Harmful Effects of Hyperglycemia

- Increased capillary basement membrane thickening causing microvascular problems
- Impairment of phagocytosis (ability to fight infections)
- Abnormally high levels of minor (glycosylated) proteins: advanced glycosylated end products (AGES) that interfere with the protein's normal physiology
- Glucose metabolized to sorbitol via the polyol pathway
- Increased aldose reductase
- Faulty lipid metabolism yields hypercholesterolemia and hypertriglyceridemia
- Increased neonatal morbidity and mortality

OXIDATIVE STRESS with increased levels of Reactive Oxygen Species (ROS) results from 4 major pathways

- Increased blood pressure
- Hemorrheologic factors affected adversely:
  - Increased platelet adhesiveness
  - Increased serum fibrinogen levels
  - Increased blood viscosity
  - Decreased red blood cell flexibility
  - Increased coagulation factors like plasminogen activator inhibitor-1 (PAI-1)
  - Increased lipoprotein A
  - Increased CRP (INFLAMMATION)
- Increased activation of some isoforms of protein kinase C (PKC) causing reduced vascular contractility & oxidative stress with damage to endothelium
  - Increased sialic acid levels in the blood
  - Increased Coronary Artery Disease
  - Increased dental cavities and gum disease
  - Increased weight
  - Increased incidence of cataracts

Skin disorders

DEPRESSION

The Polyol Pathway

Glucose + NADPH $\xrightarrow{\text{Aldose Reductase}}$ **Sorbitol + NADP**

Sorbitol + NAD $\xrightarrow{\text{Sorbitol Dehydrogenase}}$ **Fructose + NADH**

Dyslipidemias and Diabetes

- Enhanced VLDL Secretion
- Increased Small Dense LDL Production
- Hypertriglyceridemia
- Decreased HDL Secretion
- TREATMENT: STATINS (Crestor or Lipitor)

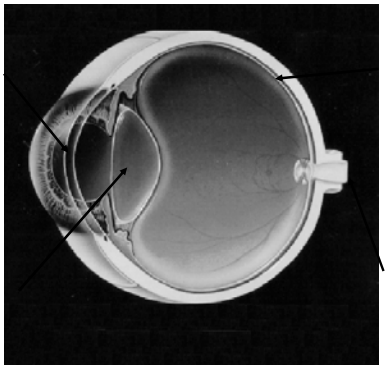
Harmful Effects of Hyperglycemia (cont.)

- Increased activation of some isoforms of protein Kinase C (PKC) causing reduced vascular contractility and oxidative stress
- Increased sialic acid levels in the blood
- Increased coronary artery disease
- Increased dental cavities and gum disease
- Increased weight
- Increased incidence of cataracts & glaucoma
- Numerous other problems like skin problems, ED, depression, foot disorders

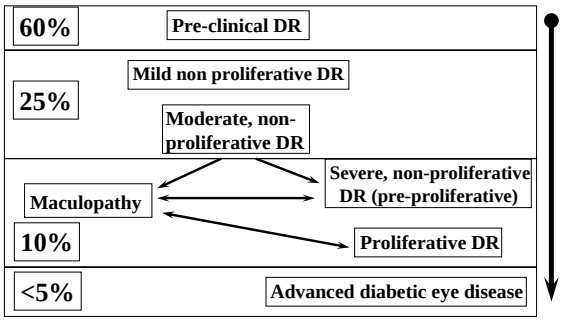
Treating Diabetes Complications

- Retinopathy: Normalize Blood Glucose, Annual Dilated Pupil Exams, Laser Therapy and Vitrectomy if needed
- Nephropathy: Normalize Blood Glucose, ACE Inhibitors
- Neuropathy: Normalize Blood Glucose, Capsaicin, Gabapentin, Lyrica, Anti-Depressants (Cymbalta), Preventative foot care
- Cardiovascular disease: normalize glucose, statins, ACE-I, aspirin, anti-oxidants

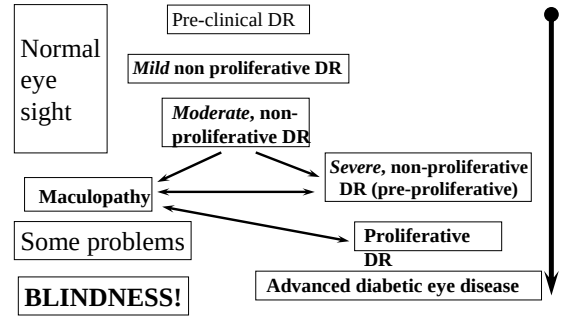
The Human Eye



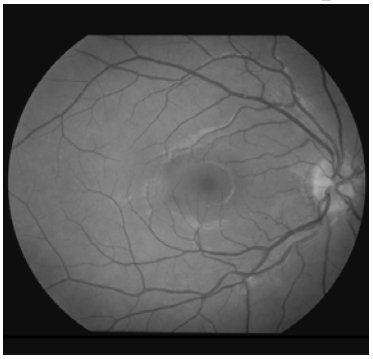
Natural History of Diabetic Retinopathy



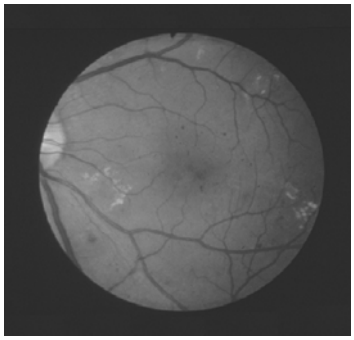
Natural History of Diabetic Retinopathy



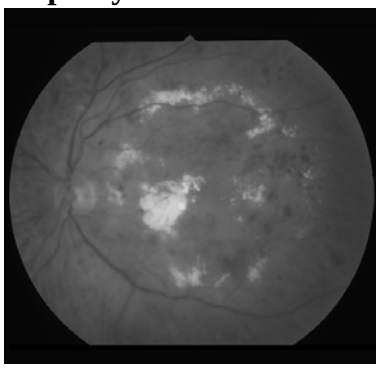
Pre-clinical Diabetic Retinopathy



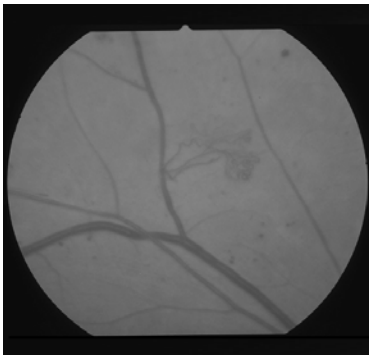
Moderate NPDR:
Red Lesions and Hard Exudates



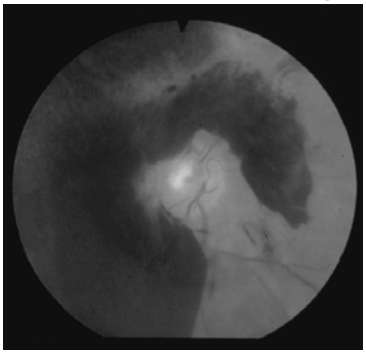
Maculopathy



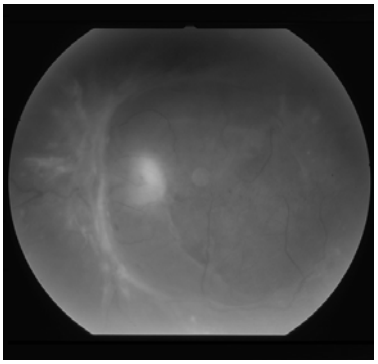
PDR: New Vessels Elsewhere



PDR: Vitreous Haemorrhage



ADED: Retinal Detachment



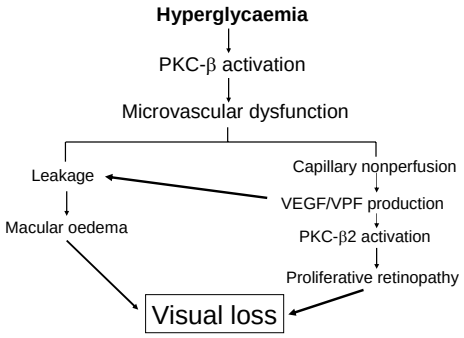
Treatment of DR:

- **Photocoagulation (laser therapy):**
  - **Panretinal (proliferative)**
  - **Focal and/or grid (maculopathy)**
  - **Vitrectomy**
- **Medical:**
  - **Metabolic control**
  - **Blood pressure control**

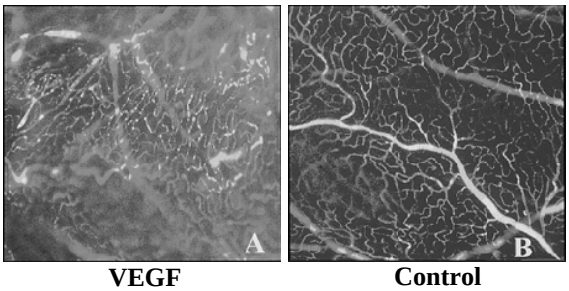
What should a person with diabetes do to prevent blindness?

- Keep blood glucose values as close as possible to non-diabetic levels [below 6.1 mmol/l (110 mm/dl) and below 7.8 mmol/l (140 mm/dl) after meals]
- Keep blood pressure below 130/80 mmHg
- HAVE HIS/HER EYES CHECKED ONCE A YEAR for diabetic retinopathy

Diabetic Microvascular Dysfunction

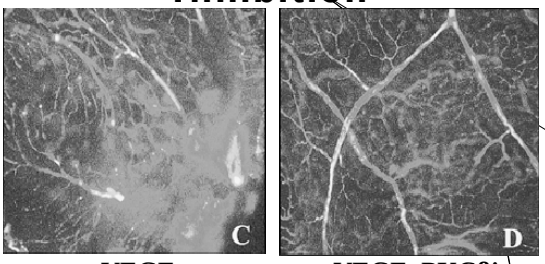


VEGF vs. Control



VEGF **Control**

VEGF and PKC-ß Inhibition



VEGF VEGF+PKCßi

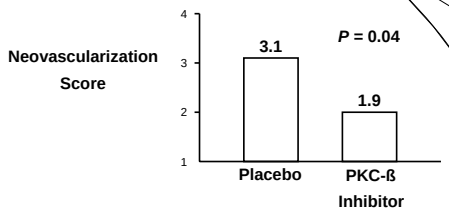
VEGF and PKC-ß

- PKC activation is critical step in hypoxic and hyperglycemic stimulation of VEGF expression
- PKC-ß activation is required for VEGF to induce its proliferative and permeability effects

PKC-ß Inhibition

- Selective inhibition of PKC-ß has been shown to block hyperglycemia-induced expression of VEGF at multiple points along the pathway
- Results in ameliorating effect on diabetes-induced vascular complications

Effect of PKC-ß inhibition on Neovascularization



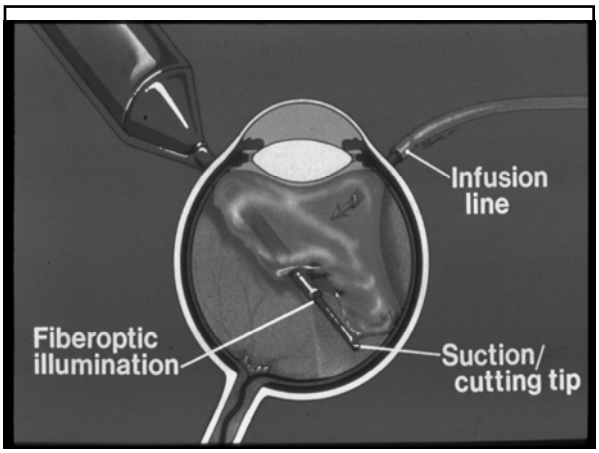
Danis P, et al. *IOVS* 1998; 39:171-179

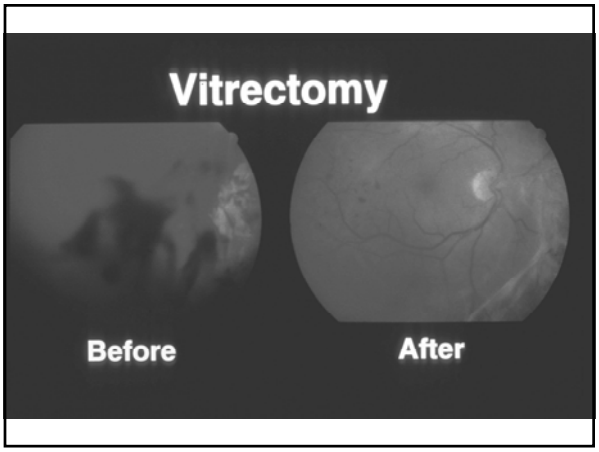
LY 333531 Ruboxistaurin

- Investigational compound in Phase III trials being developed as a pharmaceutical treatment for DR/DME
- Selective inhibitor of PKC-ß designed to measure reduction in progression of PPDR to PDR
- Being studied to treat underlying *cause* of DR/DME (hyperglycaemia-induced microvascular dysfunction) rather than treating symptoms

The natural history of diabetic retinopathy is well known,

BUT at present the only treatment available for sight-threatening retinopathy is with the laser, an invasive form of treatment





SKIN CONDITIONS FOUND IN DIABETES

Disorders of the skin that are usually associated with diabetes:

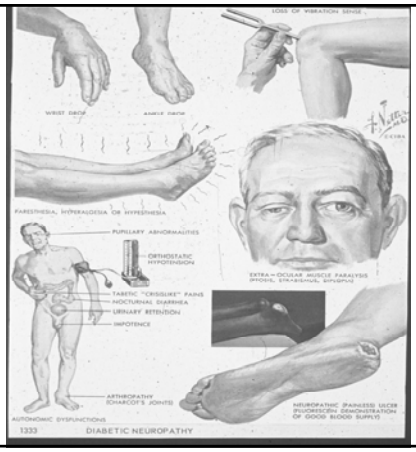
- Necrobiosis lipoidica diabeticorum
- Diabetic dermopathy (shin spots, brown spots)
- Lipodystrophy
  - Hypertrophy
  - Atrophy
- Insulin allergy
- Skin reactions to oral hypoglycemic agents

Disorders of the skin and other diseases that are frequently associated with diabetes:

- Skin infections
  - Bacterial infections
  - Moniliasis
  - Dermatophytosis
- Xanthomas
  - Xanthelasma
  - Xanthoma diabeticorum
- Arteriosclerosis obliterans
- Neuropathy
- Endocrine-metabolic
  - Acromegaly
  - Cushing's syndrome
  - Hemochromatosis
  - Xanthrochromia (carotenemia)

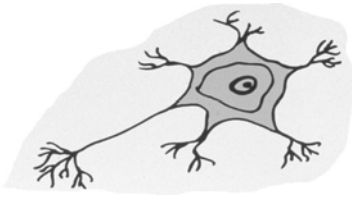
DIABETES & DEPRESSION

- The incidence of moderate depression in diabetes patients approaches 40 % of patients.
- The stress of living with diabetes and a chronic condition accounts for some of the increased incidence.
- Many diabetes patients are not evaluated nor treated for depression.



Diabetes Neuropathies

- Focal neuropathy
- Distal symmetrical polyneuropathy
- Autonomic neuropathy



Visceral (Autonomic) Neuropathies

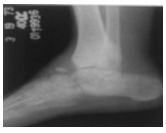
- Impaired CV reflexes
- Gastroparesis
- Diarrhea or constipation
- Neurogenic bladder
- Sexual dysfunction
- Neurotrophic arthropathy
- Neurotrophic ulcer

Chronic Complications: Autonomic Neuropathies

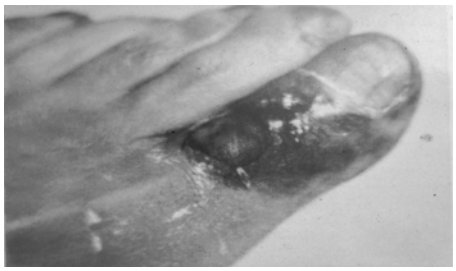
- Orthrostatic hypotension
- Reduced hypoglycemic awareness
- Bladder dysfunction
- Gastroparesis / Constipation
- Diarrhea
- Fecal incontinence
- Sexual dysfunction

Foot Problems: Warning Signs and Systems

- Loss of peripheral pulses
- Loss of distal foot and toe sensation
  - Semmes / Weinstein 10 gram monofilament testing



Diabetic Gangrene



Diabetics are prone to develop gangrene, especially of the toes and feet, as result circulatory embarvassment incident to atherosclerotic vascular disease. A minor injury or local dermatitis may be the immediate cause. Prompt and vigorous treatment of the diabetics as well as the local lesions is indicated.

Neuropathy

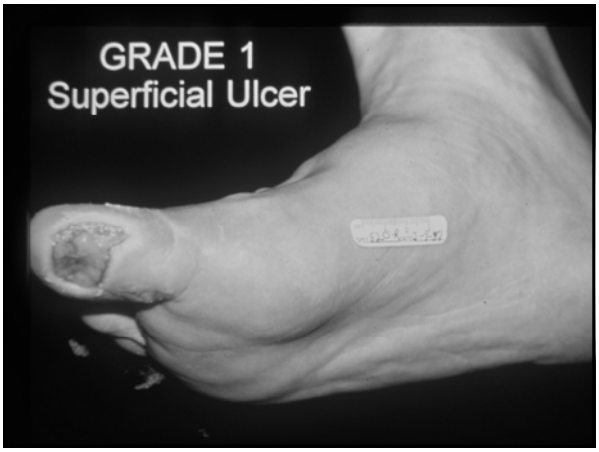
- Approximately 80% of lower extremity amputations (LEA) have a preliminary finding of PERIPHERAL NEUROPATHY
  - $27,000+ for LEA
  - $21,000+ for rehabilitation
- 50% of LEA's could have been prevented with proper foot care
- It is estimated that 15%–25% of diabetes patients will have a foot ulcer at some time over the course of their disease

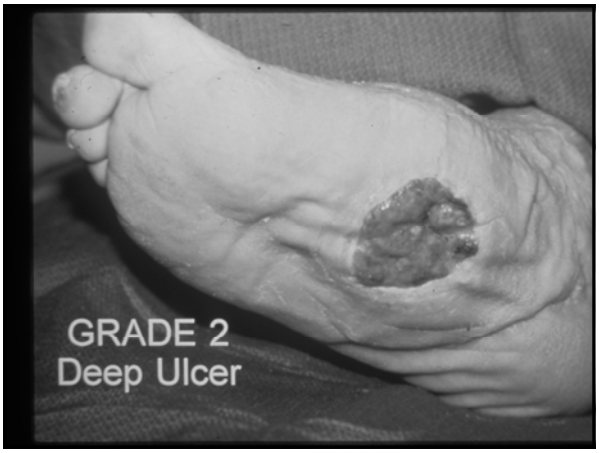
Neuropathy

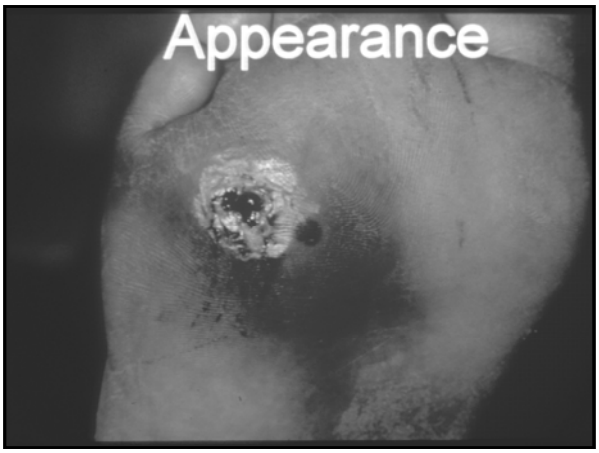
- Peripheral neuropathy can precipitate foot ulcers
- Vascular Disease inhibits healing
- Hyperglycemia inhibits healing

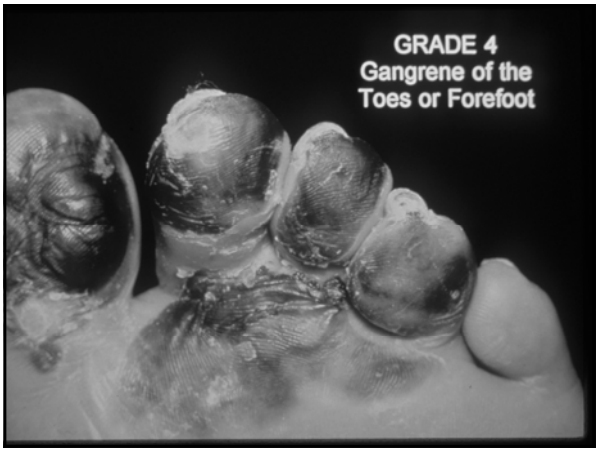
Neuropathy

- 4 mechanical ways to damage feet
  - Direct Injury
  - Ischemia
  - Repetitive Stress
  - Infection
- Avoid Iodine, hydrogen peroxide, astringents
- Control blood glucose levels
- Smoking cessation



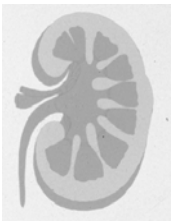



Appearance


GRADE 4
Gangrene of the
Toes or Forefoot


GRADE 5
Gangrene of
the Foot

Renal Complications of Diabetes:Nephropathy



- Assessment of serum creatinine and urinary protein
- Intensify glycemic control
- Normalize blood pressure => 130/80 mm Hg
  - Caution with calcium channel blockers, beta blockers
- Use of ACE inhibitors/ARB's
  - Role of angiotensin II
  - Reduced progression to ESRD
- Dietary counseling: low protein diet

Medications Used to Treat Diabetes Complications

- Tricyclic antidepressants, SSRI's (Cymbalta)
- Aspirin, NSAIDS, Anti Convulsants (Lyrica)
- Vitamin C, Vitamin E, MgCl, glucose tabs
- Reglan, Erythromycin, Antacids, PPI's, Capsaicin, Histamine 2 blockers
- ACE inhibitors, ARB's, diuretics, Trental, Plavix
- Ca channel blockers, tadalafil or sildenafil
- Lipid lowering meds (Zetia, Crestor, Lipitor)
- Hypoglycemic meds (oral agents and insulin)

Meds to Treat/Prevent CV Disease in Diabetes Patients

- Aspirin
- ACE Inhibitors or ARBS or both
- Statins plus Coenzyme CQ-10
- Ezetimibe and/or Fibrates
- Anti-Oxidants and other micro-nutrients, especially Magnesium, folic acid + B vitamins
- Normalize blood glucose levels with a good treatment regimen

Future **possible** Medications to Treat Microvascular Diabetes Complications

- **Ruboxistaurin (Arxxant)** is a PKC-Beta inhibitor. June 2005, Dr. Tuttle reported at ADA that it stopped the progression of kidney damage and reduced microalbuminuria by 25 %.
- **Benfotiamine** is a derivative of thiamine that blocks oxidative stress by activating transketolase**.**
- **PARP (Poly-ADP-ribose Polymerase) inhibitors** are being developed that block the 4 major pathways leading to oxidative stress and vessel damage.
- **Superoxide desmutase** will also block the oxidative stress pathways & hopefully will block complications.
- **Aldose Reductase Inhibitors: epalrestat** 300 mg/day improved retinopathy.
- **Alpha Lipoic Acid:** shows some promise with 2 large studies in progress.
- **Pimagedine:** inhibits AGE's and showed positive effects in treating nephropathy.