Diabetes mellitus
Decrease in hepatic glucose production

Insulin secretion

Increase in peripheral glucose uptake

80% of postprandial glucose
Diabetes mellitus (DM)

- DM: a group of chronic metabolic diseases characterized by
  - Hyperglycemia resulting from defects in insulin secretion, insulin action, or both;
  - Disturbances of fat and protein metabolism,
  - Constellation of chronic complications
    - Vascular complications
      - Microvascular complications (eyes, kidneys, nerves)
      - Macrovascular complications (heart and blood vessels)
    - Metabolic complications/emergencies
      - Diabetic ketoacidosis
      - Hyperosmolar hyperglycemic state
      - Hypoglycemia (upon treatment of DM by insulin or insulin secretagogues)
Diabetes mellitus

6th leading cause of death

Renal failure
10x ↑ in DM

Retinopathy
⅓ of patients w DM

Amputation
10-20x ↑ in DM

Life expectancy ↓
5-10 years

Cardiovascular
disease ↑ 2-3x

Nerve damage in
60% to 70% of patients

DM is the no. 1 cause of renal failure, new cases of blindness, and non-traumatic amputations
Patients are at higher risk of periodontal disease

Etiologic classification of DM

1. Type 1 DM (T1DM)
2. Type 2 DM (T2DM)
3. Gestational DM (GDM) ~7% of pregnancies
   Any degree of glucose intolerance in the 2nd-3rd trimester
   ↑ in older age, obese, w + family history females
   High risk ethnicities (Hispanic, native American & African American), multiparas, previous large babies
   Screening at 24-28 weeks
   81-94% return to normoglycemia after delivery but w/ increased risk of developing type 2 DM (30-60%) or impaired glucose tolerance within 10-20 years
   Newborn → hyperglycemic; quickly becomes hypoglycemic

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4. Other specific types of DM

Monogenic DM syndromes
- Neonatal DM (before 6 mo of age, can be transient or permanent) due to ß-cell $K_{\text{ATP}}$ channel or insulin gene mutations
- Maturity-onset diabetes of the young (MODY) ~2% of DM AD defect in insulin secretion or glucose metabolism (13 genes are identified) with no insulin resistance

Diseases of the exocrine pancreas (pancreatitis, cystic fibrosis)

Endocrinopathies that induce hyperglycemia
- Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma
- Somatostatinoma and aldosteronoma-induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion

Drug-induced DM (glucocorticoids)

Infectious DM
- Coxsackievirus B, cytomegalovirus (CMV, HHV-5), adenovirus, and mumps

Genetic syndromes with DM
- Down’s, Klinefelter’s, Turner’s and Wolfram’s syndrome

Posttransplantational DM – due to stress and immunosuppressive drugs
Diagnostic criteria for DM

● Glucose concentrations for diagnosing DM
  ○ Casual glucose ≥ 11.1 mmol/l
  ○ Fasting plasma glucose (FPG) ≥ 7.0 mmol/l
    ■ Fasting is defined as no calorie intake for 8 h
  ○ 2h PG ≥ 11.1 mmol/l after oral glucose (75 g) tolerance test (OGTT)
  ○ Confirmation on a second day by any of the above methods
  ○ Hemoglobin A1c ≥ 6.5% (48 mmol/mol)

● Glucose reference range: 4.1-5.6 mmol/l
Fasting plasma glucose

Diabetes mellitus

Impaired fasting glucose

Normal

Oral glucose tolerance test (75 g glucose)
2 hr plasma glucose

Diabetes mellitus

Impaired glucose tolerance

Normal

Prediabetes

5.6 mmol/l

7.0 mmol/l

11.1 mmol/l

7.8 mmol/l
Prediabetes (PD)

PD: increased risk for development of DM and cardiovascular disease. In adults and children, PD is associated with obesity. Lifestyle changes are most effective in most cases, annual conversion of prediabetes into full-blown T2DM: 7-11%

The following 3 states are associated with PD

1. Impaired glucose tolerance (IGT): diagnosed only when challenged with the oral glucose load used in the standardized OGTT
   Mainly peripheral (muscle) insulin resistance with impaired late-phase insulin secretion
   Disease of females and elderly
2. Impaired fasting glucose (IFG) ≥ 5.6 mmol/l but < 7.0 mmol/l
   Largely due to hepatic insulin resistance, with loss of first phase insulin secretion
   Disease of males and middle aged
3. Hemoglobin A1c (HbA1c) in prediabetes: 5.7-6.4% (39-47 mmol/mol)
   Glycosylation of hemoglobin α chains, expressed as the percent of total hemoglobin. Reflects the mean blood glucose over the past 2-3 months, cannot be manipulated by the patient in the short term & not affected by meals or acute glucose changes
β-cell centric model of DM

Inflammation & autoimmunity

Genes + Environment (e.g., viruses, microbiome, physical activity, dietary factors)

β-cell destruction

Inflammation & metabolic stress

β-cell dysfunction

Hyperglycemia

Diabetes Mellitus

Complications
Factors causing hyperglycemia: liver, muscle, fat tissue, brain, colon / biom and immune system disorders contribute to the development of β cell dysfunction while others due to β cell dysfunction or downstream effects contribute to development of hyperglycemia (decreased insulin, decreased incretin, β cell defect, stomach / small intestine due to reduced amylin and kidney).
T1DM

- Immune-mediated DM
  - Lack of insulin (prone to ketoacidosis) due to autoimmune destruction of pancreatic β cells
    - Genetic markers: strong HLA-II associations (DR3-DQ2, DR4-DQ8), poligenic origin
    - Immunologic markers: autoantibodies against insulin (IAA), glutamic acid decarboxylase (GAD65 or GAD2), tyrosine phosphatase (IA-2, IA-2β) or zinc transporter 8 (ZnT8)
  - Commonly occurs in childhood and adolescence, but it can occur at any age - 10% with DM have type 1
    - Patients are rarely obese; usually have other autoimmune disorders: Basedow-Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, vitiligo, and pernicious anemia
Development of immune-mediated DM

Immune dysregulation

Factors inducing autoimmunity
- Viral infections
- Lack of vitamin D
- Toxins

Environmental triggers
- Infections
- Puberty, stress, infections

Genetic predisposition
- Susceptibility (DQ8 & DQ2) and protective genes (DQ6)

Maternal factors
- Infections during pregnancy
- ABO incompatibilities
- Stress?

Beta cell amount
- Normal insulin secretion
- Autoantibodies: IA-2, GAD65, ZNT8

Insulitis: ß cell damage

Accelerating factors
- Progressive ↓ of insulin release
- Glucose intolerance
- Autoantibodies

Freshly discovered T1DM

Loss of 1st phase of insulin secretion

Prediabetes

Stage I
- Autoantibodies: +
- Hyperglycemia: -
- Symptoms: -

Stage II
- Autoantibodies: +
- Hyperglycemia: +
- Symptoms: -

Stage III
- Autoantibodies: +
- Hyperglycemia: +
- Symptoms: +
○ The first manifestation of T1DM is the loss of the 1\textsuperscript{st} phase of insulin response following an intravenous glucose tolerance or $\uparrow$HbA1c
  ■ The pancreas is not producing adequate insulin in response to increased glucose levels
○ Over time, this translates into glucose intolerance, leading to either diabetic ketoacidosis (in $\frac{1}{3}$ of cases) or severe symptoms of hyperglycemia. This is when most people with T1DM are diagnosed (~90% of pancreatic $\beta$-cells are lost)
○ Once T1DM develops, patients must be treated with insulin to control blood glucose levels and prevent complications. Insulin or the connecting C-peptide can no longer be detected in the blood. Unlike in T2DM, insulin sensitivity remains normal
● Clinical manifestations (see diabetic ketoacidosis)
  ○ Polyuria – osmotic diuresis due to high blood sugar
  ○ Polydipsia – dehydration from osmotic diuresis
  ○ Polyphagia – hunger, less energy for your cells (fatigue)
  ○ Blurred vision – hyperosmosis
Pathogenesis of immune-mediated T1DM

Antigen presentation by B cells and DCs drives the activation of β-cell-specific T cells
• Idiopathic T1DM
  ○ Strongly inherited (African, Asian ancestry), no immunological evidence for autoimmune ß-cell destruction, and not HLA associated
    ■ Episodic ketoacidosis with varying degrees of insulin deficiency and dependency between the ketoacidotic episodes
  ○ Fulminant type 1 DM – new subtype (2000)
    ■ Viral infection and the subsequent immune reaction in genetically susceptible individuals (HLA) cause rapid and almost complete ß-cell destruction
    ■ Fulminant type 1 DM accounts for 15-20% of type 1 DM cases in Japan
T2DM

- The most prevalent form of diabetes - 90% with DM have T2DM
- Etiology
  - Strong genetic basis (90% with family history) with complex and not clearly defined inheritance or markers; poligenic inheritance
  - Gradual and insidious onset
    - Frequently occurs in women with prior GDM and in individuals with obesity, hypertension or dyslipidemia (metabolic syndrome). Obesity itself causes some degree of insulin resistance.
    - The risk increases with age, obesity, and lack of physical activity.
    - Hyperglycemia is sufficient to cause damage in various target tissues (macrovascular complications) by the time of diagnosis
Defective insulin secretion is central to the pathophysiology of T2DM

- The secretory pulses of insulin, both rapid and ultradian are smaller and less regular (even in the fasting state, β cells secrete insulin in a pulsatile manner)
  - Absent first phase insulin reaction (first-phase insulin release: to shut off liver glucose production)
  - Diminished, delayed or exaggerated second phase insulin reaction (results in reactive hypoglycemia as a forerunner of T2DM (!!!!))
- Loss of efficiency in insulin synthesis: the ratio of proinsulin to insulin ratio is elevated
- Progressors vs non-progressors
  - Progressors: with the deterioration of the insulin sensitivity the hormone secretion is not keeping pace.
Normal response | Type 2 DM

**Insulin**

- Normal
- Type 2 DM

**Glucagon**

- Normal
- Type 2 DM
A less insulin-sensitive or more insulin-resistant person requires more insulin to compensate.
As a person gets older, more overweight, and more sedentary, the pancreas needs to produce higher levels of insulin. Obesity does not automatically lead to T2DM – some people have β cells that are able to produce enough insulin to compensate indefinitely.

In persons who have a genetic predisposition for impairment of the above normal compensatory system, at some point, the β cells can no longer keep up, and impaired glucose tolerance and eventually T2DM develops.

A highly insulin-sensitive individual (young, healthy, lean) produce a small amount of insulin to maintain normal blood glucose levels.
Possible mechanisms of β-cell defects

Genetic abnormalities may effect β-cell apoptosis, regeneration, glucose sensing, hormone synthesis etc (first degree relatives of DM, GDM, PCOS & elderly)

Acquired factors Malnutrition *in utero* and early childhood

Islet cell changes in T2DM

- **Abnormally regulated α-cell function**: Impaired glucagon suppression by hyperglycemia; excessive response to amino acids, or mixed meals and decreased response to hypoglycemia

- **Decreased β-cell function**: decreased β-cell mass 40-60% (↑ apoptosis)

Physiological decline of insulin secretion: ~1%/yr. In T2DM ~6%/yr.

- **Glucolipotoxicity**: insulin secretion ↓
  - prolonged and acute hyperglycemia induces ROS production and impairs β-cell function; elevation of FFA also impairs β-cell function

- **Incretin (GLP-1, GIP) resistance** (normally: enhance insulin / block glucagon secretion)

- **Amyloid deposition**: endoplasmic stress; ↑ apoptosis of β-cells

- **Islet cell inflammation**: IL-1β: ↑ β-cell apoptosis, ↓ insulin release
• Obesity and insulin resistance: factors released from adipose tissue (FFA, TNF-α, resistin, leptin) and tissue accumulation of lipids impair β-cell function

Insulin resistance is a condition in which greater than normal amounts of insulin are required to produce a normal biological response in peripheral tissues

In insulin resistance, the action of insulin is impaired
  
  To stimulate IC glucose uptake and glycogen synthesis
  To inhibit gluconeogenesis and lipolysis

  Consequence: Increase in lipolysis and an elevation in FFA → decrease insulin secretion and ↑ β-cell apoptosis

In insulin resistance, the action of insulin is unaltered to stimulate fatty acid synthesis and inhibit ketogenesis in liver

Insulin resistance is established: muscle, liver, adipose tissue, kidney, GI, vessels and β-cells

The insulin resistance prior to T2DM: metabolic syndrome

Mechanisms contributing to the development of insulin resistance

  1. ectopic lipid accumulation in insulin-sensitive tissues (PKC activation; ceramid, DAG ↑)
  2. Mitochondrial dysfunction (ROS↑, adiponectin↓)
  3. Systemic inflammation

      Pro-inflammatory cytokines contribute to molecular mechanisms of insulin resistance

      M1 macrophages, Th1,17, CD8 ↑, Treg, Th2↓

  4. ER stress and the unfolded proteins
**Inherited causes**
- Rare mutations:
  - Leptin, POMC mutation
  - Leptin, MC-4, insulin & PPAR-γ receptor mutation
  - Glucose transporter
  - Signaling proteins
- Common forms:
  - Largely unidentified

**Acquired causes**
- Obesity
- Inactivity
- Smoking
- Aging
- PCOS
- Drugs
- Hyperglycemia
- Elevated FFA

**Insulin resistance**

- **Adequate compensatory β-cell function**
  - Compensatory hyperinsulinemia
    - Metabolic syndrome

- **Inadequate compensatory β-cell function**
  - Relative insulin deficiency
    - Type 2 DM

**β-cell dysfunction / growth genes**

Approximately 20% of obese patients do not have insulin resistance, while as many as 20% of thin, normal-weight people do.
Chronic consumption of lipogenic calories

\[ \text{Hyperinsulinemia} \rightarrow \text{insulinopenia} \]

- Glucotoxicity
- Gluconeogenesis
- apo \( B \)
- VLDL-C

Lipotoxicity

Lipolysis↑

Fatty liver

Resistance to appetite suppressing effects of insulin, leptin, GLP-1, amylin, peptide YY

Brain DA ↓, 5HT↑

Obesity

Increased glucose reabsorption (SGLT2)

\[ \text{↑ threshold for glucose spillage into urine} \]

↓ glucose uptake

Atherogenic dyslipidemia

Coagulation factors↑

PAI-1, CRP ↑

Vascular insulin resistance

Microvascular dysfunction
Natural history of type 2 DM

Adapted from *Type 2 Diabetes BASICS*. Minneapolis, MN: International Diabetes Center; 2000.
T2DM synopsis

- Initially, the glucose tolerance is almost normal: the β cells compensate for the insulin resistance, therefore, the serum glucose level remains within the normal range.

- In the progressors, the β-cells can not keep up with increasing insulin resistance (increased fat accumulation in peripheral insulin sensitive tissues & deteriorating fat oxidizing ability of muscles).

- Worsening of glucose tolerance: due to the β-cell decompensation postprandial glucose levels rise.

- Upon further β cell function deterioration and increased hepatic glucose production, the fasting glucose level rise, damaging further the insulin secretion and insulin action (glucose toxicity).
Impaired glucose tolerance

T2DM in non-Caucasian populations

Increased genetic predisposition*

Increased visceral obesity, lower BMI cutoff

Lower cutoff values for waist circumference: ≥ 85, ≥ 80 cm

Cytokines substrates, hormones

Insulin resistance

Impaired glucose tolerance

T2DM

*TCF7L2 gene mutation (Transcription factor 7-like 2 protein) or polymorphism [mainly in Mexican Americans - due to GLP1 level↓ → 2TDM, in Han Chinese GDM]

Lower β-cell amount or β-cell dysfunction has a key role in Asian population
The percentage of visceral abdominal fat rather than the BMI per se that is associated with changes in insulin sensitivity. And while the majority of people with central adiposity have an elevated body mass index (BMI), there are individuals, particularly among certain ethnic groups, such as Asians, who may have significant visceral obesity despite the fact that their BMI is less than 25 kg/m².
The 2TDM is preventable ~ 90%

- Healthy diet
- BMI ≤ 25 kg/m²
- Daily physical activity for at least 30 minutes
- Avoid cigarettes & alcohol
Vascular complications of DM

**Macrovascular complications**

**Brain** (cerebrovascular diseases)
- Transient ischemic attack
- Cerebrovascular accident
- Cognitive impairment

**Heart** (coronary artery diseases)
- Acute coronary syndromes
- Congestive heart failure

**Extremities** (peripheral vascular diseases)
- Hypertension
- Intermittent claudication (ulceration, gangrene, amputation)

**Microvascular complications**

**Eye**
- Retinopathy
- Cataracts
- Glaucoma

**Kidney** (nephropathy)
- A2 → A3 albuminuria → renal failure

**Nerves** (peripheral or autonomic neuropathy)
- Erectile dysfunction
- Foot problems
Development of vascular complications

Long-term exposure to hyperglycemia promotes vascular complications by oxidative stress and ROS

DM primarily damages those cells that are least protected against IC hyperglycemia, FFA ↑ and ROS:
- ß cells, cardiomyocytes, mesangial cells (kidney) nerve cells (retina and peripheral nerves) and endothelial cells (vessels, retina, kidney, peripheral nerves)

IC hyperglycemia induces mitochondrial ROS overproduction; decreases GAPDH activity (~66%↓) and activates five pathological (inflammatory) metabolic pathways
1. Increased polyol pathway flux: makes cells prone to oxidative stress
2. Activation of hexoseamine pathway: PAI-1, TGF-ß ↑
3. Protein kinase C activation: structural changes of small vessels
4-5. Accumulation of advanced glycation end-products and receptors (IC, EC): activation of growth/transcription factors and cytokines

Inflammation increases white blood cell activation, damages endothelial barriers & IC proteins and ↓NO levels

Persistent consequences of hyperglycemia-induced mitochondrial ROS overproduction may also explain the continuing tissue damage after improvement of glycemic levels („hyperglycemic memory”)

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PARP – poly(ADP-ribose) polymerase
GAPDH – glyceraldehyde-3 phosphate dehydrogenase
Gene transcriptional changes in the presence of ROS may result in cell hypertrophy, proliferation, remodeling, or apoptosis and are manifested as coronary or peripheral arterial diseases, retinopathy, neuropathy, and nephropathy.

The development of DM and its complications, as discussed above, are due to a common etiopathogenesis. The development and progression of complications are influenced by genetic predisposition, environmental factors, insulin resistance, immune dysfunction / inflammation, glycolipotoxicity and comorbidities (hypertension, hyperlipidemia).
Diabetic retinopathy

- Most common cause of blindness before age 65, retinal ischemia from blood vessel changes
  - Non-proliferative or background retinopathy – the earliest stage of retinopathy characterized by
    - Microaneurysms
    - Intraretinal “dot and blot” hemorrhages
    - Hard exudates (macular edema)
  - Proliferative retinopathy – the final stage of retinopathy
    - Hypoxia → growth Factor↑ → neovascularization (vascular growth into vitreous body, or hemorrhage [vitreous body, retina]) → fibrovascular proliferation → shrinkage of proliferation may lead to retinal detachment (loss of vision)
- The development of cardiovascular complications is expected to increase five times in the presence of diabetic retinopathy
Cataract

Background or non-proliferative retinopathy

Proliferative retinopathy – retinitis proliferans

Hemorrhages

"Cotton-wool" spots

Neovascularization

Cataract
Diabetic nephropathy

- Most common cause of end-stage renal disease
- Over 20% with DM > 20 yrs have clinically apparent, progressive nephropathy (thickening of glomerular basement membrane, glomerulosclerosis)
- A2 (micro)albuminuria (30-300 mg albumin/24 hrs) is the first sign of nephropathy (A2 albuminuria may be reversed by ACE and angiotensin receptor blockers)
- Overt nephropathy – albumin excretion > 300 mg/24 hrs usually accompanied by hypertension
- Development and progression of diabetic renal insufficiency can be worsened by
  - Higher blood pressure: SBP > 135 mmHg, DBP > 85 mmHg
  - Neurogenic bladder leads to hydronephrosis and infections
  - Urinary tract infections and obstructions
  - Nephrotoxic drugs: NSAIDs, chronic analgesic abuse, radiowcontrast dyes etc
A2 albuminuria
Diabetic neuropathy

- Affecting 60-70% of patients with DM and the most common cause of non-traumatic amputations, loss of sensation & function
- Mitochondria of sensory neurons located in dorsal root ganglia are vulnerable in DM
- Pathomechanism is highly variable: contributions from vascular damage (small vessel ischemia) and metabolic disruption (see pathologic metabolic routes)
- Metabolic factors seem to prevail in frequent forms of sensorimotor peripheral neuropathies, whereas an inflammatory process superimposed on ischemic nerve lesions seems to be responsible for severe forms of focal neuropathies.
# Types of diabetic neuropathy

**Sensorimotor peripheral neuropathies**

- Symmetric, distal, bilateral of upper/lower extremities (frequent)
  - Stocking glove distribution, symptoms of numbness and tingling (pins and needles paresthesias) to painful burning and stabbing
  - End result is 100% numbness with loss of protective sensation (Charcot's joints)

**Mononeuropathies (peripheral, cranial nerves)**

**Diabetic amyotrophy**

**Autonomic neuropathies**

- **Gastroparesis diabeticorum**
  - Early satiety, abdominal distension/bloating after meals
  - Diabetic diarrhea (during the night)
    - Secondary to GI stasis with an overgrowth of bacteria in the gut
  - Neurogenic bladder (detrusor paresis)
    - Small, frequent voiding and may progress to urinary retention and overflow incontinence
  - Impaired CV reflex responses
    - Orthostatic hypotension, fixed tachycardia, continuous hypertension, respiratory sinus arrhythmia disappear
  - Impotence
    - Caused by circulatory and nervous system abnormalities (male patients)

**Foot (neuropathic) problems**
Weakness causes imbalance between small flexor & extensors, causing severe deformity
Claw toes (depression of metatarsal head with distal displacement of the metatarsal fat pad result is increased pressures in these areas → ulcers)
Macrovascular diseases

- About 80% of diabetic patients die of CVD
  - Coronary artery disease: acute coronary syndrome, silent ischemia (2-3 times the incidence of MI than non-diabetic)
  - Cerebrovascular disease
  - Peripheral vascular disease
    - Occlusive: legs and distal arteries
    - Ischemic: renal artery stenosis
  - Hypertension and impairment of autonomic regulation
    - T1DM hypertension develops as a result of diabetic nephropathy (30 %)
    - T2DM hypertension is part of metabolic syndrome. Prevalence of diabetic nephropathy: 15-20%
  - Congestive heart failure
  - Greater incidence of atherosclerosis
- SGLT2 inhibitors (gliflozins) and GIP-1 receptor agonists (incretins) may decrease adverse CV and renal outcomes
Metabolic complications – diabetic ketoacidosis (DKA)

- DKA is associated with uncontrolled T1DM or less commonly in severely decompensated T2DM
- Precipitating factors leading to DKA
  - Illness and infection or increase in insulin counter-regulatory hormones
    - ↑ production of glucagon and glucocorticoids by adrenal gland promotes gluconeogenesis and ↑ production of epi- and norepinephrine increases glycogenolysis
  - Inadequate insulin dosage
  - Initial manifestation of T1DM in adult patients
  - Chronic untreated hyperglycemia (glucose toxicity and hyperinsulinemia)
  - Fasting
Two major features of DKA

1. Uncompensated osmotic diuresis
   - Volume depletion (6.5 liters)
     - Nausea and vomiting & inadequate oral intake
   - Hyperosmolarity (hypotonic losses)
     - Secondary to renal H₂O loss and H₂O depletion from sweating, nausea and vomiting and associated K loss
   - Electrolyte loss
     - ICF/ECF electrolyte imbalance (e.g., hyperkalemia despite 400 mmol K⁺ deficit)
     - Urine electrolyte loss

2. Ketogenesis – unrestrained & underutilized; no insulin is present to prevent ketone body formation
   - Fat is utilized for energy
     - Serum ketone bodies - 10-20 mM
     - Acidosis: pH 6.8-7.3, HCO₃⁻ < 15 mmol/L
Decrease in bw
Polyphagia

*Contra-insular factors: glucagon, catecholamines, cortisol, GH
Hyperosmolar hyperglycemic state

Acute, life threatening (5-20% mortality) complication of T2DM with concomitant illnesses leading to reduced fluid intake (elderly [reduced ability to drink or sense thirst], febrile illness, stroke etc); 1/3 overlap with DKA, but less common than DKA (1-5% mortality)

Pathophysiology and signs

- ↓ insulin (sufficient to prevent lipolysis & ketogenesis; but insufficient to prevent hyperglycemia) & ↑ contra-insular hormones due to stress → ↑ glucose production
- Hyperglycemia > 33.3 mmol/l
- Hyperosmolality ≥ 320 mOsm/kg → osmotic diuresis
  - ADH release without fluid replacement → dehydration → hypotension → RAAS ↑ → kidney shut-down (exacerbation of hyperglycemia)
- Dehydration (~ 9l fluid deficit) without ketoacidosis
  - Small ketonuria, ± ketonemia, pH > 7.3, se bicarbonate > 15 mmol/l
  - Focal, global neurology deficit due to hypotension and severe electrolyte loss (often will mimic a cerebrovascular accident: hemisensory deficits, hemiparesis, aphasia, seizures); coma in 20% of cases only
  - Inflammatory cytokines, PAI-I, ROS ↑: thrombus formation (mesenterical artery, bilateral femoral artery, MI, DIC, cerebrovascular)
Relative insulin deficiency*

Contra-insular factors: glucagon, catecholamines, cortisol, GH

Impaired IC glucose utilization

Increased gluconeogenesis (liver, muscle) and glycogenolysis

Hyperglycemia

Non or minimally stimulated ketosis

Glucosuria, osmotic diuresis

Water and electrolyte loss

Na⁺ and K⁺ loss

Dehydration

Decreased fluid intake

Coma, death

Impaired kidney perfusion
## Hormonal regulation in hypoglycemia

<table>
<thead>
<tr>
<th>Glucose (mmol/l)</th>
<th>Response</th>
<th>Response mediated by</th>
<th>Effect of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.4</td>
<td>Insulin shuts off</td>
<td>Low glucose level, α adrenergic effects of circulating catecholamines, Sympathetic innervation of β islet cells</td>
<td>↓ glucose uptake (muscle and adipose) ↑ glycogenolysis (liver), ↑ gluconeogenesis (liver &amp; kidney), ↑ lipolysis (adipose tissue)</td>
</tr>
<tr>
<td>&lt; 3.9</td>
<td>Autonomic nervous system activated</td>
<td>Low glucose level</td>
<td>↓ insulin secretion, ↑ glucagon secretion, ↑ glycogenolysis (liver &amp; muscle), ↑ gluconeogenesis (liver &amp; kidney), ↑ lipolysis (adipose tissue)</td>
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<tr>
<td>&lt; 3.3</td>
<td>Hunger ↑</td>
<td>Parasympathetic system</td>
<td>Eating</td>
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<td></td>
<td>Glucagon ↑</td>
<td>Low glucose level, declining insulin β adrenergic effects of circulating catecholamines, Sympathetic innervation of α islet cells</td>
<td>↑ glycogenolysis (liver), ↑ gluconeogenesis (liver)</td>
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<tr>
<td></td>
<td>GH ↑</td>
<td>Low glucose level</td>
<td>↑ lipolysis antagonizes insulin action in muscle</td>
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<tr>
<td></td>
<td>ACTH, cortisol ↑</td>
<td>Low glucose level</td>
<td>↑ lipolysis and muscle breakdown</td>
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</tbody>
</table>
# Classification of hypoglycemia (< 4.1 mmol/l)

<table>
<thead>
<tr>
<th>Fasting hypoglycemia</th>
<th>Postprandial hypoglycemia</th>
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<tbody>
<tr>
<td><strong>With low insulin level</strong></td>
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<tr>
<td>Alcohol</td>
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<td>Endocrine deficiencies</td>
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<td>Liver or renal insufficiency / failure</td>
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<td>Septic shock</td>
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<td>Pregnancy</td>
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<td>Tumors</td>
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<td>Inborn errors of carbohydrate metabolism</td>
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<td><strong>With high insulin level</strong></td>
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<tr>
<td>Insulin effect in diabetes patients</td>
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<tr>
<td>Factitious hypoglycemia</td>
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<td>Autoimmune hypoglycemia</td>
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<td>Pentamidine</td>
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<td>Insulinoma</td>
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<td><strong>Structural / organic</strong></td>
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<td>Alimentary</td>
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<td>Early T2DM</td>
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<tr>
<td><strong>Functional or „reactive” hypoglycemia</strong></td>
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<tr>
<td>Idiopathic postprandial syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Fasting hypoglycemia with low insulin level

- Alcohol (↓hepatic gluconeogenesis but not glycogenolysis)
  In individuals fasting, exercising or sensitive to alcohol, 12-24 hours after alcohol consumption (the glycogen stores are depleted) → hypoglycemia
  The energy required for metabolism of alcohol is diverted away from the energy needed to take up lactate (substrate of gluconeogenesis)
  Neuroglycopenic symptoms of hypoglycemia may be confused with alcohol intoxication
- Endocrine deficiencies (poor gluconeogenesis and/or poor glycogenolysis)
  Adrenal insufficiency (primary or secondary), hypopituitarism (loss of ACTH and GH), isolated growth hormone deficiency (very rare), hypothyroidism (uncommon cause of hypoglycemia), isolated glucagon deficiency (rare), and sympathetic nervous system defects
- Liver insufficiency / failure: In advanced liver failure deficient glycogen stores or inadequate gluconeogenesis
- Renal insufficiency / failure: In diabetes, a dose adjustment of insulin (cleared by the kidney) is often necessary to avoid hypoglycemia
- Septic shock: Hypoglycemia can occur due to decreased gluconeogenesis.
- Pregnancy: Decreased gluconeogenesis due to decreased substrate supply (diversion of energy to fetus) and/or nutrient intake
- Tumors: Large mesenchymal tumors may secrete IGF-2, or tumors are require large amount of glucose and liver/kidney are unable to match
- Inborn errors of carbohydrate metabolism: Infants present with fasting hypoglycemia in glycogen storage disease, gluconeogenic enzyme deficiencies (rare and present during the first days of life)
Fasting hypoglycemia with high insulin level

- The most common cause of hypoglycemia, due to an imbalance between insulin supply and insulin requirements in patients with diabetes mellitus:
  - Insulin overdose
  - Inadequate food intake or excessive exercise
  - Impaired glucose counter regulatory mechanisms in T1DM
    - Deficient glucagon response: deficient catecholamine response associated with autonomic neuropathy
    - Hypocortisolism (T1DM + autoimmune primary adrenal insufficiency)
  - Gastroparesis (due to delayed gastric emptying, autonomic neuropathy)
  - Pregnancy
  - Renal insufficiency (decreased insulin degradation and impaired renal cortex gluconeogenesis)

- Type 1 DM: common in those with good glycemic control (nocturnal hypoglycemia)
- Type 2 DM: administration of oral insulin secretagogues (sulfonylureas) or insulin
  They are cleared by the kidney, so elderly patients with compromised renal function are at risk for developing hypoglycemia

- Factitious hypoglycemia (self-induced or suicide and murder): Insulin administration or intake of oral insulin secretagogues

- Autoimmune hypoglycemia (extremely rare): Insulin auto antibodies bind to insulin after it is secreted following a meal; hypoglycemia occurs 3-4 hours later as insulin-antibody immune complexes dissociate. Insulin receptor autoantibodies that bind to insulin receptor mimicking the action of insulin

- Pentamidine (treatment/prophylaxis of PCP in patients with AIDS): Pentamidine can cause hyperinsulinemia (and hypoglycemia) by direct injury to the β cells. Following the acute injury and destruction of the β cells → hyperglycemia

- Insulinoma (rare) (M:F 8:1): Nearly all insulinomas are found in the pancreas and 90% of them are single and benign as part of MEN1
Postprandial hypoglycemia

● Structural / organic
  ○ Alimentary
    ■ Due to rapid emptying of gastric contents (after gastric surgery) to the small intestine → a rapid elevation of insulin (via vagal signals and enteropeptides) → hypoglycemia
  ○ In early T2DM, the first phase of insulin release is lost and the second phase is prolonged: 3-5 hours later the delayed insulin secretion can cause hypoglycemia

● Functional or „reactive” hypoglycemia
  ○ Idiopathic postprandial syndrome (dg by exclusion)
    ■ Symptoms occurring a few hours following a meal: light-headedness, headache, dizziness, weakness, poor concentration, and tremulousness
<table>
<thead>
<tr>
<th>Autonomic nervous system symptoms (glucose &lt; 3.6 mmol/l)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic &amp; adreno-medullary</td>
<td>Tremor, anxiety, palpitations, pallor</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>Hunger, sweating (diaphoresis), paresthesias</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Neuroglycopenic symptoms (glucose &lt; 2.8 mmol/l)</th>
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<tbody>
<tr>
<td>Glucose &lt; 2.8 mmol/l</td>
<td>Irrational or uncontrolled behavior</td>
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<tr>
<td></td>
<td>Weakness, slurred speech, blurred vision,</td>
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<td></td>
<td>impaired cognition (lethargy, confusion)</td>
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<tr>
<td></td>
<td>slowed reaction time ↓ concentration,</td>
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<tr>
<td></td>
<td>extreme fatigue and somnolence</td>
</tr>
<tr>
<td>Glucose &lt; 1.7 mmol/l</td>
<td>Completely disoriented behavior</td>
</tr>
<tr>
<td></td>
<td>Loss of consciousness (coma) inability to</td>
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<tr>
<td></td>
<td>arouse from sleep</td>
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<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>May progress to death</td>
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</tbody>
</table>
Electrocardiography
Supraventricular tachyarrhythmias
Atrial fibrillation & flutter
Ventricular tachyarrhythmias
Tachyarrhythmias > 100 beats/min

- Based on the width of QRS complex
  - Narrow-complex tachyarrhythmias (QRS < 0.12 sec) or supraventricular tachycardias: originate within or above AV node and rapidly activate ventricles within the normal His-Purkinje system
  - Wide-complex tachyarrhythmias (QRS > 0.12 sec) or ventricular tachycardias: originate outside the normal conduction system (ventricular tachycardia) or travel via an abnormal His-Purkinje system (supraventricular tachycardia with aberrancy) activating the ventricles abnormally
Supraventricular tachyarrhythmias (based on mechanism)

- **Automatic arrhythmias**
  - Sinus tachycardia
  - Atrial tachycardia
  - Some forms of multifocal atrial tachycardia

- **Re-entrant arrhythmias**
  - Atrial flutter and atrial fibrillation
  - Paroxysmal supraventricular arrhythmias
    - SA nodal re-entrant tachycardia
    - Intra-atrial re-entrant tachycardia
    - AV nodal re-entrant tachycardia
    - Macro re-entrant (bypass-mediated or AV re-entry) tachycardia

- **Triggered arrhythmias** (probable mechanism)
  - Atrial tachycardia (due to digitalis-toxicity) and some forms of multifocal atrial tachycardias
Sinus tachycardia

● Atrial frequency: 100-200 beats/min
● P wave morphology: normal
● P wave before every QRS complex, PR short, TP short
● Normal ventricular complexes (100-200 beats/min)
● Causes
  ○ Physiological: pain, fear, exercise, caffeine(?)
  ○ Pathological: fever, anemia, hypovolemia, hypoxia
    ■ Endocrine: thyrotoxicosis
  ○ Drugs: atropine, β-adrenergic agonists, theophylline
  ○ Illicit drugs: alcohol, cocaine, amphetamine, metamphetamine
● Special cases:
  Inappropriate sinus tachycardia (the above factors can not explain sinus tachycardia)
  Sinus node re-entry tachycardia
Heart rate is 124 beats/min during sinus tachycardia
Atrial tachycardia

- Atrial frequency: 100-250 beats/min
- Abnormal P wave (form and shape depends on the ectopic focus)
- PR usually normal
- Ventricular activity is normal
- Types
  - Unifocal: similar P morphology
  - Multifocal: at least three different P morphology
● Mechanism: ectopic focus
  ○ Causes:
    ■ Acute myocardial ischemia, digitalis toxicity (triggered), acute exacerbations of chronic lung disease, acute alcohol toxicity, or major electrolyte disturbances
    ■ Can occur in healthy individuals
  ○ Ectopic focus is usually small, single within the atrial muscle (right atrial origin: 80%, left atrial origin: 20%), and the impulse spreads centrifugally
  ○ Multifocal – in pulmonary disease
Forms of atrial tachycardia
1. Non paroxysmal < 120/min, no symptoms
2. Benign – short paroxysm (< 30 sec), responds well to pharmacotherapy
3. Sustained > 12 hrs – refractory to drugs and may lead to tachy-cardiomyopathy
4. Multifocal
5. With block (digoxin effect)

The only supraventricular tachycardia commonly attributed to triggered activity is that seen with digitalis toxicity. Digitalis toxicity can produce delayed afterdepolarizations (DADs) that can lead to atrial tachycardias. Clinically, since digitalis toxicity also produces AV block, digitalis-toxic arrhythmias often manifest as atrial tachycardia with block.
Paroxysmal atrial tachycardia
Atrial tachycardia 2:1 block

Digitalis toxicity
Downsloping ST depression
Multifocal atrial tachycardia

- Multifocal atrial tachycardia is the most common form of automatic atrial tachycardia.
- Multiple (usually at least three), discrete P waves with at least 3 different morphologies; the automatic foci within the atria firing at different rates. The arrhythmia is usually associated with exacerbation of chronic lung disease, especially in patients receiving theophylline

- Features:
  - At least three different P-wave morphologies
  - Atrial rate > 100 bpm
  - The PP, PR, and RR intervals all vary

ECG shows multifocal atrial tachycardia at a rate of ~154 beats/min. Note the irregular rhythm and at least four P wave shapes.
Atrial flutter

- The most frequent form of macro re-entry tachycardia
  - Macro re-entry: in the wall of the right atrium (cavo-tricuspidal isthmus) – counter-clockwise rotation (see figure)
  - The re-entry cycle length is usually 200-240 msec (atrial frequency: 250-350 beats/min)
  - Saw tooth flutter (F) waves mainly in: II., III. aVF and V₁
  - AV conduction
    - Fix conduction: ventricular rhythm is regular. Odd numbered ratios of AV block (3:1 and 5:1 block) are much less common than even numbered ratios (2:1 and 4:1 block); 2:1 (ventricular rate: 150)
    - Variable conduction: the ventricular rhythm „irregularly regular”
  - Often combined with fibrillation, pulmonary disease, old age and hyperthyroidism
Typical, ordinary, classical or counter-clockwise atrial flutter: the right atrial macro-re-entry passes in craniocaudal direction of the anterolateral side of the atrium and then through the cavo-tricuspid isthmus & back to the atrial septum (ablation of cavo-tricuspid isthmus: successfully eliminates flutter in 90% cases)

Reverse typical form: Clockwise rotation

Atypical forms: it is not related to the cavo-tricuspid isthmus
Atrial flutter 2:1

Atrial flutter 2:1

Atrial flutter 3:1

Atrial flutter 4:1
Atrial fibrillation (AF)

- The most frequent form of arrhythmia (10% over age 70)
- No P waves
  - Fibrillatory waves (f wave) can be either fine (amplitude < 0.5mm) or coarse (amplitude > 0.5mm).
  - The atrial cycle length varies continuously (usually < 200 msec); atrial frequency: 350-600 beats/min
- Ventricular contraction: irregular: 100-180 bpm
  - Arrhythmia absoluta (pulsus irregularis perpetuus)
  - Pulse deficit: peripheral pulse is not as rapid as the apical rate
    - Short RR intervals, inadequate ventricular filling, low stroke volume (absence of palpable peripheral pulse)
## Risk factors and comorbidities of AF

<table>
<thead>
<tr>
<th>Cardiac causes</th>
<th>Non-cardiac causes</th>
</tr>
</thead>
</table>
| • Mitral stenosis (QRS vector: around + 90°) or mitral prolapse and aortic valve diseases  
  • Acute heart failure  
  • Congenital diseases  
  • Ostium secundum defect (right ventricular conduction disturbance in young patients)  
  • Ostium primum defect (right bundle branch block, left anterior superior block in young patients)  
  • Coronary disease  
  • Constrictive pericarditis  
  • Cardiomyopathies  
  • Wolff-Parkinson-White syndrome (ventricular rhythm: 220-300 beats/min)  
  • AV nodal disease (60-80 beats/min ventricular rhythm) | • Thyrotoxicosis (180-200 ventricular depolarization)  
  • Hypertension  
  • Advanced age  
  • Acute bleeding  
  • Obesity  
  • Sleep apnea  
  • Alcohol consumption („holiday heart”)  
  • Pulmonary embolism  
  • Restrictive pulmonary disease  
  • Inherited form ~ 5%  
  • Abnormal K channel gene(s)  
  • “Lone AF” – unknown mechanism  
  • Psoriasis |

(Independent risk factors)
# Types of AF

<table>
<thead>
<tr>
<th>Based on time</th>
<th>Based on frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Paroxysmal AF: stopped spontaneously within 7 days; or within 48 hours by electrical or pharmacological cardio version</td>
<td>• <em>Tachyarrhythmia absoluta</em></td>
</tr>
<tr>
<td>• Persistent AF: for 7 days constantly, terminated by electrical cardio version after 48 hours</td>
<td>• Normofrequent atrial fibrillation</td>
</tr>
<tr>
<td>• Long standing persistent AF: Established atrial fibrillation for more than 12 months</td>
<td>• <em>Bradyarrhythmia absoluta</em></td>
</tr>
<tr>
<td>• Permanent AF: if not terminated in any way; No attempt is made to restore and maintain sinus rhythm</td>
<td>• Atrial fibrillation w III. degree AV block, &amp; regular junctional or ventricular escape rhythm</td>
</tr>
</tbody>
</table>
Pathophysiology of AF

There are probably two (simultaneously present) electrophysiologic mechanisms of AF:

1. One or more automatic, triggered, or microreentrant foci (drivers) mainly in the left atrium fire at rapid rates and cause fibrillation-like activity
2. Multiple reentrant circuits (rotors) meandering throughout the atria that annihilate and reform wavelets, thereby perpetuating the fibrillation

- Paroxysmal AF: the most common triggers & sustainers of AF are rapid discharges from the pulmonary veins
- In persistent AF, interstitial atrial fibrosis contributes to slow, discontinuous, and anisotropic conduction and reentry
ERP – effective refractory period
The triggers initiate unidirectional block and generally involves premature or rapid ectopic activity
Triggered activity: early- or delayed after depolarization
● Consequences of AF
  ○ Impaired quality of life
  ○ Thromboembolic consequences (stroke); 3.0–7.4 %/year
  ○ Cardiomyopathy: progressive atrial enlargement

Atrial fibrillation
Atrial fibrillation, left ventricular bigeminy, ventricular couplet and ventricular tachycardia
AV nodal re-entrant tachycardia (Junctional tachycardia)

- The most common paroxysmal supraventricular tachycardia
- Pre-requisite: dual AV nodal track
  - Typical (slow-fast) AV nodal re-entry tachycardia (AVNRT)
    - During the refractory period of the fast track, an early impulse is conducted by the slow pathway then with the involvement of retrograde fast track a re-entry circuit develops.
    - RP time < 70 msec: P wave merges into QRS, or appears at the end of the QRS complex (pseudo r’ in V1, and pseudo s in II., III. & aVF)
  - Atypical (fast-slow) AVNRT
    - Anterograde conduction by the fast track, retrograde by the slow one
    - Long RP distance
Slow conduction, short refractory period

Fast conduction, long refractory period

Functional dissociation of AV node can occur at any age but mainly in middle aged females
Posterior input to the atrioventricular node (dashed arrow) serves as the anterograde slow pathway of the re-entry circuit, and anterior input to the atrioventricular node (solid arrow) serves as the retrograde fast pathway. The shaded areas indicate the target sites for radio-frequency ablation of the fast and slow pathways.

P wave is not visible

P wave is negative (anterograde pathway)
Slow-fast pathway

- Frequent – 90%
- Atrial ES initiates
- Short RP tachycardia
- Negative P waves in II., III. and aVF, if the atrial and ventricular activation is simultaneous – P wave is hidden in or buried at the end of QRS
- A QRS narrow (130-250 beats/min)

Fast-slow pathway

- Rare occurrence
- Ventricular ES initiates
- Long RP tachycardia
- Negative P waves well after the QRS complex. Negative P waves follow the T wave or just slightly before the next QRS complex
Wolff-Parkinson White (WPW) syndrome
• In the pre-excitation syndrome (between 1 and 3% of the general population) the electrical signal arrive at the ventricles early due to an accessory pathway (bundle of Kent) - Wolff-Parkinson White (WPW) syndrome

• Patients with WPW often exhibit more than one accessory pathway (up to 8), this has been seen in individuals with Ebstein’s anomaly

• Complications of WPW
  ○ Episodes of atrial fibrillation
  ○ Macro re-entrant (bypass-mediated or AV re-entry) tachycardia (junctional tachycardia) see later
Wolff-Parkinson White syndrome (WPW-syndrome)

- Short PR interval (0.12 sec)
- QRS time 0.10-0.18 sec
- Delta wave is present
- Secondary ST and T changes
Dominant R wave in lead $V_1$
Should be differentiated from:
Right bundle branch block
Right ventricular hypertrophy
Posterior MI

Negative QRS in $V_1$
Should be differentiated from:
Left bundle branch block
Anterior MI
Wolff-Parkinson-White syndrome type A
Accessory pathway: **left posteroseptal**
Wolff-Parkinson-White syndrome type B
Accessory pathway: right lateral
Complications of WPW: Macro re-entrant (bypass-mediated or AV re-entry [AVRT]) tachycardia
1. WPW

2. Orthodromic AVRT

3. Antidromic AVRT
Orthodromic AVRT

- Frequent
- Anterograde path: through normal conducting system
- Retrograde conduction: accessory pathway
  - P wave follows the ventricular activity
  - Delta wave is not present
- QRS time normal
- Frequency: 140-250 beats/min

Antidromic AVRT

- Rare (10%)
- Anterograde conduction: accessory pathway
- Retrograde conduction: normal conducting system
- Wide QRS wave (Wide QRS complex supraventricular tachycardia)
Mechanisms of ventricular tachyarrhythmias

● Automatic arrhythmias
  ○ Some ventricular tachycardias associated with acute medical conditions
    ■ Acute MI or ischemia (first few hours of an acute MI)
    ■ Electrolyte and acid–base disturbances or hypoxia
    ■ High sympathetic tone

● Re-entrant arrhythmias
  ○ Ventricular tachycardia and fibrillation associated with some chronic heart diseases
    ■ Previous MI (from about 12 h to several years after the acute event)
    ■ Dilated and hypertrophic cardiomyopathy
    ■ Channelopathies
● Triggered arrhythmias (probable mechanism)
  ○ Pause-dependent *torsade de pointes or torsades* (early afterdepolarizations) associated with drugs that prolong QT interval
  ○ Catechol-dependent *torsade de pointes* (delayed afterdepolarizations) associated with digitalis toxicity or idiopathic

● Brugada syndrome
  ○ Syncopal, sudden unexpected nocturnal death syndrome in males (inhomogeneous repolarization in the RV outflow tract + polymorphic VT)
  ○ Loss of function mutations in the rapid sodium channel (SCN5A)
  ○ *Agent provocateur*: febrile state, K↑↓, Ca↑, alcohol/cocaine intoxication, Na-channel blockers, large carbohydrate meals
## Classification of ventricular tachyarrhythmias

<table>
<thead>
<tr>
<th>Based on time</th>
<th>Based on morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Three, coupled ventricular extrasystoles = ventricular tachycardia</td>
<td>• Monomorphic ventricular tachycardia</td>
</tr>
<tr>
<td>• Non-sustained ventricular tachycardia: spontaneous termination within 30 seconds</td>
<td>• Polymorphic ventricular tachycardia</td>
</tr>
<tr>
<td>• Sustained ventricular tachycardia: lasting for more than 30 sec</td>
<td>• Ventricular flutter: above 300 bpm frequency, QRS rhythm is maintained</td>
</tr>
<tr>
<td>• Permanent ventricular tachycardia: there at least for 12 hours within a day</td>
<td>• Ventricular fibrillation: disorganized electrical activity, which is not recognizable QRS</td>
</tr>
<tr>
<td>• Incessant ventricular tachycardia: ventricular tachycardia persisting for days</td>
<td>• <em>Torsade de pointes</em></td>
</tr>
<tr>
<td>• Repetitive ventricular tachycardia: short, intermittent ventricular tachycardia episodes, interrupted with sinus tachycardia</td>
<td></td>
</tr>
</tbody>
</table>
Monomorphic ventricular tachycardia

- **Clinical aspects**
  - Age over 35 years with frequent collapse, palpitation, syncope
  - Jugular pulse: „cannon a-waves” – atrial contraction with closed tricuspid valve due to AV dissociation

- **ECG signs**

- **1. Rate, rhythm and axis**
  - Rate: 120-300 beats/min
  - Rhythm: regular (< 0.04 sec change)
  - Axis: usually 40° change compared to normal condition (either to right or to left)
    - If aVR lead is positive – depolarization should originated from the apical region
2. Signs of independent atrial activation

**Direct signs**
- In spite of ventricular tachycardia: sinus node regularly discharges – P wave dissociation
  - Please note: P wave dissociation is diagnostic in ventricular tachycardia, its absence does not exclude the diagnose
- However the atrial frequency is usually slower, than the ventricular activation
- Useful tip: for P wave try to search on ST segment; P wave is positive in lead I. and II.

**Indirect signs**
- Captured beats
  - Atrial impulse can create QRS complex. The QRS occurs earlier
- Fusion beats
  - Fusion of sinus beats and a ventricular beats. The QRS is narrow
- Concordance in precordial leads
Monomorphic ventricular tachycardia

at the onset of monomorphic tachycardia in aVR

Axis change

P wave dissociation
3. QRS time and morphology
   - QRS morphology bizarre, time: usually > 0.12 sec
     - Left ventricular origin – looks like right bundle branch block
     - Right ventricular and septal origin – looks like left bundle branch block
   - Concordance is present in chest leads
     - Positive concordance (QRS complexes are predominantly positive) – origin of tachycardia: posterior ventricular-wall
     - Negative concordance (QRS complexes are predominantly negative) – origin of tachycardia: anterior ventricular-wall
Positive concordance
Origin of tachycardia: posterior ventricular wall

Negative concordance
Origin of tachycardia: anterior ventricular wall
Polymorphic ventricular tachycardia

- Polymorphic ventricular tachycardias are classified based upon their association with a normal or prolonged QT interval (*torsade de pointes*).

1. Polymorphic ventricular tachycardia with a normal QT interval
   - Unstable rhythm with a continuously varying QRS complex morphology
   - A rate of at least 200 beats/min
   - The outcome of polymorphic VT
     - In case of permanent form – hemodynamic collapse can occur
     - In case MI – ventricular fibrillation can occur
     - However, many episodes terminate spontaneously
Non-sustained polymorphic ventricular tachycardia
The QRS complexes are variable in morphology and RR intervals; The QT interval is normal.

Ventricular flutter
The QT interval is normal and the QRS complex morphology is very variable. The patient had an underlying sinus tachycardia, suggesting increased sympathetic activity secondary to an ischemic event.
Ventricular fibrillation
2. Polymorphic ventricular tachycardia with long QT interval or torsade de pointes tachycardia (150-200/min)
   - Axis rotates in every 5-20 beats
   - If sinus rhythm is present: QT time is long and U wave is visible
   - *Torsade de pointes* tachycardia can evolve into permanent tachycardia and later into ventricular fibrillation
Torsade de pointes tachycardia
Causes of *torsade de pointes* tachycardia

- **Drugs**
  - Antiarrhythmic drugs: Vaughan Williams class Ia and III
  - Antibacterial substances: erythromycin, trimethoprim
  - Other drugs: tricyclic antidepressants, phenothiazins

- **Electrolyte disturbances**
  - Hypokalemia and hypomagnesemia

- **Congenital conditions**
  - Jervell Lange-Nielsen syndrome, Romano-Ward syndrome

- **Poisonings**: insecticides, arsenic, barium

- **Other causes**
  - Ischemia, myxodema, sub-arachnoid hemorrhage
Brugada syndrome

ECG: pattern of RBBB and ST segment elevation (≥ 2 mm) in leads V₁ to V₃.

Indian Pacing Electrophysiol. J. 2001;1(1):6