Diabetes and Nondiabetic Hypoglycemia
Diabetes Mellitus
Definition

- A group of diseases characterized by high blood glucose concentrations resulting from defects in insulin secretion, insulin action, or both.
A crisis in the making

Millions of Americans Diagnosed with Diabetes
A Crisis in the Making

- 20 million American adults have impaired glucose tolerance (IGT)
- 13-14 million Americans have impaired fasting glucose (IFG)
- 40-50 million Americans have metabolic syndrome
- In 2002, diabetes-related costs in the US were $132 billion
- Average annual cost for medical care for people with diabetes is $13,243 vs $2,560 for persons without diabetes
American Diabetes Association
Standards of Care
Welcome!

You are connected to the National Guideline Clearinghouse™ (NGC), a public resource for evidence-based clinical practice guidelines. NGC is an initiative of the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. NGC was originally created by AHRQ in partnership with the American Medical Association and the American Association of Health Plans (now America’s Health Insurance Plans [AHIP]). Click on About NGC to learn more about us.

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NGC News

NGC seeks your input! Tell us what you like and don’t like. What changes or additional features would you like to see? Tell us how we can improve your experience.

What’s New this Week

- New/updated AAP, CDC/AAP/AEP, GINA, GOLD, and ICSI guidelines.
- New submission: The Infectious Diseases Society of America and the American Thoracic Society have released consensus guidelines on the management of community-acquired pneumonia in adults.

The 4th annual Guidelines International Network (G-1-N) conference, will be held August 22-25, 2007. Register online beginning January 15th. Submit abstracts until March 29th.

Pandemic/Avian Flu Resources: Visit www.pandemicflu.gov for valuable community and healthcare resources.
Diabetes and Prediabetes

**Types**

- Type 1 (formerly IDDM, type I)
- Type 2 (formerly NIDDM, type II)
- Gestational diabetes mellitus (GDM)
- Prediabetes (impaired glucose homeostasis)
- Other specific types
Diabetes Type 1

Represents about 5-10% of all cases of diabetes

Two forms

- Immune mediated—beta cells destroyed by autoimmune process
- Idiopathic—cause of beta cell function loss unknown

Diabetes Care, 30;S1, January 2007
Type 1 Diabetes

In the human cell, insulin must bind with receptors before glucose can enter the cell. Without enough insulin, very little glucose is transported to the cell.

Type 1 Diabetes

1. The stomach changes food into glucose.
2. Glucose enters the bloodstream.
3. The pancreas makes little or no insulin.
4. Little or no insulin enters the bloodstream.
5. Glucose builds up in the bloodstream.

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Diabetes Type 1 Symptoms

- Hyperglycemia
- Excessive thirst (polydipsia)
- Frequent urination (polyuria)
- Significant weight loss
- Electrolyte disturbance
- Ketoacidosis
Type 1 Diabetes Causes

- Immune-mediated
  - Genetic predisposition
  - Autoimmune reaction may be triggered by viral infection, toxins
  - Destroys β-cells in pancreas that produce insulin
- Idiopathic (cause unknown)
  - Strongly inherited
  - African or Asian ancestry

Diabetes Care, 30:S1, January 2007
Type 1 Diabetes Pathophysiology

- At onset, affected persons are usually lean, have abrupt onset of symptoms before age 30
- Honeymoon phase: after diagnosis and correction of hyperglycemia and metabolic derangements, need for exogenous insulin may drop dramatically for up to a year
- 8 to 10 years after onset, β-cell loss is complete
Diabetes Type 2

- Most common form of diabetes accounting for 90% to 95% of diagnosed cases
- Combination of insulin resistance and beta cell failure (insulin deficiency)
- Progressive disease
- Ketoacidosis rare, usually arises in illness
In the human cell, insulin must bind with receptors before glucose can enter the cell. Most people with type 2 have more than enough insulin but the receptors are resistant to insulin’s action.
Diabetes Type 2 Symptoms

- Insidious onset
- Often goes undiagnosed for years
- Hyperglycemia
- Excessive thirst (polydipsia)
- Frequent urination (polyuria)
- Polyphagia
- Weight loss
Diabetes Type 2 Risk Factors

- Family history of diabetes
- Older age
- Obesity, particularly intra-abdominal obesity
- Physical inactivity
- Prior history of gestational diabetes
- Impaired glucose homeostasis
- Race or ethnicity
Diabetes Type 2
Pathophysiology

- Results from a combination of insulin resistance and β-cell failure
  - Insulin resistance: decreased tissue sensitivity or responsiveness to insulin
- Endogenous insulin levels may be normal, depressed, or elevated, but inadequate to overcome insulin resistance
Diabetes Type 2
Pathophysiology

- Insulin resistance →
- Compensatory ↑ in insulin secretion → glucose remains normal
- As insulin production fails, ↑ post-prandial blood glucose
- Liver production of glucose increases, resulting in ↑ fasting blood glucose
- Glucotoxicity and lipotoxicity further impair insulin sensitivity and insulin secretion
Gestational Diabetes Mellitus (GDM)

- Glucose intolerance with onset or first recognition during pregnancy
- Occurs in 7% of all pregnancies (200,000 cases annually)
- Does not include women who have diabetes diagnosed before pregnancy
- Usually diagnosed during the 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester of pregnancy when hormonal changes cause insulin resistance
- May or may not require insulin treatment

Diabetes Care 30;Supplement 1, January 2007
Prediabetes (Impaired Glucose Homeostasis)

- Impaired fasting glucose (IFG)
  - fasting plasma glucose (FPG) above normal (>100 mg/dL and <126 mg/dL)

- Impaired glucose tolerance (IGT)
  - plasma glucose elevated after 75 g glucose load (>140 and <200 mg/dL)

Diagnosis and classification of Diabetes Mellitus; Diabetes Care 2007;30:S42-46
Metabolic Syndrome

Characteristics

- Insulin resistance
- Compensatory hyperinsulinemia
- Abdominal obesity
- Dyslipidemia (elevated TG, low HDL)
- Hypertension

Risk factor for cardiovascular disease and glucose intolerance
Methods of Diagnosis

- Fasting plasma glucose (FPG)
- Casual plasma glucose (any time of day)
- Oral glucose tolerance test (OGTT)*

*not generally recommended for clinical use
Revised Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th>FPG mg/dl</th>
<th>OGTT 2 hr mg/dl</th>
<th>Casual PG mg/dl</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;140</td>
<td></td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>≥100 and &lt;126</td>
<td>≥140 and &lt;200</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥126</td>
<td>≥200</td>
<td>&gt;200 + symptoms</td>
</tr>
</tbody>
</table>

Screening for DM

- All persons $\geq 45$ years; repeat every 3 years
- High risk persons: screen at younger age and more frequently
  - Overweight (BMI $\geq 25$)
  - First-degree relative with diabetes
  - High-risk ethnic population
  - Delivered baby $\geq 9$ lb or diagnosed GDM
  - Hypertensive
  - HDL $\leq 35$ mg/dl or TG $\geq 200$
  - Prediabetes
  - Polycystic ovary syndrome
Diabetes—Treatment

Goals

- FPG 90—130 mg/dl
- A₁c <7%
- Peak PPG <180 mg/dl
- Blood pressure <130/80 mmHg
- LDL-C <100 mg/dl
- Triglycerides <150 mg/dl
- HDL-C >40 mg/dl*

*for women HDL-C goal may be increased by 10 mg/dl

Diabetes Control and Complications Trial (DCCT)

- Subjects: 1400 young adults (13-39 years) with Type 1 diabetes
- Compared intensive BG control with conventional tx
- Results: Intensively treated patients had a 50-75% reduction in progression to retinopathy, nephropathy, neuropathy after 8-9 years
- Clear link between glycemic control and complications in Type 1 diabetes

United Kingdom Prospective Diabetes Study (UKPDS)

- Subjects: 5102 newly-diagnosed Type 2 diabetic patients
- Compared traditional care (primarily nutrition therapy) with A1C of 7.9% with intensively treated group (A1C of 7%)
- Intensively treated group microvascular complications ↓ by 25% and macrovascular disease ↓ by 16%.

United Kingdom Prospective Diabetes Study Group: Intensive blood glucose control with sulfanylureas or insulin compared with conventional treatment and risk of complications in Type 2 diabetes. UKPDS 34, Lancet 352:854, 1998a
United Kingdom Prospective Diabetes Study (UKPDS)

- Combination therapy (insulin or metformin with sulfonylureas) was needed in both groups to meet glycemic goals with loss of glycemic control over the 10-year trial.
- Confirmed progressive nature of the disease.
- As the disease progresses, MNT alone is generally not enough; should not be considered a failure of diet.
United Kingdom Prospective Diabetes Study (UKPDS)

- Prior to randomization into intensive or conventional treatment, subjects received individualized intensive nutrition therapy for 3 months.
- Mean A1C decreased by 1.9% (~9% to ~7%) and patients lost an average of 3.5 kg

Diabetes Management
Evaluation of Glycemic Control: SMBG

- SMBG should be carried out 3+ times daily for those using multiple insulin injections (A)
- For pts using less frequent insulin injections or oral agents or MNT alone, SMBG is useful in achieving glycemic goals (E)
- Instruct the pt in SMBG and routinely evaluate the pts ability to use data to adjust therapy (E)

Evaluation of Glycemic Control: A1C

- Perform the A1C test at least 2 times a year in pts who are meeting treatment goals and have stable glycemic control (E)
- Perform the A1C test quarterly in pts whose therapy has changed or who are not meeting glycemic goals (E)
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes when needed (E)

Diabetes Self-Management Education (DSME)

- People with diabetes should receive DSME according to national standards when their diabetes is diagnosed and as needed thereafter (B)
- DSME should be provided by health care professionals who are qualified to provide it based on their training and continuing education (E)
- DSME should address psychosocial issues since emotional well-being is strongly associated with positive diabetes outcomes
- DSME should be reimbursed by third-party payors.

Required Elements of Recognized DSME Programs

- Diabetes disease process
- Nutrition
- Physical activity
- Medications
- Monitoring / using results
- Acute complications
- Chronic complications
- Goal setting and problem solving
- Psychosocial adjustment
- Preconception care, pregnancy, and GDM (if applicable)
Physical Activity

- Improves insulin sensitivity in Type 2 diabetes
- Reduces hepatic glucose output
- Reduces cardiovascular risk factors
- Controls weight
- Improves mental outlook
Physical Activity

- To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, at least 150 min/week of moderate-intensity aerobic physical activity (50-70% MHR) and/or at least 90 minutes/week of vigorous aerobic exercise (>70% MHR) is recommended.

- Should be distributed over at least 3 days a week with no more than two consecutive days without physical activity (A).

Physical Activity

- In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise three times a week, targeting all major muscle groups, progressing to three sets of 8-10 repetitions at a weight that cannot be lifted more than 8-10 times (A)

Effect of Exercise on Blood Glucose

- In well-controlled diabetes, lowers blood glucose
- In poorly-controlled (underinsulinized) diabetes, blood glucose and ketones will increase
- If BG > 250-300 mg/dl, postpone exercise until control improves
Activity in Presence of Specific Long Term Complications of Diabetes

- Retinopathy: vigorous aerobic or resistance exercise may trigger hemorrhages or retinal detachment
- Peripheral neuropathy: lack of pain sensation increases risk of injury and skin breakdown; non weight-bearing exercise may be best

Activity in Diabetes

- Autonomic neuropathy: may decrease cardiac responsiveness to exercise, ↑ risk of postural hypotension, impaired thermoregulation, etc
- Persons with diabetes should undergo cardiac evaluation prior to initiation of increased activity program
Hypoglycemia and Exercise in Insulin Users

- Common after exercise
- Add 15 g CHO for every 30-60 minutes of activity over and above normal routines
- Ingest CHO after 40-60 minutes of exercise
- Drinks containing 6% or less of CHO can replace CHO and fluid
- Adjust fast-acting insulin dose 1-2U for strenuous activity lasting >45 to 60 minutes
### Adjustment Pre-Meal Rapid-Acting Insulin for Exercise

<table>
<thead>
<tr>
<th>Level of Exercise</th>
<th>% dose reduction for 30 min of exercise</th>
<th>% dose reduction for 60 min of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very light</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Moderate</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>Vigorous</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Source: American Dietetic Association Guide to Diabetes, 2005, p. 77
Classes of Oral Glucose-Lowering Medications

- Insulin secretagogues: sulfonylureas and meglitinides
- Biguanides (metformin)
- Thiazolidinediones (TZD, e.g. pioglitazone, rosiglitazone)
- Alpha-glucosidase inhibitors (acarbose, miglitol)
- Gliptins (Januvia, Galvus)

Insulin Secretagogues

- Sulfanylureas: Glipizide (Glucotrol), glyburide (Glynase Prestabs) glimepiride (Amaryl)
- Meglitinides: Repaglinide (Prandin) Nateglinide (Starlix)
- Promote insulin secretion by the $\beta$-cells of the pancreas
- May cause weight gain and hypoglycemia
- Not effective in persons with little or no beta-cell activity
Sulfanylureas:
Indications

More effective in persons who
- Have had diabetes for <5 years
- Developed diabetes after age 40
- Have a fasting blood glucose level <200 mg/dl
- Do not have dislipidemia
- Are not overweight
Sulfanylureas: Adverse Effects

- Weight gain (2-5 kg) secondary to increased insulin secretion and overtreatment of hypoglycemia

- Hypoglycemia
  - More common in older adults and those with impaired liver and kidney function
  - Also may occur with physical activity and inconsistent carbohydrate intake

Source: American Dietetic Association Guide to Diabetes, 2005, p. 83
Meglitinides

- Repaglinide and nateglinide (Prandin and Starlix)
- Short acting insulin secretagogues
- Generally taken with meals to blunt post-prandial glucose
- Allows more flexible meal timing
- Take 15 minutes before meals
- Omit if meal is skipped or <240 kcals
Meglitinides: Adverse Effects

- Hypoglycemia
- Weight gain
- Generally less pronounced than with sulfanylureas
- Can be used in patients with renal disease
- Avoid in malnourished, elderly, persons with liver disease

American Dietetic Association Guide to Diabetes, 2005, p. 84-85
Biguanides

- Metformin (Glucophage)
- Decrease hepatic glucose production by suppressing gluconeogenesis
- Enhances insulin sensitivity in muscles
- Metformin also available in combination with other medications
  - Metformin glyburide (Glucovance)
  - Metformin/glipizide (Metaglip)
  - Metformin/rosiglitazone (Avandamet)
Biguanides

- Does not stimulate insulin secretion
- May lead to modest weight loss (4-6 lb) during first 6 months of treatment
- Little risk of hypoglycemia in monotherapy
- Reduces triglycerides and LDL-cholesterol levels

Biguanides: Indications

- Persons with type 2 diabetes who are overweight, have elevated cholesterol levels, and elevated fasting blood glucose levels
Biguanides

- Improves ovulatory function in women with polycystic ovary disease (PCOS)
- Reduces risk of gestational diabetes (GDM) in women with PCOS
- Reduces risk of diabetes in persons with impaired glucose tolerance

American Dietetic Association Guide to Diabetes MNT and Education, 2005, p. 86
Thiazolidinediones (TZD)

- Pioglitazone (Actos), Rosiglitazone (Avandia)
- Improves peripheral insulin sensitivity
- Most useful in overweight persons with insulin resistance
- HDL-C increases, TG often decrease
- LDL-C may increase, but larger particles
- Adverse effects: weight gain and edema
- Patients with advanced CHF or liver disease should not take these
Alpha-Glucosidase Inhibitors

- Acarbose (Precose) and miglitol (Glyset) inhibit intestinal brush-border enzymes
- Work in the small intestine to inhibit enzymes that digest carbohydrates, delaying CHO absorption
- Lowers post-prandial glycemia
Alpha-Glucosidase Inhibitors

- Do not cause hypoglycemia with monotherapy
- Can cause hypoglycemia when used in conjunction with insulin or sulfanylureas
- Treat hypoglycemia with glucose tablets or milk (medication delays digestion of complex carbs and absorption of sugars)
- Does not cause weight gain, but can cause flatulence, diarrhea, cramping, abdominal pain

Insulin

- All people with Type 1 diabetes need insulin to survive
- Many people with Type 2 diabetes need insulin to achieve good blood glucose control
  - Failure to achieve adequate control with oral medications
  - Acute injury, infection, surgery, pregnancy
Four Properties of Insulin

- Action: speed of onset and duration
- Concentration: U-100 is the concentration of insulin available in the US (100 units/ml)
- Purity
- Source: most insulins are made biosynthetically, treated to yield human insulin
Rapid-Acting Insulins

- Insulin lispro (Humalog) and insulin aspart (Novalog)
- Used as bolus or mealtime insulins
- Onset: within 15 minutes
- Peak: 60-90 minutes
- Duration: 3-5 hours
Short-Acting Insulins

- Regular insulin (Novolin R, Humulin R)
- Onset: 15 to 60 minutes
- Peak: 2-3 hours
- Duration: 5 to 8 hours
- Slow onset means it must be taken 30 to 60 minutes before meals

Lispro vs Regular Insulin

Plasma Insulin Profile After Regular Insulin and Insulin Lispro

Intermediate-Acting Insulins

- NPH, Humulin N, Novolin N)
- Cloudy appearance
- Onset: 1-2 hours after injection
- Peak: 6 to 12 hours
- Duration: 18-24 hours
Long-acting insulins

- **Insulin glargine (Lantus)**
- **Insulin detemir (Levemir)**
  - Relatively constant peakless over 24 hours
  - Clear in solution
  - Cannot be mixed with other insulins
  - Usually given at bedtime but can be given before any meal; time must be consistent
Insulins Glargine vs NPH
Pre-Mixed Insulins

- 70/30: 70% NPH, 30% regular
- 50/50: 50% NPH, 50% regular
# Action Times of Human Insulin Regimens

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>&lt;15 min</td>
<td>0.5–1.5 hr</td>
<td>2–4 hr</td>
</tr>
<tr>
<td>(Lispro, Aspart)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td>0.5–1 hr</td>
<td>2–3 hr</td>
<td>3–6 hr</td>
</tr>
<tr>
<td>(Regular)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2–4 hr</td>
<td>6–10 hr</td>
<td>10–16 hr</td>
</tr>
<tr>
<td>(NPH)</td>
<td></td>
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</tr>
<tr>
<td>Mixtures</td>
<td>0.5–1 hr</td>
<td>Dual</td>
<td>10–16 hr</td>
</tr>
</tbody>
</table>
Insulin Mealtime Dose

- Mealtime or bolus dose: rapid-acting (or short-acting) insulin is given before meals to mimic normal insulin response to a meal.
- Adjusted based on the CHO content of the meal.
- Can establish an insulin-to-carbohydrate ratio for an individual.
Insulin Basal or Background Dose

- Insulin required in post-absorptive state to restrain endogenous glucose output from the liver
- Limits lipolysis and excess flux of fatty acids to the liver
Insulin Dosing: Type 1

- Normal weight persons with Type 1 require 5 to 1 U/kg of body weight.
- About 50% is used to provide for basal or background insulin needs (NPH or glargine).
- Remainder (lispro or aspart) is divided up among the meals or giving about 1 to 1.5 U insulin per 10 g CHO consumed.
- Higher amount is needed in the morning due to higher levels of counter-regulatory hormones and surge in blood glucose levels (dawn phenomenon).
Insulin Dosing: Type 2

- Persons with Type 2 may require insulin doses in the range of 0.5 to 1.2 U/kg
- Large doses (>1.5 U/kg) may be required at first to overcome insulin resistance

Insulin Pump Therapy

- Provides basal rapid-acting or short-acting insulin pumped continuously
Insulin Dosing

- A single dose is seldom effective in achieving good blood glucose control in either type of diabetes
- Insulin may be added at bedtime for persons with Type 2 diabetes to suppress nocturnal glucose production and normalize fasting glucose with oral meds during the day
Flexible Insulin Regimens
Allow Flexible Meal Plans

- Involve multiple insulin injections (3 or more) or the use of an insulin pump
- Half of the required insulin dose is given as a basal or background insulin
- Half is divided and given before meals (bolus or premeal insulin)
- Allows increased flexibility in choosing when and what to eat
Flexible Insulin Regimens Allow Flexible Meal Plans

- The total CHO content of meals is the major determinant of the mealtime rapid-acting insulin dose
- Individuals can be taught how to adjust mealtime insulin based on CHO content of the meal
- However, consistency in meal intake promotes improved glycemic control
Fixed Insulin Regimens

- Pre-mixed insulin or fixed daily dose
- No mealtime insulin doses
- Requires day-to-day consistency in timing and amount of carbohydrate eaten