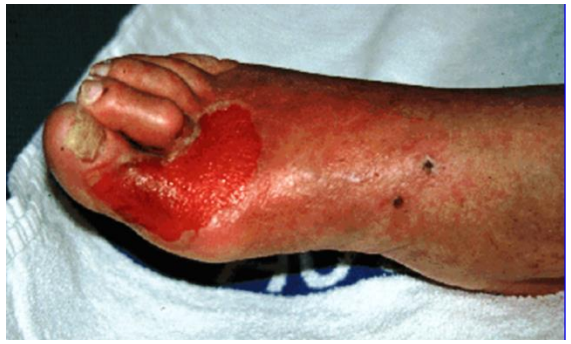
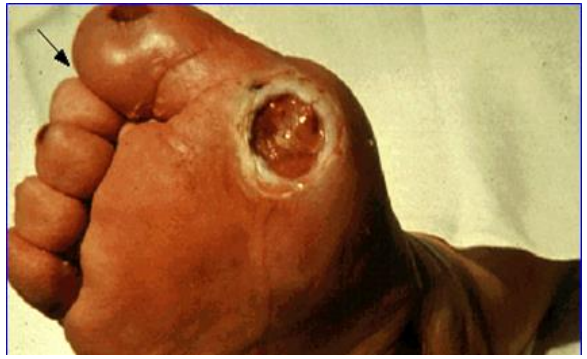
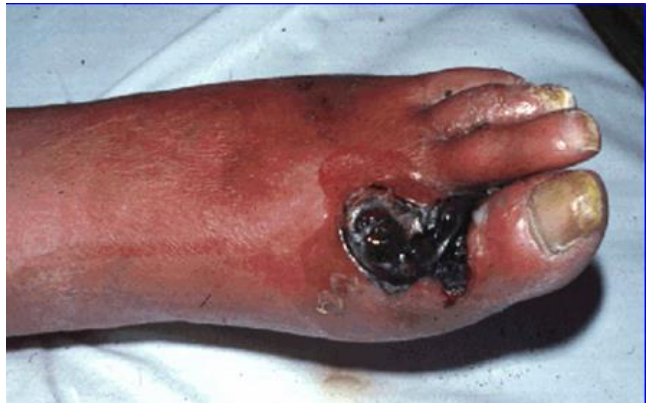
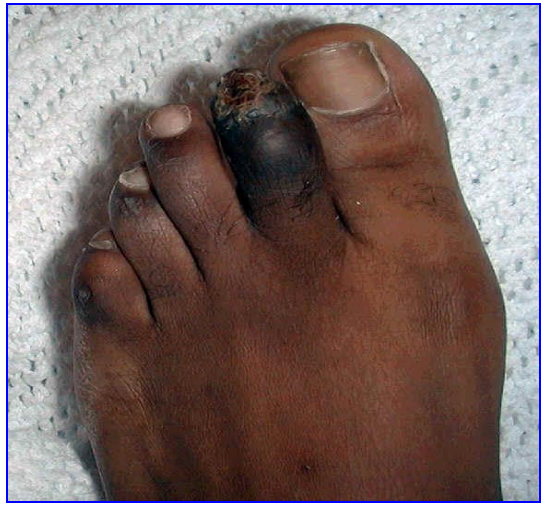



**Figure 33-54** The high-risk neuropathic foot. **A** and **B,** Two lateral views of a patient with typical signs of a high-risk neuropathic foot. Notice the small-muscle wasting, clawing of the toes, and marked prominence of the metatarsal heads. At presentation with type 2 diabetes mellitus, this patient had severe neuropathy with foot ulceration on both the right foot (shown here) and the left foot. (From Andersson DK, Svardsudd K. Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care.* 1995;18:1534-1543.)


# Treatment: Lower Extremity Complications

- Prevention:
  - Identification of high-risk patients
  - Education of the patient
- Patient education should emphasize

  (1) careful selection of footwear

  (2) daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma

  (3) daily foot hygiene to keep the skin clean and moist

  (4) avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot)

  (5) prompt consultation with a health care provider if an abnormality arises.

- six interventions with demonstrated efficacy in diabetic foot wounds:
  (1) off-loading
  (2) debridement
  (3) wound dressings
  (4) appropriate use of antibiotics
  (5) revascularization
  (6) limited amputation.

# Infections

- Individuals with DM have a greater frequency and severity of infection.
- The reasons for this include:
  1. Abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia
  2. Diminished vascularization

- Many **common infections** are more **frequent and severe** in the diabetic population

1. Rhinocerebral mucormycosis
2. Emphysematous infections of the gall bladder and urinary tract,
3. "malignant" or invasive otitis externa (*P. aeruginosa* infection)

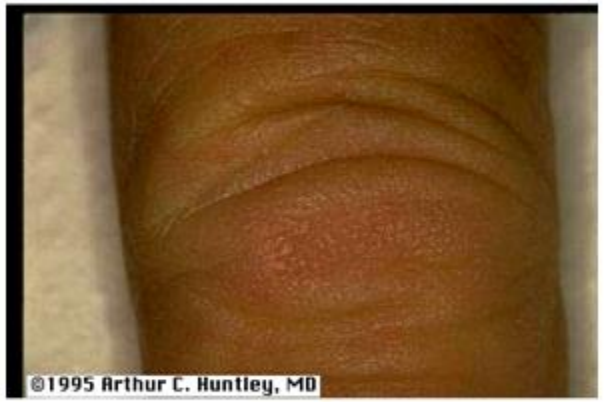
# Dermatologic Manifestations

- The **most common skin manifestations** of DM are protracted wound healing and skin ulcerations.
- Diabetic dermopathy, sometimes termed *pigmented pretibial papules*, or "diabetic skin spots," begins as an erythematous area and evolves into an area of circular hyperpigmentation.
- These lesions result from minor mechanical trauma in the pretibial region and are more common in elderly men with DM.

- Bullous diseases, such as bullosa diabeticorum (shallow ulcerations or erosions in the pretibial region), are also seen.

- *Necrobiosis lipoidica diabeticorum* is a rare disorder of DM that predominantly affects:
  - **Young women** with type **1** DM, **neuropathy**, and **retinopathy**.
- It usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration.
- They may be painful.

- **Vitiligo** occurs at increased frequency in individuals with type 1 diabetes.
- ***Acanthosis nigricans*** (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes.
- **Generalized or localized *granuloma annulare*** (erythematous plaques on the extremities or trunk)
- ***scleredema*** (areas of skin thickening on the back or neck at the site of previous superficial infections)
- ***Lipoatrophy* and *lipohypertrophy*** can occur at insulin injection sites but are now unusual with the use of human insulin.
- **Xerosis and pruritus**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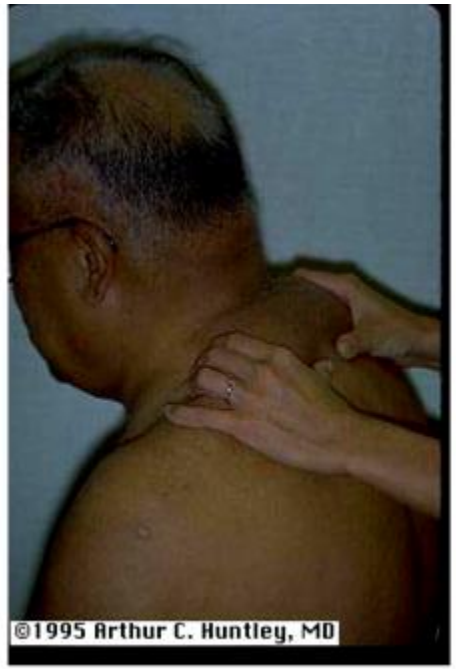
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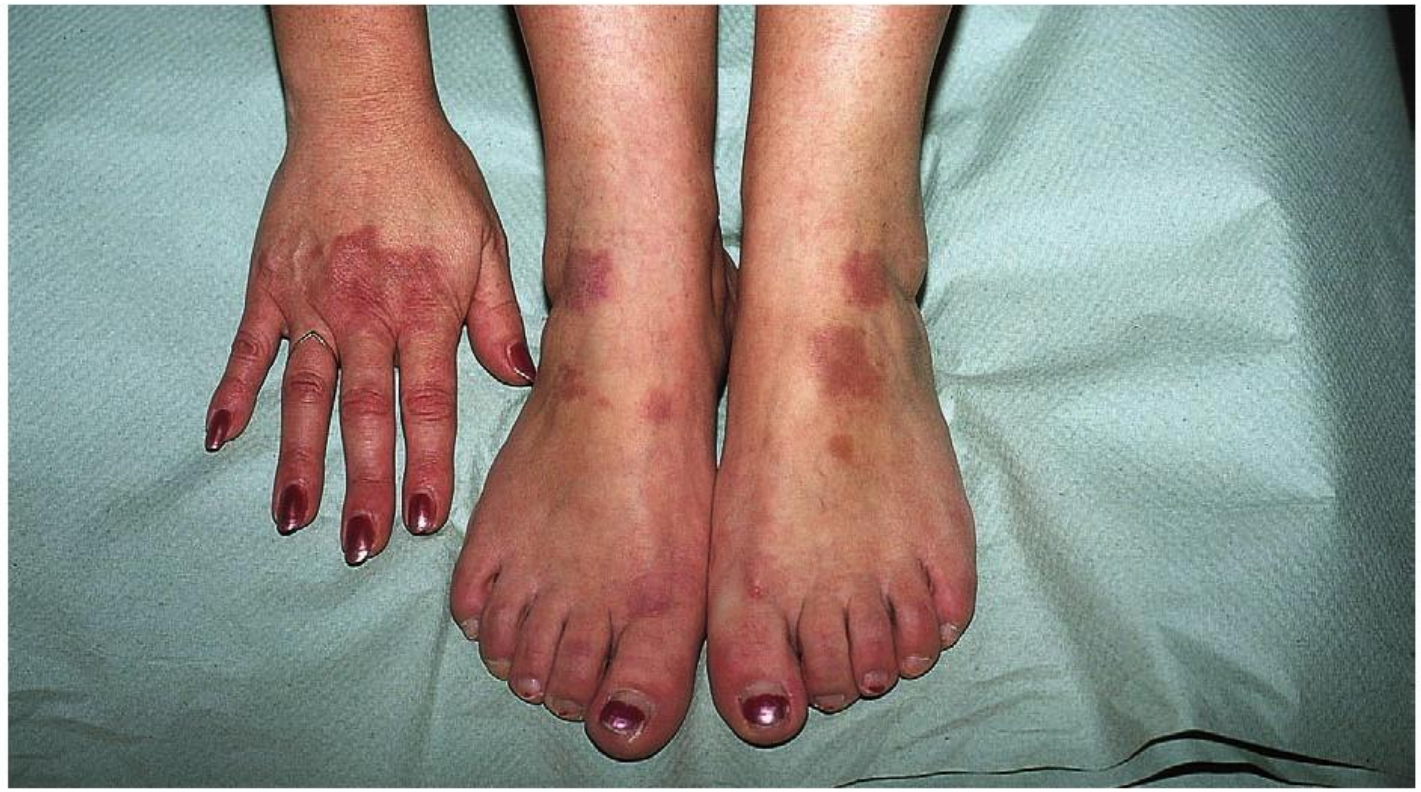

**Figure 139** Granuloma annulare. Although this skin condition is occasionally seen in diabetic patients, several large studies have failed to reveal a significant association between the two disorders, both of which are relatively common

36-Y Old  woman with  history of DM for 16 years/treated with insulin.

clinical findings in the pictures?