DIABETES MELLITUS
Lois E Brenneman, MSN, ANP, FNP, C

DIABETES MELLITUS

EPIDEMIOLOGY

- Prevalence is 7% persons aged 45-64 yrs; significantly increased in >65 yrs
- Highly endemic in certain populations: black, Hispanic Native American, Asian
- Highly under-diagnosed (8 million people are unaware)
- Retinopathy at least 7 years before clinical diagnosis
- Higher risk for CHD, CVA, PVD; higher incidence dyslipidemia, HTN, obesity

DEFINITION:

Heterogeneous group of disorders caused by relative or absolute insulin deficiency resulting in abnormal CHO and fat metabolism

EPIDEMIOLOGY AND CATEGORIES:

Type I diabetes

- Old terminology: Insulin dependent diabetes mellitus (IDDM)
- 10-15% of persons w diabetes
- Peak incidence 10-15 yrs (11.5 per 100,000 children)

Type 2 diabetes (old terminology NIDDM)

- Old terminology: Non-insulin dependent diabetes mellitus (NIDDM)
- 85-90% of persons with diabetes have Type 2
- Effects 22.7 per 10,000 persons
- Peak incidence 50-55 yrs
- Risk Factors: advanced age, family history obesity, sedentary life-style, gestational DM, others
- Prevalence: much higher in American blacks, Hispanics and Native Americans.
### RISK FACTORS FOR DEVELOPING TYPE II DIABETES

- Race
- Certain medications
- Stress
- Inactivity
- Family history
- Age
- Pregnancy
- High Cholesterol
- Obesity

### Type I diabetes

- Destruction of pancreatic beta cells
  - Insulin deficiency
  - Hyperglycemia
- Multiple etiologic factors
  - Genetic susceptibility
  - 50% concordance in ID twins
  - 90% in type II
- Viral infections: possibly Coxsackie virus, mumps
- **Autoimmune phenomenon** - 90% have islet cell antibodies within first year of diagnosis

### Type II diabetes

Combination of 3 Factors contribute to elevated glucose levels

1. Increased hepatic **glucose production**
2. Peripheral **insulin resistance** in muscles
   - Causes increased basal insulin secretion
   - Eventually pancreatic exhaustion
3. **Pancreatic exhaustion**: impaired pancreatic insulin secretion
   - Increased basal insulin secretion

### ABNORMAL GLUCOSE METABOLISM-REGULATION

- **LIVER**: Increased glucose production
- **MUSCLE**: Peripheral insulin resistance
- **PANCREAS**: Impaired insulin secretion

Elevated glucose levels
INSULIN RESISTANCE

- Impaired biologic response to endogenous or exogenous insulin in tissues
- Insulin resistance with impaired secretion are defining features of type 2 DM
- Insulin resistance syndrome: group of related clinical/laboratory findings
  glucose intolerance, central obesity, dyslipidemia, hypertension, altered fibrinolysis

Etiology

defective insulin-mediated glucose uptake and utilization which reflects the inhibition of
  glucose transport

Pharmacologic treatment

- Glucophage (metformin)
- Rezulin (troglitazone) and others in this class

Drug treatment for primary prevention not currently available

Studies underway to determine which treatments may help or delay onset *

- Lifestyle modification and metformin are being examined
- Troglitazone arm of study was pulled due to idiopathic liver failure

Major contributing factor to hyperglycemia

Strongly associated w macrovascular complications (from resistance -> hyperinsulinemia)

- Cardiovascular
- Cerebrovascular
- PVD

* Diabetes Prevention Program (DPP) National Institute of Diabetes and Digestive and Kidney Disease

DIAGNOSIS

Clinical Signs and Symptoms:

Type I diabetes

- Polyuria, polydipsia, polyphagia - “3 ‘Ps” - weight loss, fatigue, irritability.
- May be in frank ketoacidosis at time of diagnosis (not uncommon)

Type II diabetes

- Relatively asymptomatic
- 3 ‘Ps’ - less common; presentation may be more mild
- Fatigue is most common symptom; visual changes common
- Recurrent infections, visual difficulties and peripheral neuropathies.
- Polydipsia and polyuria does occur but is not as marked as Type I
- Commonly diagnosed on routine exam e.g. work physical, etc.

Laboratory testing

U/A not useful DX for following DM (except for DKA)

- Most DM “spill” sugar into urine at some time but not reliable
- Elderly may not ‘spill’ glucose even at relatively high blood levels
- Amount of glycosuria is dependant on age, pregnancy, etc.

Ketones testing - advisable esp during illness to monitor for ketoacidosis
Blood glucose preferred. DX if any one of following

- One random BS > 200 w classic s/s
- 2 FBS > 140 mg/dl
- GTT (75 g load): BS > 200 at 2h and 1 other time between 0-2h.

HgbA1c - used to monitor know DM - not used as screening test

- Monitors glucose levels over a longer period of time - 4 months or so
- Measure of levels over time vs FBS which can fluctuate widely
- Values take precedence over FBS in making therapeutic decisions

RECOMMENDATIONS FOR DIABETES SCREENING OF ASYMPTOMATIC PERSONS

Test at age 45; repeat q 3 yrs for pts 45 or older

Test before age 45; repeat more frequent then q 3 yrs if risk factors

- Obesity: >20% of IBW or BMI 27 kg/m2
- First degree relative w DM
- Member of high-risk ethnic group (black, Hispanic, Native American, Asian)
- History of gestational diabetes or delivering baby > 9 lbs
- Hypertensive >140/90 mm Hg
- HDL < 35 mg/dl and/or triglyceride level > 250 mg/dl
- History impaired GTT or impaired FBS on prior testing


CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS AND IMPAIRED GLUCOSE HOMEOSTASIS

Normal Glucose homeostasis

- FBS < 110 mg/dl
- 2 hr PPG < 140 mg/dl

Impaired glucose homeostasis

- FBS 110-126 mg/dl
- 2 hr PPG 140-199 mg/dl

Diabetes Mellitus *

- Random glucose > 200 mg/dl
- FBS >126 mg/dl
- 2 hr PPG <140 mg/dl

* Guidelines call for symptoms of DM (polyuria, polyphagia, polydipsia and unexplained weight loss) plus positive findings on any 2 of above 3 tests on different days

DIABETIC COMPLICATIONS

- Mechanism independent of glucose metabolism
- Insulin-mediated biochemic pathways lead to
  - enhanced vascular smooth muscle proliferation,
  - platelet adhesiveness
  - vasoconstriction
- Cardiovascular disease increases w DM; greater w coexisting hyperlipidemia
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TREATMENT GOALS:

- Reduce diabetic symptoms
- Prevent acute complications DKA, hyperosmolar-nonketotic coma, hypoglycemia
- Achieve normal growth and development for children
- Prevent long-term sequelae of DM
  - Diabetic retinopathy, nephropathy, neuropathy, gastropathy, etc.
  - Controversy exists as to whether such is possible

THERAPEUTIC APPROACH TO IMPAIRED FASTING GLUCOSE

- Start with lifestyle modification
- Pharmacologic therapy has not improved prognosis and has risk of hypoglycemia
DCCT (Diabetics Control and Complications Trial) statement

Ultimate goal is normalization or near normalization of blood glucose within the constraints of hypoglycemia.

Results published in New England Journal of Medicine 329 (14), September 30, 1993

Established that keeping blood glucose levels as close to normal as possible slows onset and progression of eye, kidney and nerve disease - any sustained lowering helps even if person has history of poor control (1441 volunteers with Type 1 from 1983-1993)

National Institute of Diabetes and Digestive and Kidney Diseases (part of NIH)

<table>
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<th>THERAPEUTIC GOALS FOR DIABETES</th>
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<tr>
<td>Short-term goals</td>
</tr>
<tr>
<td>- Correction of hyperglycemia and ketosis</td>
</tr>
<tr>
<td>- Elimination of hypoglycemia</td>
</tr>
<tr>
<td>- Integration of pt back into society</td>
</tr>
<tr>
<td>Long-term goals</td>
</tr>
<tr>
<td>- Preservation of residual insulin prod in type I</td>
</tr>
<tr>
<td>- Early physiologic insulin replacement</td>
</tr>
<tr>
<td>- Facilitating long term glycemic control</td>
</tr>
<tr>
<td>- Forestalling &quot;brittleness&quot;</td>
</tr>
<tr>
<td>- Attain/main near-normal body wt</td>
</tr>
<tr>
<td>- Optimize insulin sensitivity</td>
</tr>
<tr>
<td>- Minimize insulin requirements</td>
</tr>
<tr>
<td>- Optimize cardiovascular risk</td>
</tr>
<tr>
<td>- Optimize physical fitness</td>
</tr>
<tr>
<td>- Realistic exercise schedules</td>
</tr>
<tr>
<td>- Optimum weight maintenance</td>
</tr>
<tr>
<td>- Improves insulin sensitivity, cardiovascular risk</td>
</tr>
<tr>
<td>- Prevention of microvascular complications</td>
</tr>
<tr>
<td>- Optimum glycemic control</td>
</tr>
<tr>
<td>- Normotension</td>
</tr>
<tr>
<td>- Avoid excess sodium and protein intake</td>
</tr>
<tr>
<td>- Prevention of macrovascular disease</td>
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<tr>
<td>- Aggressive conventional risk factor reduction</td>
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ROLE OF WEIGHT IN TYPE 2 DIABETES

- Ideal Body Weight (IBW)
  - Females: 100 for first 5 ft; 5 lb each add inch
  - Males: 106 for first 5 ft; 5 lbs each add inch
  - +/- 10% for small/large frames

- Ideal may not be achievable but reducing obesity markedly improves control
- Most Type 2 diabetics would not be diabetic at normal weight
- Increasing obesity increases risk of developing Type 2 diabetes
- Type 1 diabetics are not typically overweight esp when young

DIETARY THERAPY

- Consult with dietitian for all Type 2 is beneficial
- Studies suggest that high CHO with high fiber actually improves diabetic control

Control of obesity is key to treating Type 2 diabetes
- 80% are obese
- Obesity contributes to insulin resistance
- Even modest weight reduction produces significant improve diabetic control
- Behavior modification, support groups, family
- Participation necessary to achieve goals
- Certain oral hypoglycemics promote weight gain (sulfonylureas, "glitazones")

Diet composition less critical for type II than achieving IBW

Dietary goals
- Emphasis CHO counting and consistency: complex CHO, high fiber is goal
- Three (3) meals and 315 gm CHO snacks to cover insulin peaks
- Fat intake:
  - Fat gram counting; maintain low fat intake (<30%)
  - Significant content should be polyunsaturated
- Sodium intake: less than 2000 mg/day
- Optimize fiber intake
- Limit protein intake esp if renal compromise

- Recommended distribution
  - CHO: 55-60%
  - Fat 25-35% (prefer < 30%)
  - Protein 15-20%
- Carbohydrates (CHO consumption should be complex and high fiber)
- Insulin matching to total CHO through gram counting may allow modest dietary sucrose
Glycemic Index

- **Compares rise in blood sugar after ingestion of simple sugars/CHO**
- Equal amounts of starch may not cause equal rise in glucose
- Example: potatoes and pasta contain equal calories; potatoes have less rise
- Developed 1981: measures rise in blood glucose after consumption of particular food
- High index foods result in rise in blood glucose which triggers increased insulin
- Increased secretion “overshoots” glucose level so blood glucose falls
- Hypoglycemia/hunger result from increased pancreatic insulin
- Further intake of CHO follows -> increase blood sugar
- Continuous cycling (months/years) stresses glucose control mechanism -> insulin resistance

<table>
<thead>
<tr>
<th>Glycemic Index of Common Foods</th>
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<tbody>
<tr>
<td>Puffed rice</td>
<td>Carrot</td>
</tr>
<tr>
<td>Rice cakes</td>
<td>Rolled oats</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>Banana</td>
</tr>
<tr>
<td>Sugar</td>
<td>Corn</td>
</tr>
<tr>
<td>Bread white</td>
<td>Rice</td>
</tr>
<tr>
<td>Bread wheat</td>
<td>Honey</td>
</tr>
<tr>
<td>Sugar</td>
<td>All bran cereal</td>
</tr>
<tr>
<td>Baked potato</td>
<td>Kidney Beans</td>
</tr>
</tbody>
</table>

**ADA Diet** 7 food groups
- Protein, bread, fruit, milk, fat, low and intermediate CHO, vegetables.
- Based on exchange system

**Fiber**
- Insoluble (bran, celery)
- Soluble globular fiber (pectin in fruit)
- Delays glucose absorption; attenuate the PP glucose peak.
- Lowers elevated triglycerides often present.

**ROLE OF EXERCISE**

- Increases cellular glucose uptake via increasing numbers of cell receptors.
- Insulin absorbed more rapidly if injected into limb which is then exercised -> hypoglycemia
- Hypoglycemia with exercise is common with Type 1
  - Snack before exercise is helpful
  - Decrease dose of insulin which would peak during time frame of exercise
  - Avoid exercise during insulin peak period; avoid exercise recently injected extremity
**ROLE OF MEDICATIONS**

**Type 1** - Insulin is the only option  

**Type 2**  
Oral hypoglycemic agents can be used  
Insulin is used where oral agents fail

### ORAL HYPOGLYCEMICS

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Secretagogue (stimulates pancreatic insulin secretion)</td>
</tr>
<tr>
<td></td>
<td>glipizide (Glucotrol)</td>
</tr>
<tr>
<td></td>
<td>glimepiride (Amaryl)</td>
</tr>
<tr>
<td></td>
<td>glyburide (Glynase)</td>
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<tr>
<td>Biguanides</td>
<td>Insulin sensitizer</td>
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<tr>
<td></td>
<td>metformin (Glucophage)</td>
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<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Decreases insulin peak via inhibit breakdown of CHO</td>
</tr>
<tr>
<td></td>
<td>acarbose (Precose)</td>
</tr>
<tr>
<td></td>
<td>miglitol (Glyset)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Reduces insulin resistance</td>
</tr>
<tr>
<td></td>
<td>pioglitazone (Actos)</td>
</tr>
<tr>
<td></td>
<td>rosiglitazone (Avandia)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Secretagogue (stimulates pancreatic secretion)</td>
</tr>
<tr>
<td></td>
<td>repaglinide (Prandin)</td>
</tr>
<tr>
<td></td>
<td>nateglinide (Starlix)</td>
</tr>
</tbody>
</table>

* Different mechanism than sulfonylurea

### TIME ACTIVITY OF HUMAN INSULINS

<table>
<thead>
<tr>
<th>INSULIN TYPE</th>
<th>ONSET (HR)</th>
<th>PEAK (HR)</th>
<th>EFFECTIVE DURATION (HR)</th>
<th>MAXIMUM DURATION (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Lispro</td>
<td>&lt;0.25</td>
<td>1</td>
<td>3.5-4.5</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1.0</td>
<td>2-3</td>
<td>3-6</td>
<td>4-6</td>
</tr>
<tr>
<td>NPH</td>
<td>2-4</td>
<td>4-10</td>
<td>10-16</td>
<td>14-18</td>
</tr>
<tr>
<td>Lente</td>
<td>3-4</td>
<td>4-12</td>
<td>12-18</td>
<td>16-20</td>
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<tr>
<td>Ultra lente</td>
<td>6-10</td>
<td>Varies with dose</td>
<td>18-20</td>
<td>20-30</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1.1</td>
<td>None</td>
<td>&gt;24</td>
<td></td>
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