Diabetes: Treatment and Management

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What is diabetes?
• DM is a chronic disorder characterized by a lack of insulin or increased resistance to insulin
• Insulin is needed for proper uptake of glucose
• Clinical result is hyperglycemia
  – retinopathy
  – nephropathy
  – neuropathy

Statistics
• Approximately 23.6 million Americans with diabetes
  • ≈8.3% of total population
  • 11.3 % of adults
  • 25-30% undiagnosed (7 million)
• Another 79 million Americans have pre-diabetes and are likely to develop diabetes if do not change habits
  – 35% of adults age 20 or older

The Diabetes Epidemic
• Incidence has increased 13.5% from 2005, and over 700% in last 40 years
  • WHY??

The Diabetes Epidemic
• Improvements in diabetes care
  – Pts living longer with diabetes
• Increased number or minority populations in US
  – Rates of DM among minority populations are often 2-3 times greater
• Growth in elderly populations:
  – 10% > 60 vs 16-20% > 80
• Increasing prevalence of obesity which causes increased insulin resistance

Statistics
• In 2007, medical expenditures for diabetes $116 billion
  – $27 B direct care
  – $58 B to treat diabetes related complications
  – $31 B in excess general medical costs
• Medical costs 2.3 x higher in diabetic vs non-diabetic pt
• Actual national burden of diabetes likely exceeds $174 B when indirect costs considered
• Seventh leading cause of death in 2006
<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>TYPE 2</th>
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</thead>
<tbody>
<tr>
<td>• Formerly IDDM or juvenile onset</td>
<td>• Formerly NIDDM or adult onset</td>
</tr>
<tr>
<td>• Prevalence: 0.2%</td>
<td>• Prevalence: ≈8.0%</td>
</tr>
<tr>
<td>• 10% of all DM</td>
<td>• 90% of all DM</td>
</tr>
<tr>
<td>• Most common age of onset &lt; 30</td>
<td>• Most frequent age of onset &gt; 40</td>
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<tr>
<td>• Destruction of insulin producing B-cells in pancreas (auto-immune? viral?)</td>
<td>• Often asymptomatic</td>
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<tr>
<td>• Total lack of endogenous insulin</td>
<td>• Characterized by insulin resistance</td>
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<tr>
<td>• Need to be on insulin to survive</td>
<td>• Strong genetic predisposition</td>
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<tr>
<td></td>
<td>– One parent, 50% likelihood</td>
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<td>– Both parents, 80%</td>
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**Gestational Diabetes**

- Affects 4% of all pregnancies
- High risk populations:
  - Pregnant woman greater than age 25
  - Abnormal body weight
  - Have first degree relatives with diabetes
  - Hispanic, Asian, Native American, African American descent
- Screen in 24th to 28th week of pregnancy

**Pre-Diabetes**

- Blood sugar levels higher than normal, but not yet high enough to be diagnosed with DM
  - FBS: 100-126 mg/dl
  - A1c: 5.7-6.4
- ADA estimates 79 million Americans have pre-diabetes
  - 30 minutes of exercise combined with 5-10% reduction in body weight resulted in 58% reduction in diabetes

**Symptoms**

- Often asymptomatic, especially Type 2
- Classic symptoms
  - polydipsia
  - polyphagia
  - polyuria
- Others: weight loss, delayed wound healing, dry mouth, dry skin, recurrent infections, refractive changes
Risk Factors

- Family history
- Specific ethnic backgrounds
  - African Americans
  - Native Americans
  - Hispanic
  - Asian American
  - Pacific islander
- Sedentary Lifestyle

Pertinent medical history
- obesity
- cardiovascular disease
- HTN
- High cholesterol
- Polycystic ovarian syndrome
- Psychiatric illness
- Gestational DM
- IFG/IGT

Traditional Diagnosis

- Fasting blood glucose > 126 mg/dL
- OGTT > 200 mg/dL (2 hour sample)

- Random testing > 200 mg/dL with symptoms very suggestive of DM
- Any random testing >200 mg/dl should be referred for further testing

New Diagnosis Criteria

- Panel of "experts" at ADA annual meeting now recommend A1C be used for diagnosis of diabetes
- Glycosolated hemoglobin
- Tells blood sugar control over 3 months
  - normal range 4% to 6%

<table>
<thead>
<tr>
<th>HgbA1c</th>
<th>BS Level</th>
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<tbody>
<tr>
<td>4</td>
<td>60</td>
<td>9</td>
<td>210</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>10</td>
<td>240</td>
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<tr>
<td>6</td>
<td>120</td>
<td>11</td>
<td>270</td>
</tr>
<tr>
<td>7</td>
<td>150</td>
<td>12</td>
<td>300</td>
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<tr>
<td>8</td>
<td>180</td>
<td>13</td>
<td>330</td>
</tr>
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New Diagnosis Criteria

- ≥ 6.5 would be indicative of DM
  - First major change in 30 years
  - In adults and children, not pregnant women
    - Advantages:
      - Convenience: no fasting
      - More accurate: average over 3 months
    - Disadvantage:
      - Cost?

Recommended Criteria for Screening Asymptomatic Individuals for Type 2 DM

- All pts ≥45 yrs at 3 yr intervals
- Younger age or more frequently in pts who:
  - are obese
  - have a first-degree relative with diabetes
  - are members of high-risk ethnic population
  - gestational diabetes or delivered a baby > 9 lbs
  - are hypertensive
  - HDL < 35mg/dl or triglycerides > 250 mg/dl
  - have impaired glucose regulation

Treatment of Type 2 DM

- Goal: to produce desirable blood glucose levels with minimal adverse effects and maximal patient compliance
- Treatment begins with diet and exercise and ends with insulin
- Often, adequate control can be achieved with oral agents
  - If not, insulin is utilized
**Sulfonylureas**

- **Mode of action:**
  - increase insulin secretion and increase sensitivity of receptors
- **Side effects:**
  - low incidence of side effects or drug interactions; hyperopic refractive shifts
- **Contraindications:**
  - pregnancy, acute hyperglycemia

**Sulfonylureas**

- **First generation agents (ex Diabinese)**
  - more adverse effects
  - less expensive
- **Second generation agents (ex Glyburide)**
  - better absorption
  - more potent, so lower dosage
  - more expensive

**First generation**

- **Acetohexamide (Dymelor)**
  - beneficial for patients with gout
- **Chlorpropamide (Diabinese)**
  - long half-life; bad with renal disease
- **Tolazamide (Tolinase)**
  - slowest absorption of all sulfonylureas
- **Tolbutamide (Orinase)**
  - rapid metabolism; good with renal disease

**Second generation**

- **Glipizide (Glucotrol)**
  - only sulfonylurea that should not be taken with food
- **Glimepiride (Amaryl)**
  - no benefit over other agents
- **Glyburide (Diabeta, Micronase, Glynase)**
  - hyperopic shift, as much as 2 diopters

**Metformin: Glucophage**

- **Biguanide:** only one available in US
- **Mode of action:**
  - decreases hepatic production of glucose
  - increases peripheral glucose uptake by muscle
- **Used as second line to sulfonylureas or in combination with them**
- **Beneficial in obese patients**
- **May improve lipid profile**

**Metformin: Glucophage**

- **Side effects**
  - GI upset
  - lactic acidosis: very serious
- **Contraindications**
  - pregnancy
  - alcohol abuse
  - not with radiological contrast
  - with caution if renal impairment
Glitazones

• Class: Thiazolidinedines (TZD’s)
• Rosiglitazone (Avandia) and pioglitazone (Actos)
• Mode of action:
  – decreases insulin resistance
  – decreases glucose production
• Used as first line or in combo with sulfonylureas or metformin

Glitazones

• Side effects
  – HA’s: most common
  – increased fertility
  – weight gain
• Contraindications
  – pregnancy or breast feeding
  – hepatic insufficiency

Avandia

• NEJM May, June 2007: Avandia (rosiglitazone, GlaxoSmithKline) has an increased cardiovascular risk
  – Perhaps as much as 40%
  – Estimated that as many as 6 million people have taken drug since on market 8 years ago
    • Estimated US sales of $2.2 billion in 2006

Update

• July 2010
  – FDA Panel recommended keeping Avandia on market, but with warnings
    • Did not feel the evidence presented was overwhelming
  – Some new studies seems to indicate that risk may be almost the same with Actos
  – FDA did put stop to trial comparing Avandia and Actos due to safety concerns
• Controversy continues….

Update: Sept 24, 2010

• Avandia pulled from market in Europe
• Additional restrictions in US
  – US patients can only take if unable to control blood sugar with any other drug
  – If already on drug, must sign statement that they understand risks if wish to continue

Alpha-glucosidase Inhibitors

• Acarbose (Precose) and Miglitol (Glyset)
• Mode of action:
  – decreased absorption of glucose in intestines
• Used alone or in combo with sulfonylureas
• Side effects:
  – mild GI symptoms (universal)
• Contraindications:
  – inflammatory bowel disease, pregnancy
Meglitinides

- Repaglinide (Prandin) and Nateglinide (Starlix)
- Mode of action:
  - Increase insulin secretion from pancreas
- Used alone or in combo with metformin
- Best used to control mealtime glucose
- Side effects:
  - HA’s, GI symptoms, hypoglycemia
- Contraindications:
  - Liver or renal dysfunction, pregnancy

Exenatide (Byetta)

- Injectable drug used to treat Type 2 DM
  - Synthetic hormone (incretin mimetic) that increases insulin secretion from pancreas, slows absorption of glucose from the gut, and reduces action of glucagon
  - Also reduces appetite
  - Injected 30-60 minutes before first and last meal of the day
- FDA approved May 2005

Exenatide (Byetta)

- Can be used in conjunction with sulfonylureas, TZDs or metformin
- Side effects: hypoglycemia, gastrointestinal
  - Concern regarding acute pancreatitis
    - August 2008 four additional deaths reported.
    - FDA considering labeling change
- Long Acting Release formula injected once weekly is being studied
  - Initial reports show more effective A1c control with additional weight loss vs. bid
  - Also investigating nasal administration

DPP-4 Inhibitors

- Relatively new class of medications
- Prevents breakdown of a naturally occurring compound in body, GLP-1, which reduces blood glucose levels in the body
- These allow GLP-1 to remain active in the body longer, and lower blood glucose levels ONLY when they are elevated
  - NO risk for hypoglycemia

DPP-4 Inhibitors

- Sitagliptin (Januvia™ by Merck)
  - FDA approved October 2006
  - Taken orally once a day
  - Side effects:
    - Include URI, stuffy nose, and HA
  - Contraindications:
    - Pregnancy, renal insufficiency
    - If taken with sulfonylureas, lower dose of sulfonylurea may be indicated
    - Caution with Digoxin

DPP-4 Inhibitors

- Saxagliptin (Onglyza) by Bristol-Myers Squib/AstraZeneca
- Second approved DPP-4 Inhibitor
  - FDA approved July 2009
  - Once a day
## DPP-4 Inhibitors
- Alogliptin (Nesina, Takeda Pharmaceuticals)
- FDA approved January 2013
- 14 clinical trials; 8,500 patients
  - Safe and effective
  - Reduced HbA1c at 6 mos by 0.4-0.6 points
- Kazano=alogliptin and metformin
- Oseni=alogliptin and pioglitazone

## Pramlintide Acetate (Symlin)
- Synthetic analog of human amylin, a naturally occurring hormone found in the beta cells of the pancreas
- Used as injection in Type 1 or Type 2 DM in conjunction with mealtime insulin

## Liraglutide (Victoza)
- Once daily injected medication for tx of type 2 DM
  - FDA Approved January 2010
- GLP-1 receptor agonist which helps the pancreas create more insulin after a meal

## Insulin
- Mode of action:
  - replaces insulin in body
- Used with type 2 patients who do not respond to oral agents
- Side effects:
  - redness, swelling, itch at injection site
  - risk of hypoglycemia
- Contraindications: hypersensitivity

## Insulin
- Insulin Pumps
  - Mimics natural insulin patterns
- Long acting Insulins
  - Glargine (Lantus) and Detemir (Levemir)
  - Last 24 hrs with no peak
  - More expensive than traditional insulin
- Inhaled insulin
  - FDA approved Jan 2006 (Exubera by Pfizer)
  - Removed from market 2010
    - Poor sales?
    - Lung CA?

## ACE Inhibitors
- Ex lisinopril (Prinivil), benazaopril (Lotensin), captopril (Capoten) etc
- Typically used for treatment of hypertension
- With diabetes: Used for kidney-protective properties to help prevent ESRD
Current recommendations for Treatment of DM

- Control BS levels
  - HgbA1c < 7
- Control HTN
- Control Cholesterol levels
  - Total cholesterol < 200
- No smoking
- Exercise
- Yearly foot exams, dental exams, and dilated retinal exams

Diabetic Retinopathy

- Leading cause of blindness 20-74 year old
- 8-12% of all new cases of legal blindness
- 50,000 Americans legally blind
- Early diagnosis and treatment can decrease vision loss by 50-60%
- Factors which influence development of DR
  - duration of disease
  - control of BS

Diabetic Retinopathy

- Duration of Disease:
  - <10 years 1%
  - 11-13 years 23%
  - > 16 years 60%
- Control of BS (UKPDS)
  - for every 1% decrease in HgbA1C there is a 35% reduction in risk for retinopathy

Diabetic Retinopathy

- Joslin Diabetes Center study
  - Only 60% of DM's receive "timely eyecare"
  - $624 million and 400,000 patients' sight saved if annual eye exam and appropriate treatment
  - March 2001: *Ophthalmology* 35% of DM reported no annual DFE

Diabetic Retinopathy

- Non-proliferative Diabetic Retinopathy (NPDR)
  - mild
  - moderate
  - severe
  - very severe
- Proliferative Diabetic Retinopathy (PDR)
  - Including high-risk

Nonproliferative Diabetic Retinopathy (NPDR)

- Loss of retinal capillary pericytes
- Weakens capillary walls
- Causes non-perfusion in capillary beds and hypoxia
- Divided into mild, moderate, and severe (and very severe)
### Mild NPDR
- Microaneurysms (ma)
- Dot/blot hemorrhages

Follow-up: 1 yr
- 5-10% of pts with no retinopathy will progress to retinopathy within 1 year
- 5-10% with mild NPDR will also progress within 1 year

### Moderate NPDR
- Marked hemorrhages/ma
- Cotton wool spots (CWS)
- Venous beading (VB)
- Intra-retinal microvascular abnormalities to mild degree (IRMA’s)

Follow Up: 6 months
- as many as 16% of pts with mod NPDR can progress to proliferative disease within 4 years

### Severe/ Very Severe NPDR
- 4-2-1 Rule:
  - Marked hemes/ma in all 4 quadrants
  - VB in 2 or more quadrants
  - Marked IRMA’s in one quadrant
- Very severe: 2 of the 3 above criteria

Follow-up: 3-4 months
- Between 10-50% of pts with this level progress to PDR within 1 year
- Laser is sometimes recommended
  - Type 2 DM, associated with a 50% reduction in the rate of severe vision loss, vitrectomy and progression to high-risk PDR

### Proliferative Diabetic Retinopathy (PDR)
- Hallmark is retinal neovascularization
  - response to ischemia from capillary closure
  - grow onto lattice of vitreous
  - new vessels are fragile and easily rupture
- Neo divided into 2 categories
  - NVD: on or within 2 DD of optic disc
  - NVE: neovascularization elsewhere

Follow-up: Retinal consult within 2 weeks

### High Risk PDR
- NVD >1/4 to 1/3 disc area
- Any NVD with a PRH or VH
- Moderate to severe NVE with VH or PRH
- Poses very high risk of severe VH and vision loss within 2 years

Follow-up: Immediate Retinal consult (24-48 hours)

### Clinically Significant Macular Edema (CSME)
- Characteristics
  - retinal thickening at or within 500 microns (1/3 DD) of center of macula
  - hard exudates at or within 1/3 DD if associated with thickening of adjacent retina
  - thickening greater than 1 DD in size part of which is within 1 DD of center of macular
- May occur at any stage of retinopathy
- Treatment: retinal consult within 2 weeks
CSME

- Level of Retinopathy
  - mild NPDR = 3%
  - moderate to severe NPDR = 40%
  - Proliferative = 71%

- Type 2: Duration and Insulin
  - no insulin
    - 10 years 5%
    - 20 years 15%
  - on insulin
    - 10 years 10%
    - 20 years 30-35%

Care of the diabetic patient

- Dilated retinal exams
- Timely intervention and referral to retinal specialist
- Patient education
  - inform of ocular side effects
  - retinopathy possible even with good vision
  - report ocular symptoms associated with DM
  - advise about organizations for support