DIABETES MELLITUS

Definition of diabetes mellitus (DM)
DM is a group of common metabolic disorders characterized by:

- reduced insulin secretion
- decreased glucose utilization
- and increased glucose production
- Insulin biosynthesis

Insulin biosynthesis

Preproinsulin: 86 aa → cleavage of amino terminal signal peptide → Proinsulin: cleavage of 31 aa long C-peptide → Insulin

Epidemiology of diabetes mellitus

- <20 years: 0,19%
- >20 years: 8,6%
- 65 years: 20,1%

In the USA: African Americans 13%, 10.2% in Hispanic Americans 10,2%, Native Americans 15,5%, non-Hispanic whites 7,8%

Incidence:

- Finland: 35/100,000
- Pacific Japan and China: 1-3/100,000
- Northern Europe, USA: 8-17/100,000

Diabetes mellitus is the leading cause of: end-stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness.

Spectrum of glucose homeostasis and diabetes mellitus

<table>
<thead>
<tr>
<th>Type of diabetes</th>
<th>FPG (mg/dL) (mM/L)</th>
<th>2h OGTT (mg/dL) mM/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td>&lt;110  6.1</td>
<td>&lt;140  7.8</td>
</tr>
<tr>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>110-125  6.1-6.9</td>
<td>140-199  7.7-11</td>
</tr>
<tr>
<td>Not insulin requiring</td>
<td>≥126  ≥7.0</td>
<td>≥200  ≥11</td>
</tr>
<tr>
<td>Insulin required for control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin required for survival</td>
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</table>

Etiologic classification of diabetes mellitus

I. Type 1 diabetes
(β-cell destruction, usually leading to absolute insulin deficiency)

   A. Immune-mediated
   B. Idiopathic

II. Type 2 diabetes
(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

   A. Genetic defects of β-cell function characterized by mutations in:
      - Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
      - Glucokinase (MODY 2)
      - HNF-1α (MODY 3)
      - Insulin promoter factor (IPF) 1 (MODY 4)
      - HNF-1β (MODY 5)
      - NeuroD1 (MODV6)
      - Mitochondrial DNA
      - Proinsulin or insulin conversion
      - Etiologic classification of diabetes mellitus 2

   B. Genetic defects in insulin action
      - Type A insulin resistance
      - Leprechaunism
      - Rabson-Mendenhall syndrome
      - Lipodystrophy syndromes

   C. Diseases of the exocrine pancreas
      - pancreatitis
      - pancreatectomy
      - neoplasia
      - cystic fibrosis
      - hemochromatosis
      - fibrocalculous pancreatopathy
      - Etiologic classification of diabetes mellitus 3

   D. Endocrinopathies
      - acromegaly
      - Cushing's syndrome
      - glucagonoma
      - pheochromocytoma
      - hyperthyroidism
      - somatostatinoma
      - aldosteronoma

   E. Drug- or chemical-induced
      - Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine, β-blockers
      - Etiologic classification of diabetes mellitus 4

   F. Infections
      - congenital rubella, cytomegalovirus, coxsackie

   G. Uncommon forms of immune-mediated diabetes
      - “stiff-man” syndrome
• anti-insulin receptor antibodies

_H. Other genetic syndromes sometimes associated with diabetes_

• Down’s syndrome
• Klinefelter’s syndrome
• Turner’s syndrome
• Wolfram’s syndrome
• Friedreich’s ataxia
• Huntington’s chorea
• Laurence-Moon-Biedl syndrome
• myotonic dystrophy
• porphyria
• Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

Classification of DM in an individual patient

**Type 1 DM:** onset of disease prior to age 30, lean body habitus, requirement of insulin as the initial therapy, propensity to develop ketoacidosis, an increased risk of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, and vitiligo.

**Type 2 DM:** develop diabetes after the age of 30, are usually obese (80% are obese, but elderly individuals may be lean), may not require insulin therapy initially, may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or PCOS, insulin resistance is often associated with abdominal obesity and hypertriglyceridemia. Although most individuals diagnosed with type 2 DM are older, the age of diagnosis is declining.

The pathogenesis of type 1 DM

**Genetic**

• Concordance in identical twins: 30-70%
• Risk is 10-fold in 1st degree relatives
• HLA DR3 and DR4
• DQA1*0301, DQB1*0302, DQA1*0501, DQB1*0201
• Protective genes: DQA1*0102, DQB1*0602

**Autoimmune factors**

• islet cell autoantibodies: glutamic acid decarboxylase (GADA), islet cell antibody (ICA), islet ganglioside, carboxypeptidase H
• activated lymphocytes in the islets, peripancreatic lymph nodes, and systemic circulation
• T lymphocytes that proliferate when stimulated with islet proteins; and
• release of cytokines within the insulitis

**Immunologic markers**

• GADA-s are present in:
• >75% of type 1 DM
• 5-10 % of type 2 DM
• <5% of GDM
• In relatives there is a predictive value for type 1 DM

**Environmental triggers**

• are putative:
• viruses (Coxsackie and rubella)
• bovine milk proteins
• nitrosourea compounds

The pathogenesis of type 2 DM

**Genetic considerations**
• predisposition is very strong, polygenic and multifactorial
• concordance in identical twins: 70-90%
• risk is 40% if both parents have type 2 DM

Pathophysiology
• impaired insulin secretion
• peripheral insulin resistance
• excessive hepatic glucose production
  – Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM
  – Adipocytes secrete leptin, TNF-α, free fatty acids, resistin, and adiponectin that modulate insulin secretion, insulin action, and body weight and contribute to the insulin resistance.

Risk factors for type 2 diabetes mellitus
• Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
• Obesity (BMI ≥ 25 kg/m²)
• Habitual physical inactivity
• Race/ethnicity (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)
• Previously identified IFG or IGT
• History of GDM or delivery of baby >4 kg
• Hypertension (blood pressure ≥ 140/90 mmHg)
• HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)
• Polycystic ovary syndrome or acanthosis nigracans
• History of vascular disease

Impaired insulin secretion in type 2 DM
• Insulin resistance
  – initially hyperinsulinemia
  – exhaustion of β-cells → hypoinsulinemia
• “Glucose toxicity” → worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function.
• Elevation FFA levels (“lipotoxicity”) and dietary fat also worsen islet function.

Increased hepatic glucose production in type 2 DM
• Occurs early in the course of DM
• Failure of hyperinsulinemia to suppress gluconeogenesis
  – fasting hyperglycemia
  – decreased glycogen storage by the liver in the postprandial state
  ↓
Insulin resistance in the liver

Criteria for the diagnosis of diabetes mellitus
• Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)
• Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)
• Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test
c Random is defined as without regard to time since the last meal
b Fasting is defined as no caloric intake for at least 8 h
c The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Source: Modified from American Diabetes Association
**Forms of glucose tolerance**
- FPG < 5.6 mmol/L (100 mg/dL): normal
- FPG 5.6-7.0 mmol/L (100-126 mg/dL): IFG
- FPG ≥ 7.0 mmol/L (126 mg/dL): DM.
- Plasma glucose levels between 7.8-11.1 mmol/L (140-200 mg/dL) 2 h after a 75-g oral glucose load: IGT
- Individuals with IFG or IGT are at substantial risk for developing type 2 DM (40% risk over the next 5 years) and cardiovascular disease.

**Glycation products in DM**
- Glycated hemoglobin Hemoglobin A1C: 120 days
  - 1% change = 35 mg/dl (1.9 mmol/L) plasma glucose
- Fructosamine: 2 weeks

**Further laboratory assessment**
- Hemoglobin A1C
- C-peptide
- Microalbuminuria, se. creatinine/microalbumine
- Serum lipid levels
- Thyroid dysfunction
- Islet cell antibodies (ICA, GADA)
- Echocardiography, ergometry, carotid USG in patients with high-risk for coronary disease

**Screening for diabetes mellitus**
(Recommendation of the American Diabetes Association (ADA))
- Determination of FPG recommends screening all individuals >45 years every 3 years
- Screening individuals with additional risk factors at an earlier age.
- Insulin resistance syndromes

**Metabolic syndrome**
- central or visceral obesity (abdominal circumference)
- and 2 of the followings: hypertension, hypercholesterinemia, decreased HDL, elevated triglycerides, type 2 diabetes or IGT/IFG

**Rare forms:** Acanthosis nigricans, polycystic ovary syndrome (PCOS)
**Importance:** hyperinsulinemia → accelerated cardiovascular disease

**Principles of long-term treatment of DM**
**The goals of therapy:**
1. Eliminate symptoms related to hyperglycemia. Symptoms usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL)
2. Reduce or eliminate the long-term microvascular and macrovascular complications of DM
3. Allow the patient to achieve as normal a lifestyle as possible.

**Optimal diabetes therapy involves more than plasma glucose management**
**Members of the health care team are:** primary care provider, endocrinologist or diabetologist, certified diabetes educator, nutritionist
**When the complications of DM arise:** neurologist, nephrologist, vascular surgeon, cardiologist, ophthalmologist, and podiatrist
Management of DM

- Patient education
- Diet, lifestyle
- Insulin therapy
- Oral antidiabetic drugs (glucose-lowering agents)
- Screening for complications
- Special conditions and aspects

Topics for the education of the patient with DM

- Self-monitoring of blood glucose
- Urine ketone monitoring (type 1 DM)
- Insulin administration

Guidelines for diabetes management during illnesses

- Management of hypoglycemia
- Foot and skin care
- Diabetes management before, during, and after exercise
- Risk factor-modifying activities.

Nutritional recommendations for all persons with diabetes

- Protein: ~15-20% of kcal/d (~10% for those with nephropathy)
- Saturated fat: <10% of kcal/d (<7% for those with elevated LDL)
- Polyunsaturated fat: ~10% of kcal; avoid trans-unsaturated fatty acids
- 60–70% of calories to be divided between carbohydrate and monounsaturated fat, based on medical needs and personal tolerance. Glucose: 140-220 g/die
- Use of caloric sweeteners, including sucrose, is acceptable.
- Fiber (20-35 g/d) and sodium (≤3 g/d) as recommended for the general healthy population
- Cholesterol intake ≤300 mg/d
- Alcohol worsens diabetes.
- Weight loss is desired in obese patients with type 2 DM

The benefits of physical exercise in DM

Exercise is a central treatment modality for type-dependent diabetes. Its benefits are: cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, weight loss, lowering plasma glucose (during and following exercise), increasing insulin sensitivity

The ideal goals for glycemic control

<table>
<thead>
<tr>
<th>Index</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose*</td>
<td>5.0-7.2 mmol/L (90-130 mg/dL)</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose</td>
<td>&lt;10 mmol/L (&lt;180 mg/dL)</td>
</tr>
<tr>
<td>A1C</td>
<td>7-8%</td>
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</tbody>
</table>

*Plasma glucose values are 10–15% higher than whole blood values.

Properties of insulin preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time of action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset, h  Peak, h Effective duration, h</td>
</tr>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
</tr>
</tbody>
</table>
Insulin regimens for the treatment of diabetes

- Conventional
- Intensified
- Pump (with or without continuous glucose monitoring)

**General daily dose of insulin:**
- Type 1 DM: 0.5 - 1.0 U/kg divided into multiple doses
- Type 2 DM: 0.3 - 0.4 U/kg
- Intensive therapy can preserve endogenous insulin secretion

Oral glucose-lowering therapies in T2DM

**Insulin secretagogues**

**Sulfonylureas**
- Agents: glybenclamide, glimepiride, glipizide, glipizide (extended release), glyburide, glyburide (micronized)
- Advantages: lower fasting blood glucose
- Side effects: hypoglycemia weight gain, hyperinsulinemia
- Contraindications: renal/liver disease

**Nonsulfonylureas (meglitidines)**
- Agents: repaglinide, nateglinide
- Advantages: short onset of action, lower postprandial glucose
- Side effects: hypoglycemia
- Contraindications: renal/liver disease

**Incretin analogues**
- Agents: exenatide, liraglutide
- Slow gastric emptying, Advantages: No hypoglycemia, appetite suppression, considerable weight reduction
- Disadvantages: Increased risk of thyroid C-cell tumors

**DPP-4 inhibitors**
- Agents: saxagliptin, sitagliptin, vidagliptin
- Conserve β-cell mass, promote insulin secretion in the absence of hypoglycemia or weight gain, preferential effect on postprandial blood glucose
- Disadvantages: Reduced dose in renal insufficiency
- Side effects: relatively few

**Adjuvants**

**Amylin analogues**
- Pramlintide
• Action: delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety.
• Disadvantages: only in T1DM and for only adults

**Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors**
• Agents: empagliflozin, canagliflozin, dapagliflozin, ipragliflozin
• Action: blocks glucose reabsorption in the proximal renal tubule, leading to weight loss and A1C reduction in T2DM

**Biguanides**
• Agents: Metformin
• Mode of action: ↓ Hepatic glucose production, weight loss, ↑ glucose utilization, ↓ insulin resistance
• Advantages: Weight loss, improved lipid profile, no hypoglycemia
• Disadvantages: lactic acidosis, diarrhea, nausea
• Contraindications: serum creatinine >1.5 mg/dL (men), >1.4 mg/dL (women), radiographic contrast studies, seriously ill patients, acidosis

α-glucosidase inhibitors
• Agents: acarbose, miglitol
• Mode of action: ↓ glucose absorption
• Advantages: No risk of hypoglycemia
• Side effects: GI flatulence, ↑ liver function tests
• Contraindications: renal/liver disease

**Thiazolidinediones**
• Agents: pioglitazone
• Mode of action: PPAR (peroxisome proliferator-activated receptor)-γ-agonism: ↓ insulin resistance, ↑ glucose utilization
• Advantages: ↓ Insulin and sulfonylurea requirements, ↓ triglycerides
• Side effects: Frequent hepatic monitoring for idiosyncratic hepatocellular injury
• Contraindications: liver disease, congestive heart failure

**Guidelines for ongoing medical care for patients with DM**
• Self-monitoring of blood glucose (individualized frequency)
• Hemoglobin A1C testing (2-4 times/year)
• Patient education in diabetes management (annual)
• Medical nutrition therapy and education (annual)
• Eye examination (annual)
• Foot examination (1–2 times/year by physician; daily by patient)
• Screening for diabetic nephropathy (microalbuminuric test annually)
• Blood pressure measurement (quarterly)
• Lipid profile (annual)
• Influenza/pneumococcal immunizations
• Consider antiplatelet therapy

**Complications of DM**

**Acute**
• Diabetic ketoacidosis (DKA)
• Hyperglycemic hyperosmolar state (HHS)
• Lactate acidosis
• Hypoglycemia

**Chronic**

*Macroangiopathy*
• Accelerated atherosclerosis esp. in coronary, cerebral, lower limb arteries

**Microangiopathy**
• Eye disease: Retinopathy (nonproliferative/proliferative), macular edema
• Nephropathy
• Neuropathy: Sensory and motor (mono- and polyneuropathy), autonomic

**Other**
• GI (gastroparesis, diarrhea)
• Genitourinary (uropathy/sexual dysfunction)
• Dermatologic
• Infectious
• Cataracts

**Diabetic ketoacidosis**

**Symptoms**
• Can occur as the first symptom of type 1 DM. Nausea/vomiting, thirst/polyuria, polydipsia, abdominal pain, shortness of breath

**Physical findings**
• Tachycardia, dry mucous membranes/reduced skin turgor, dehydration/hypotension, tachypnea/Kussmaul respiration, fruity odor, abdominal tenderness (may resemble acute, lethargy/obtundation/cerebral edema/possibly coma

**Precipitating events**
• Inadequate insulin administration, infection (pneumonia/urinary tract infection/gastroenteritis/sepsis), infarction (cerebral, coronary, mesenteric, peripheral), drugs (cocaine), pregnancy

**The pathogenesis of diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar coma (HHS)**
The management of diabetic ketoacidosis

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring.
3. Assess serum electrolytes (K⁺, Na⁺, Mg²⁺, Cl⁻, bicarbonate, phosphate), acid-base status - pH, HCO₃⁻, pCO₂, renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h.
5. Administer regular insulin: IV (0.1 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 h. Be careful to hold potassium above 3.5 mmol/L!
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)?
7. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

Hyperglycemic hyperosmolar state (HHS)

Clinical features

- Occurs typically in elderly individuals with type 2 DM. Several week history of polyuria, weight loss, and diminished oral intake. Mental confusion, lethargy, or coma. Profound dehydration and hyperosmolality, hypotension, tachycardia, altered mental status. Nausea, vomiting, and abdominal pain and the Kussmaul respirations are absent. Often precipitated
by a serious, concurrent illness such as myocardial infarction or stroke, sepsis, pneumonia. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder.

Treatment of hyperglycemic hyperosmolar state (HHS)

- As with DKA, but: fluid replacement should initially stabilize the hemodynamic status of the patient. (1 to 3 L of 0.9% normal saline over the first 2 to 3 h). If the serum sodium is >150 mmol/L, 0.45% saline should be used. After hemodynamic stability is achieved use hypotonic fluids (0.45% saline IV) to reverse the free water deficit. IV insulin in bolus followed by a constant infusion rate.

Chronic complications of diabetes mellitus

- Cardiovascular: 77%
- Renal: 9%
- Neurologic: 6%
- Ophthalmic: 4%
- Other: 4%

Glycemic control and complications 1. The DCCT (Diabetes Control and Complications Trial)

- >1400 individuals with type 1 DM
- Individuals in the intensive management group achieved a HbA1c 7.3% vs. conventional management group (9.1%). Improvement of glycemic control reduced nonproliferative and proliferative retinopathy by 47%, microalbuminuria by 39%, clinical nephropathy by 54%, and neuropathy by 60%

Glycemic control and complications 2: The UKPDS (United Kingdom Prospective Diabetes Study)

- >5000 individuals with type 2 DM
- Individuals in the intensive management group achieved a HbA1c 7.0% vs. conventional management group (7.9%). Improved glycemic control did not conclusively reduce cardiovascular mortality but was associated with improvement with lipoprotein risk profiles, such as reduced triglycerides and increased HDL. The beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to 144/82 mmHg reduced the risk of DM-related death, stroke, microvascular end points, retinopathy, and heart failure by 32-56%.

Ophthalmologic complications of DM

DM is the leading cause of blindness between 20-74 years. Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy.

**Retinopathy**

Appears late in the 1st decade or early in the 2nd decade of the disease. Found in all individuals who have had DM for >20 years. Forms:

- Non-proliferative (retinal vascular microaneurysms, blot hemorrhages, cotton wool spots, changes in venous vessel caliber, intraretinal microvascular abnormalities.)
- Proliferative: (retinal hypoxia → neovascularization. Appears near the optic nerve and/or macula and ruptures easily, → to vitreous hemorrhage, fibrosis, and ultimately retinal detachment.)

**Macular oedema:** detection by fluorescent angiography (FLAG)

**Treatment:**

- Prevention by intensive glycemic and blood pressure control (paradoxic worsening in the first 6-12 months of improved glycemic control)
- Laser photocoagulation
Renal complications of DM
Diabetic nephropathy is the leading cause of end stage renal disease. Retinopathy is almost always present. Smoking accelerates the decline in renal function.

Pathomechanism: chronic hyperglycemia, soluble factors: growth factors, AT II, endothelin, AGEs, hemodynamic alterations in the renal microcirculation, structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through AT II receptors.

Treatment of diabetic nephropathy
Prevention is the most important. Early nephrology consultation is indicated. Interventions:
1) Near normalization of glycemia. Insulin requirement may fall. Sulfonylureas and metformin are contraindicated in advanced renal insufficiency.
2) Strict blood pressure control. Target values:
   • without proteinuria: <130/80 mmHg
   • microalbuminuria or overt nephropathy: 125/75 mmHg
3) Administration of ACE inhibitors or ARBs. If unfeasible, Ca-channel blockers (non-dihydropyridines)
4) Treatment of dyslipidemia
5) Restriction of protein intake:
   • with microalbuminuria: 0.8 g/kg
   • overt nephropathy: <0.8 g/kg
6) Dialysis, renal (or pancreas-kidney) transplantation

Diabetic neuropathy
Occurs in 50% of individuals with long-standing DM. Forms:
- Polyneuropathy (Distal symmetric polyneuropathy, polyradiculopathy), mononeuropathy: sensory loss, hyperesthesia, paresthesia, dysesthesia, sensation of numbness, tingling, sharpness, or severe burning pain, pain and motor weakness in the distribution of a single nerve
- Autonomic neuropathy
  - Cardiovascular system: resting tachycardia on Holter and ABPM, orthostatic hypotension, non-dipper hypertension, sudden death
  - Gastroparesis and bladder-emptying abnormalities
  - Hyperhidrosis of the upper and anhidrosis of the lower extremities: dry skin with cracking, which increases the risk of foot ulcers.
  - Reduction of counterregulatory hormone release: hypoglycemia unawareness

Examination: sensory loss, loss of ankle reflexes, and abnormal position sense
128 Hz tuning fork, monofilament (5.07, 10-g monofilament)

Treatment of diabetic neuropathy
- Chronic, painful diabetic neuropathy: tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, NSAIDs, and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream).
- Referral to a pain management center may be necessary.
- Therapy of orthostatic hypotension: adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose.

Gastrointestinal dysfunction
- Gastroparesis
• Altered small- and large-bowel motility

Genitourinary dysfunction
• Cystopathy
• Erectile dysfunction and retrograde ejaculation
• Female sexual dysfunction

Cardiovascular disease risk in diabetes
• Individuals diagnosed with diabetes should be considered as patients who have already had diabetes, because the long-term mortality of patients with diabetes and without myocardial infarction is the same of those with myocardial infarction and without diabetes.
• Evidence of atherosclerotic vascular disease should be sought in an individual with diabetes.
• The absence of chest pain (“silent ischemia”) is common in individuals with diabetes.
• The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate 2-fold in men and 4-fold in women.
• Additional risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, an elevation of serum creatinine, and abnormal platelet function.
• Insulin resistance results in increased thrombosis and decreased fibrinolysis
• Cerebrovascular disease is increased, 3-fold increase in stroke).
• Incidence of congestive heart failure (diabetic cardiomyopathy). Multifactorial etiology: myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

Therapy
• Antihypertensive agents: ACE inhibitors, ARB-s, β-blockers (carvedilol, nebivolol)
• Antiplatelet therapy: aspirin 81 to 325 mg/d. Antiplatelet agents prevent cardiovascular disease events in diabetes.
• Treatment of dyslipidemia. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation. Cholesterol-lowering therapy prolongs the survival of diabetics with known coronary disease. Target lipid values in diabetic individuals without cardiovascular disease:
  – LDL <1.8 mmol/L
  – HDL >1.1 mmol/L (40 mg/dL) in men and >1.38 mmol/L (50 mg/dL) in women
  – triglycerides <1.7 mmol/L (150 mg/dL). This is the order of priorities in the treatment
• Drugs: statins (simvastatin, atorvastatin, rosuvastatin), fibrates (fenofibrate)

Lower extremity complications
DM is the leading cause of nontraumatic lower extremity amputation. Approx. 15% of individuals with DM develop a foot ulcer and 14 to 24% risk with that ulcer or subsequent ulceration will have amputation. The reasons for the increased incidence: neuropathy, abnormal foot biomechanics, peripheral arterial disease, and poor wound healing. The optimal therapy is prevention.

Diabetic ulcers of the lower extremity
Origin: primarily neuropathic (no accompanying infection) and cellulitis w/wo osteomyelitis.
Diagnosis: bacterial cultures, plain radiographs, nuclear medicine bone scans, In-labeled white cell studies, MRI, bone biopsy and culture.
Therapy: off-loading: bed rest, contact casting, etc., debridement, wound dressings, appropriate use of antibiotics (cephalosporin, clindamycin, amoxicillin/clavulanate, fluoroquinolones), cefotetan, vancomycin), revascularization, limited amputation
**Education of the patient with diabetic foot**
1) Careful selection of footwear
2) Daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma
3) Daily foot hygiene to keep the skin clean and moist
4) Avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot)
5) Prompt consultation with a health care provider if an abnormality arises.
6) Evaluation by a foot care specialist: orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture.

**Infections in DM**
Greater frequency and severity of infection. Reasons: abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia and diminished vascularization. 
Infectious agents:
- *Candida, Torulopsis glabrata* and other fungal species
- rhinocerebral mucormycosis
- emphysematous infections of the gallbladder and urinary tract
- “malignant” or invasive otitis externa (usually secondary to *P. aeruginosa*)
- gram-negative organisms, *S. aureus*, and *Mycobacterium tuberculosis*, *Escherichia coli*,
- Pneumonia, urinary tract, and skin and soft tissue infections (furunculosis), vulvovaginitis
- Periodontal disease, early loss of teeth

**Dermatologic manifestations of DM**
- Protracted wound healing and skin ulcerations are the most common.
- Rubeosis diabetica on the face
- Diabetic dermopathy.
- Necrobiosis lipoidica
- Xerosis and pruritus are common and are relieved by skin moisturizers.

**The prevention of type 2 DM**
- Intensive changes in life-style (diet and exercise for 30 min/day five times/week) 58%
- Metformin: 31%
- Individuals with a strong family history, those at high risk for developing DM, or those with IFG or IGT should be strongly encouraged to maintain a normal body mass index (BMI) and engage in regular physical activity!

**Sources**
- ImageMD