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 $\rightarrow$ Aldose Reductase $\rightarrow$ Sorbitol + NADP

Sorbitol + NAD $\rightarrow$ Sorbitol Dehydrogenase $\rightarrow$ 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
## Natural History of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical DR</td>
<td>60%</td>
</tr>
<tr>
<td>Mild non-proliferative DR</td>
<td>25%</td>
</tr>
<tr>
<td>Moderate, non-proliferative DR</td>
<td>10%</td>
</tr>
<tr>
<td>Severe, non-proliferative DR (pre-proliferative)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Proliferative DR</td>
<td></td>
</tr>
<tr>
<td>Advanced diabetic eye disease</td>
<td></td>
</tr>
</tbody>
</table>
Natural History of Diabetic Retinopathy

Normal eyesight

Pre-clinical DR

Mild, non-proliferative DR

Moderate, non-proliferative DR

Severe, non-proliferative DR (pre-proliferative)

Proliferative DR

Advanced diabetic eye disease

Maculopathy

Some problems

BLINDNESS!
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

Hyperglycaemia → PKC-β activation → Microvascular dysfunction → Leakage → Macular oedema → Visual loss → Capillary nonperfusion → VEGF/VPF production → PKC-β2 activation → Proliferative retinopathy
VEGF vs. Control

VEGF

Control
VEGF and PKC-β Inhibition

VEGF

VEGF+PKCβi
VEGF and PKC-β

- PKC activation is critical step in hypoxic and hyperglycemic stimulation of VEGF expression
- PKC-β activation is required for VEGF to induce its proliferative and permeability effects
Selective inhibition of PKC-β 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-β inhibition on Neovascularization

LY 333531 Ruboxistaurin

- Investigational compound in Phase III trials being developed as a pharmaceutical treatment for DR/DME
- Selective inhibitor of PKC-β 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, \textbf{BUT} at present the only treatment available for sight-threatening retinopathy is with the laser, an invasive form of treatment.
Vitrectomy

Before

After
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)
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.
Diabetic Neuropathy

- Wrist drop
- Ankle drop
- Paresthesia, hyperalgesia, or hypesthesia
- Pupillary abnormalities
- Orthostatic hypotension
- Tabetic "crisislike" pains
- Nocturnal diarrhea
- Urinary retention
- Impotence
- Arthropathy (Charcot's joints)
- Extraocular muscle paralysis (ptosis, strabismus, diplopia)
- Neuropathic (painless) ulcer (fluorescein demonstration of good blood supply)

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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

- Orthostatic 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
Diabetics are prone to develop gangrene, especially of the toes and feet, as result circulatory embarrassment 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.