Clinical Impact of Diabetes

- Major cause of premature death and disability in the United States
- Leading cause of new cases of blindness in working-aged adults
- 50% of nontraumatic lower extremity amputations
- 35% of new cases of end-stage renal disease
- 2–4 fold increase in cardiovascular risk

Status of Diabetes Management

- Majority of patients with type 2 diabetes have only fair to poor metabolic control
  - Fasting serum glucose levels of ≥200 mg/dL
  - HbA1C levels of 9%-10%
- Postprandial blood glucose levels average ~300 mg/dL
- < 2% of American adults with diabetes receive optimal quality of care

ADA Standards of Care

- Physician Visits: 2-4 per year
- HbA1C Measurement: 2-4 per year
- Fasting Glucose Measurement/ (SMBG): 4-6 per day/daily
- Foot Exams: Every Visit
- Aspirin: Daily
- Urine Protein Measurements: Yearly
- Blood Pressure: As needed to achieve goals
- Lipid Levels: As needed to achieve goals
- Dilated Pupil Eye Exam: Yearly
- Flu and Pneumovax: As needed

Causes of Diabetes Complications

- Health care delivery problems: lack of implementation of ADA standards of diabetes care; acute healthcare system
- Cultural, language, access barriers
- Genetic factors
- Sustained hyperglycemia resulting in pathophysiological changes and damage to small and large blood vessels
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

- Disseased blood pressure
- Hematologic factors affected adversely
- Increased platelet adhesiveness
- Increased serum fibrinogen levels
- Increased blood viscosity
- Increased blood clot reactivity
- 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 fatty 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 Aldose Reductase Sorbitol + NADP

Sorbitol + NAD Sorbitol Dehydrogenase Fructose + NADH
Harmful Effects of Hyperglycemia (cont.)
- Faulty lipid metabolism yields hypercholesterolemia and hypertriglyceridemia
- Increased neonatal morbidity and mortality
- Hemorrhheologic 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)

Dyslipidemias and Diabetes
- Enhanced VLDL Secretion
- Increased Small Dense LDL Production
- Hypertriglyceridemia
- Decreased HDL Secretion

Treatment 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, EB, depression, foot disorders

Major Chronic Complications of Diabetes
- Accelerated Macrovascular Disease
- Retinopathy
- Neuropathy
- Nephropathy
- Dermopathy
- Foot Problems
- Numerous Other

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-1, aspirin, anti-oxidants

Cardiovascular Risk Factors in Patients with Diabetes
- Hypertension
- Other (Inflammation)
- Dyslipidemia/ Atherosclerosis
- Insulin Resistance
- Hyperinsulinemia
- Genetics
- Glucose Intolerance or Diabetes
- Obesity
- Hypercoagulability
- LIFESTYLE
LIFESTYLE

Major Contributor to:
- Obesity
- Smoking
- Hypertension
- Dyslipidemia
- Insulin resistance/NIDDM

Glucose Intolerance/Diabetes

Lipid Abnormalities

- Risk trials such as MRFIT, Framingham, Whitehall and others have shown elevated cholesterol to be a positive predictor of:
  - Stroke
  - PVD-peripheral vascular disease
  - CHD-coronary heart disease
  - LEA-lower extremity amputation
- The most powerful predictor was decreased HDL
- Triglycerides are usually elevated in type 2 diabetes and increase the risk at any LDL/HDL combination
- CRP is emerging as a major risk factor

Chronic Complications: Hyperlipidemia

- Goals of therapy
  - Intensify glycemic control
  - Prescribe low fat diet
  - Initiating drug therapy

Obesity

- In the recent NHANES III Survey:
  - 33% of Caucasian women, 47% of Mexican American women, and 49% of African American women were overweight
- The risk of the development of type 2 diabetes increased 1.4 fold for every 17% increase in body weight
- Obesity increases the risk for developing hypertension by 6 fold over lean individuals
- Weight Reduction:
  - reverses many cases of secondary sulfonylurea failure, improves insulin sensitivity
  - In men: pant size of > 42 inches is a major indicator of IR
  - In Women: > 35 inches
Hypertension

- The single most important prognostic factor for cardiovascular risk in patients both with diabetes and those without.
- Virtually all patients with diabetes who have proteinuria also have hypertension.
- New guidelines suggest that BPs we thought were "OK" were probably harmful, especially for persons with diabetes.

Chronic Complications: Hypertension

- Normalize blood pressure
- Use of antihypertensive drugs
- Patient education regarding exercise and the use of sodium and alcohol
- Weight management counseling

The Effect of Diabetes on Blood Coagulation Factors

- Increased Fibrinogen
  - Also independently increased by smoking and age
- Increased Factor VII
- Increased vonWillebrand Factor (8)
- Increased levels of Tissue Plasminogen Activator Inhibitor (PAI-1)
- CRP (Inflammation)

Some Statistics on Smoking

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- Ohio '89 Direct medical costs related to smoking for those over 35 were $604 per person of which nearly 70% went to Hospital Care
- Smoking increases the risk for deterioration of retinopathy 3 fold

Why is Diabetic Eye Disease Newsworthy?

- More than 150 million people worldwide have diabetes
- Most people with diabetes will develop some form of eye complications
- Diabetes is the leading cause of blindness among working-age adults in industrialized countries
- With regular screening and earlier diagnosis, these numbers can be reduced
Risk of Complications in Type 1 Diabetes

Renal failure 15-20 x
Gangrene 20 x
Blindness 15-20 x
CHD 2-6 x
Coronary death 2-3 x
Stroke 2-3 x

Effect of Diabetes on Cardiovascular Disease (CVD) Death Rates

Age-Adjusted CVD Death Rate per 10,000 Person-Years

Diabetic patients
Nondiabetic patients

Progression of Nephropathy in Diabetes

Plasma creatinine
Glomerular filtration rate
Kidney failure
Microalbuminuria - Proteinuria

Prevalence of Retinopathy by Duration of Diabetes

% affected

Diabetologia 1994

Epidemiology of impaired vision in the elderly

Complications
Pathogenesis

Hyperglycemia
Aldose-Reductase
De-novo DAG
AGE formation

Diabetic complications

The Human Eye
Cornea
Lens
Retina
Optic nerve

Natural History of Diabetic Retinopathy

- Normal eye sight
- Pre-clinical DR
- Mild non-proliferative DR
- Moderate, non-proliferative DR
- Severe, non-proliferative DR (pre-proliferative)
- Maculopathy
- Proliferative DR
- Advanced diabetic eye disease

Pre-clinical Diabetic Retinopathy

60%
Pre-clinical DR

25%
Mild non-proliferative DR

25%
Moderate, non-proliferative DR

10%
Severe, non-proliferative DR (pre-proliferative)

<5%
Proliferative DR

<5%
Advanced diabetic eye disease
**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
    VEGF/VPF production
    PKC-β2 activation
    Proliferative retinopathy
  Visual loss

Capillary Nonperfusion

- As a result of vascular damage, some capillaries become occluded (nonperfused). As a result others dilate and become leaky
- Capillary nonperfusion is the result of diabetes-induced abnormalities of both the vessel wall and the circulating blood

Protein Kinase C-Beta

- Elevated blood sugar (hyperglycaemia) results in activation of PKC-β
- PKC-β has been linked to hyperglycaemia-induced microvascular dysfunction
- This dysfunction results in the development of DR/DME and other complications

VEGF/VPF Production

- Retina damaged by capillary nonperfusion induces production of growth factors such as VEGF (vascular endothelial growth factor)
- VEGF mediates a significant portion of retinal neovascularization (new blood vessels) and excessive vascular permeability (VP) characteristic of PDR

VEGF

Combines with receptor
  Translocation of PKC-β2 from cytosolic to membranous position
  Vascular proliferation
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, resulting in ameliorating effect on diabetes-induced vascular complications.

Effect of PKC-β inhibition on Neovascularization

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

**Hypertension and Diabetes**

- Hypertension Increases Risk of Nephropathy
- Hypertension Increases Risk of Retinopathy
- Diabetics Have More Hypertension
- Hypertensives Have More Diabetes
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

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

Erectile Dysfunction
Pathophysiology

- Organic
- Psychogenic
- Mixed


ED Is Vascular

Diabetes
Hypertension
Oxidative stress
Endothelial cell injury
Thrombosis
Erectile dysfunction
Atherosclerosis
Vasoconstriction
烟

Physiology of Erection

Stimulus
Nitric oxide (NO) released
cGMP formation
Penile smooth muscle relaxation
Penile erection

Outcomes

Tadalafil: Mechanism of Action

Sexual stimulation
Nitric oxide released
Guanylate cyclase
PDE5 isoenzyme
Cilia (tadalafil)
& other PDE5 inhibitors
Decreased cytosolic Ca2+
Penile smooth muscle relaxation
Penile erection

Female Issues

- Communication/relationship issues
- Desire/decreased ability to have an orgasm
- Post-menopausal changes/lubrication
- Confronting a partner’s ability to now get an erection
- Vaginal yeast infections in women with diabetes

Advantages of Tadalafil

- Not impacted by food or drink
- 36 hour duration of activity results in many benefits to both partners: reduces pressure, greater spontaneity
- No flushing, no increased heart rate, no effect on sperm, no blue haze, more specific inhibitor just in the penis
- Can be used with Flomax up to .4 mg/day

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 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

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

Foot Examination

- Sensory Foot Examination
  - Semmes-Weinstein 5.07 nylon monofilament has been standardized to deliver 10g force when apply properly
- Footwear Assessment
  - assess the patient’s shoes
  - inside for foreign objects
  - outside for deformities
  - assess the patient’s socks
- Vibration Sensation
- Patient Education—daily inspection of feet
Neuropathy

Foot Examination

- Sensory Foot Exam Form---Filled Out for at least One Foot
- Pedal Pulses: Yes or No
  • note on back of form
- Vibration Sensation: Yes or No
  • note on back of form
- Footwear Inspection

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, Pravix
- 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

Pharmacologic Management of Symptomatic DPN

- Nonsteroidal drugs occasionally help.
- Tricyclic Antidepressants: may be first line drugs but are rapidly being replaced by other agents like tramadol and gabapentin.
- Imipramine or amitriptyline at 25-150 mgm have some proven efficacy if drug levels are maintained.

Pharmacologic Management of Symptomatic DPN (cont)

- Mexiletine: Dosage up to 450 mg/day but has many side effects and should be used short term only.
- Carbamazepine: this anticonvulsant drug has shown benefit but adverse effects are common.
- New agents with proven efficacy include: Duloxetine, pregabalin, gabapentin, topiramate, lanotrigine and tramadol.

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.

Acute Complications:

Hypoglycemia
- Blood Glucose < 60 mg/dl with symptoms
- A common complication with intensified blood glucose control
- May not be recognized
- Treat promptly with glucose tablets or inject Glucagon if the patient is unconscious
-Precipitating Factors
- Medications, insulin activity timing
- Exercise, Diet

Hyperglycemia
- Sudden Onset
- Staggering, Poor Coordination
- Anger, Bad Temper
- Pale Color
- Confusion, Disorientation
- Sudden Hunger
- Sweating
- Eventual Stupor or Unconsciousness

- Gradual Onset
- Drowsiness
- Extreme Thirst
- Very Frequent Urination
- Flushed Skin
- Vomiting
- Fruity or Wine-Like Breath Odor
- Heavy Breathing
- Eventual Stupor or Unconsciousness
Type of Acute Diabetic Emergencies

- Comas
  - Hypoglycemia
  - Ketoacidotic hyperglycemia
  - Nonketotic hyperosmolar hyperglycemia (NKHNC)
  - Lactic acidosis
  - Uremia
  - Nondiabetic comas
- Infection
- Myocardial infarction
- Stroke
- Emergency surgery

TREATING DKA

POINTS TO CONSIDER

- Precipitating cause may be in 80% of patients
- ECG is indicated in all adult patients
- Isotonic saline preferred to rehydrate patients
- IV, insulin preferred
- DKA patients are deficient in total body K+ regardless of plasma K+ concentration
- Bicarbonate should be used only when indicated
- Preventing DKA is the long-term goal of good diabetes management

OTHER CONSIDERATIONS

- Cause of DKA must be aggressively pursued
- Other supportive therapy must be considered
- Be alert to complications of treatment
  - Persistent DKA
  - Constrictive heart failure
  - Aspiration pneumonia
  - Hypoglycemia
  - Cerebral edema and death

Guidelines for Treatment of Diabetic Ketoacidosis

Insulin

1. 10 units of regular insulin intravenously as a loading dose followed by 0.1 U/kg body weight thereafter until glucose concentration is 250-300 mg/dL and the pH ≥ 7.3 or HCO₃⁻ ≥ 18 mEq/L.
2. 10 units of regular insulin intravenously as a loading dose followed by 5-10 units per hour intramuscularly.
3. When control achieved:
   a. Return to previous insulin regimen, if known, and satisfactory.
   b. Use a modified closed loop system for the administration of insulin or a peripherally insulin regimen, if an internal strategy is necessary. The rates of insulin, glucose, and potassium administration are ~2-3 units, 10 g, and 2 mEq/hour.

Potassium

1. Measure potassium and obtain an electrocardiogram before adding potassium to parenteral fluids.
2. If the potassium is 4-5 mEq/L, incorporate 20 mEq K⁺ into each liter of isotonic saline and infuse at 1 L/hour.
3. Maintain K⁺ between 4-5 mEq/L.
   a. If 4-5 mEq/L, continue K⁺ at rate of 20 mEq/hour.
   b. If 3-5 mEq/L, decrease to 10 mEq/hour.
   c. If > 6 mEq/L, stop K⁺.
   d. If 3-4 mEq/L, increase K⁺ to 30 mEq/hour.
   e. If ≤ 3 mEq/L, increase K⁺ to 40-60 mEq/hour.

Bicarbonate

1. Not recommended for routine treatment of DKA.
2. Consider if other indications present.

Phosphate

1. Not routinely recommended.
2. Deficit is approximately 1.0 mmol/kg body wt.
3. Replace 25-50% in first 24 hours if serum PO₄ < 1.0 mg/dL.
4. 1.5-2.5 mmol phosphate/hour as the potassium salt (some circumstances may justify use of the sodium salt).

Fluids

1. Isotonic saline: Infuse at rate of 1-2 L for the first hour; 1L/hr for the 2nd, 3rd, and perhaps 4th hours, based upon intake and output measurements, clinical assessment of state of hydration. Where indicated use hemodynamic monitoring and make decisions based upon pressure measurements.
2. Hypotonic saline may be alternated with isotonic saline after the first 3 L of fluid at a rate of 500 mL/hour. The use of isotonic or hypotonic replacement fluids will be determined by clinical and laboratory considerations.
3. When the plasma glucose reaches 250-300 mg/dL, administer glucose at a rate of 5-10 g/hour, either as a separate infusion or combined with isotonic saline. If volume requirements remain high, "piggy-back" dextrose and water through the intravenous line; if volume replacement for correction of hypovolemia and dehydration no longer necessary, use 3%-10% dextrose and saline at 100 mL/hour.
Suggested Readings


RECOMMEND THAT YOU JOIN THE ADA AND SUBSCRIBE TO DIABETES CARE, DIABETES SPECTRUM AND CLINICAL DIABETES.