Endocrinology & metabolism
Appetite regulation, obesity and malnutrition
Physiology in a nutshell

Peripheral regulators

- I. Hormones derived from fat tissue
  - 1. Leptin
  - 2. Adiponectin
  - 3. Resistin
- II. Pancreas hormones
  - 1. Insulin
  - 2. Pancreatic polypeptide (PP)
  - 3. Amylin
- III. Gastrointestinal peptides
  - 1. Ghrelin
  - 2. Cholecystokinin
  - 3. Peptide YY$_{3-36}$ (PYY$_{3-36}$)
  - 4. Oxyntomodulin
  - 5. Gucagon-like peptide-1 (GLP-1)

Central regulation

- I. Hypothalamic regulation: Arcuate nucleus (nARC)
  - 1. Orexigenic hypothalamic neuropeptides
    - Neuropeptide Y (NPY)
    - Agouti-Related Peptide (AgRP)
  - 2. Anorectic hypothalamic neuropeptides
    - Melanocortins: POMC derivatives
    - Cocaine- and amphetamine-regulated transcript (CART)
- II. Other hypothalamic areas
  - PVN, DMN, VMN, lateral hypothalamus
- III. Food intake and mediators of CNS reward system
GLP-1 major effects
• Inhibits glucagon secretion and hepatic glucose production
• Stimulates glucose-mediated insulin secretion
• Slows gastric emptying
• Promotes satiety
• Promotes β-cell differentiation and restores β-cell function
  • Decreases β-cell apoptosis
  • Decreases proinsulin : insulin ratio
  • Increases expression of glucose transporter and glucokinase
• Increases insulin gene transcription and insulin synthesis
Food intake

Release of incretin hormones

Active GLP-1 and GIP

GLP-1 agonist

Increased peripheral glucose uptake

Better blood glucose control

↓Glucagon in glucose dependent way from α-cells (GLP-1)

↑Insulin in glucose dependent way from β-cells (GLP-1, GIP)

Decreased hepatic glucose output

DPP-4 inhibitor

Inactive GLP-1 and GIP

Insulin β-cell

Glucagon α-cell

Heloderma suspectum

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Heloderma suspectum
The MC receptors are biologically unique in that there is an endogenous antagonist (AgRP) in addition to endogenous agonists (the melanocortins).
Long-term regulation
Appetite
Long-term (appetite) regulation is maintained by the hypothalamus (adiposity center)
Sense fat stores through circulating leptin and insulin level

Short-term regulation
Satiety
Short-term (meal-to-meal) regulator (satiety center)
Satiety signals from the gut are relayed through the brain stem to the hypothalamus and integrated with signals of fat stores
Effectors: CCK, GLP-1, ghrelin etc
● Weight loss – less tolerant regulation (leptin ↓)
  ○ Activation of orexigenic (anabolic) neuropeptides / inhibition of anorexigenic (catabolic) neuropeptides
    ■ Stimulated by insulin, leptin and ghrelin
    ■ Enhanced NPY/AGRP and decreased melanocortin (MC-4R) signaling → positive energy balance, until normal bw is achieved
    ■ Function: prevent excessive weight gain
● Weight gain – more tolerant regulation (leptin ↑)
  ○ Stimulation of anorexigenic neuropeptides / inhibition of orexigenic neuropeptides
    ■ Decreased NPY/AGRP and enhanced MC-4 signaling → negative energy balance until it is restored to baseline
  ○ Tolerant regulatory mechanism
    ■ Uncompensated weight gain reestablishes the energy homeostasis at a higher body weight set point and leptin level \{leptin resistance (?) (analogous to acquired insulin resistance)\} → obesity develops
Energy input (calories consumed) must be equal to energy output (calories expended) for body weight to remain constant.
BMI is influenced by

1. Age
2. Diet (specific dynamic effect) – thermogenesis
3. Body temperature
4. Starvation, overfeeding
5. Hormonal effects
6. Psychological, emotional effects
7. Circadian rhythms, sleep
8. Excise goods ie cigarettes, tobacco alcohol

- 1.66 Kcal/m²/hr /10 yr
Evaluation of protein stores

Somatic protein pool – muscle mass (decreased circumference of mid arm)
Visceral protein pool – liver (serum albumin, transferrin)

Evaluation of fat stores

Skin fold-measure of subcutaneous fat to predict body-fat content 3-3.5% error
Bioelectrical impedance analysis
Accurate but impractical measurements: underwater weighing, dual-energy X-ray absorptiometry (DEXA)

Body Mass Index (BMI): dividing body weight (in kilograms) by height (in meters squared) kg/m^2, it may not be appropriate for athletes or body builders

BMI < 15.0 Severely malnourished
BMI 15.0-16.9 Moderately malnourished
BMI 17.0-18.4 Mildly malnourished
BMI 18.5-24.9 Normal
BMI 25-29.9 Overweight
BMI 30-34.9 Moderately obese
BMI 35-39.9 Severely obese
BMI ≥40 Morbidly obese
Obesity

- Obesity was declared as a disease in 1984
  - Very high amount of body fat in relation to lean body mass, mainly due to disequilibrium between energy intake and expenditure
  - BMI of 30 kg/m\(^2\) or higher (WHO)

- Epidemiology of obesity (~640 M obese in 2014)
  - Trends
    - African Americans (semaphorin-4D gene abnormality) $\uparrow$ obesity
    - Asians (more visceral fat: more prone to T2DM at lower BMI)
  - Metabolic imprinting – critical periods for obesity development
    - Programming of metabolism at genomic/epigenomic level
The diagram illustrates the relationship between age and relative weight change. It highlights three critical periods:

1. **First critical period**: High maternal BMI, high gestational weight gain, rapid postnatal growth.
2. **Second critical period**: Early adiposity rebound.
3. **Third critical period**: Early pubertal development.

The factors influencing weight change include genetic, behavioural, and socioeconomic factors.
Factors contributing to obesity

- I. Genetic factors influence the number of fat cells in the body, the amount & place fat is stored, and their metabolic rates in 60-80%
  - Obese parents give rise to obese children, even when reared apart & twins are also likely to weigh the same whether reared together or apart
  - 1. Monogenic obesity in humans
    - Leptin-related mutations: leptin & leptin receptor gene
    - POMC-related mutations: POMC, prohormone convertase 1 and melanocortin-4 receptor (MC-4R)
      - POMC mutation: can be treated with MC-4R agonist [2016]
      - MC-4R mutation: 0.5-1% adults (especially in Pima Indians), 6% obese kids)
2. Congenital disorders / genetic syndromes
   - Prader-Willi syndrome
     - High level of ghrelin, obesity, hypogonadism, mental and craniofacial abnormalities
   - Bardet-Biedl syndrome
     - Obesity, retinitis pigmentosa, polydactilia, mental retardation, hypogonadism, renal failure
3. Genome-wide association studies: FTO locus (regulation of appetite, thermogenesis, adipocyte browning and epigenetic mechanisms of obesity)
II. Neuroendocrine causes of obesity

- Hypothalamic: trauma, tumor, inflammation
- Hypothyroidism, Cushing’s syndrome, PCOS (see before)
- Hyperparathyroidism
  - Obesity can increase PTH and vitamin D level or *vice versa*
- Deficiencies of GH and gonadal steroids
  - Aging – modest increase in body weight
  - Dysregulation hypothalamic-pituitary axis may contribute to increase in fat mass and sarcopenia (age related loss of muscles)
    - GH decreases with age
      - GH replacement and sustaining IGF-1 normal level – less fat, more lean tissue
    - Changes in steroid hormone level: All contribute to reduced muscle mass and increased fat distribution
      - Cortisol level is increased in both sexes
      - Testosterone is decreased in male and estrogen is decreased in female
III. Drug-related obesity
  ○ Long-term glucocorticoid treatment
  ○ Antiepileptic drugs (gabapentin, valproic acid)
  ○ Antidiabetic drugs (insulin, sulfonylureas)
  ○ Antipsychotic agents (clozapine)
  ○ Antidepressants (MAO inhibitors, tricyclic antidepressants)

IV. Other factors
  ○ Cessation of smoking (nicotine withdrawal) – 4-5 kg gain or more
  ○ Overeating and sedentary lifestyle
    ■ Energy dense food (availability, portion, size, high fat & cholesterol composition) e.g. fast foods, snacks, fructose-containing soft drinks
    ■ Television/computer viewing time ↑ (chips)
Nauru Island (Oceania) within one generation 2/3 of the population became obese and 1/3 of the population developed diabetes; currently 50%

Guru Walla (Cameroon) overeating before marriage (19 kg within 5 months)

Sumo – progressive overeating

Frequency of eating: grazers and gorgers
  □ Several small meal: lower cholesterol and blood sugar level

Behavioral, psychological and social factors

  Restrainted eating in middle-age woman of normal weight
  Night eating syndrome
  Overweight with less education (mainly in females)
  Seasonal depression and weight gain
The basal ganglia are involved in the rewarding, and reinforcing effects of food, instrumental learning and habitual behavior. The basal ganglia contribute to habitual overeating that can arise from maladaptive habit formation processes.

The brain stress systems in the extended amygdala mediate overeating to relieve a negative emotional state that emerges from withdrawal processes.

Food intake and CNS reward system

Prefrontal-cortical regions control cognitive functions such as decision-making and response inhibition through interactions with subcortical structures such as the basal ganglia and the extended amygdala. Dysfunctions in the PFC are hypothesized to underlie overeating despite aversive consequences, reflecting failures in inhibitory control over behavior.

Types of obesity

Small, insulin sensitive adipocytes
Adrenergic receptors ↓

Large, insulin resistant adipocytes w ↑ adrenergic receptors
Insulin & catecholamine-mediated lipolysis
**Hypothalamic malfunctioning (proteostasis)**
**Leptin and ghrelin resistance**

**Resistin** may contribute to the development of insulin resistance and diabetes in obesity. Circulating resistin falls after weight loss.

**Plasminogen activator inhibitor-1** (PAI-1): impairs fibrinolysis, ↑ formation of microthrombi and ↑ insulin resistance.

**Adiponectin**: ↑ PPAR and AMP-activated kinase activity – ↑ FFA oxidation and glucose uptake to muscle; ↓ hepatic glucose production. Adiponectin is increased after weight loss; reduced adiponectin level could contribute to the pathogenesis of obesity. Adiponectin mutation is frequent in metabolic syndrome.

**Inflammation**

IL-6 – ↑ insulin resistance

**TNF-α**: TNFα or TNFα receptor knock-out animals: improvement of insulin resistance and ↓ FFA amount ↓ adiponectin level

**Chemokine**: macrophage-chemotactic protein (MCP-1) – infiltration of leukocytes in the fat tissue.
Complications of obesity

Related to total fat cell size

- Metabolic syndrome
- Cardiovascular diseases (CVD)
- Premature death
- Pancreatitis, cholecystitis, cholelithiasis
- Gout
- Endometrial, breast, prostate, and colon cancer (e.g., IGF-1 ↑)
- Poor female reproductive health

Related to fat cell mass

- Osteoarthritis
- Obstructive sleep apnea and respiratory problems
  - Pickwick syndrome
- Bladder control problems
  - Stress incontinence
- Psychological
  - Depression, eating disorders
  - Distorted body image
  - Low self-esteem
Complications of obesity

- I. Metabolic syndrome ((syndrome X or insulin resistance syndrome): a cluster of metabolic conditions, that, when occurring together may indicate a predisposition to T2DM (5x) and CVD (2x)
  - 1. Visceral (omental, mesenteric) obesity
    - Ectopic fat deposition: atherogenic, diabetogenic & low grade systemic inflammatory environment
  - 2. Atherogenic (diabetic) dyslipidemia
    - a. Non-HDL-C ↑: increase in apo-B containing lipoproteins (VLDL-C, IDL-C, LDL-C, chylomicron and lipoprotein(a))
    - b. Hypertriglyceridemia (↑ TG synthesis and VLDL-C secretion)
      - Insulin resistant fat cells catabolize TGs → FFA ↑→ fat infiltration of liver, muscle and pancreas (pancreatitis)
        - Increased insulin resistance in liver and muscle
        - Decreased insulin secretion (lipo [↑ceramides] & gluco toxicity)
    - c. HDL-C ↓ (weight reduction improves HDL-C)
3. Elevated blood pressure $\geq 130/85$ mmHg
   - ↑ sympathetic activity, renal compression by adipose tissue (?)
4. Insulin resistance or glucose intolerance
   - Elevated FFA, lipid intermediates and inflammatory cytokines
5. Non-alcoholic fatty liver disease: non-alcoholic steatohepatitis and cirrhosis
   - Liposomes (small cytoplasmic organelles close to mitochondria) are increased in size
6. Prothrombotic state
   - Elevated fibrinogen and plasminogen activator inhibitor-1 (PAI-1)
   - Positive relationship between PAI-1 and plasma TGs
7. Proinflammatory state: fat & liver
   - ↑ IL-6, TNF, M1 macrophages, Th$_1$, 17 & CD8$^+$ T ly
   - ↓ M2 macrophages, T$_{reg}$, Th$_2$

Prior to World War II, metabolic syndrome was a rare disease: now, prevalence varies – average 25%
Blood pressure ≥ 130/85 mmHg

Fasting blood glucose ≥ 5.6 mmol/l

HBA₁C > 6.5 %

Central obesity
≥ 85 / 94 / 102 cm
≥ 80 / 88 cm

HDL-C < 1 mmol/l; < 1.3 mmol/l

TG > 1.7 mmol/l

LDL-C > 2.6 mmol/l

apoB, LDL-C

Body Mass Index
Waist/Hip Ratio

HDL Cholesterol
Triglycerides

Blood Pressure
Systolic BP
Diastolic BP

Insulin Resistance
Fasting Insulin
Fasting Glucose

Lipids

Obesity
II. Cardiovascular diseases
  ○ High blood pressure – twice as common in obese people compared to those with healthy weight; physical activity cuts risk of death by 30-50%
  ○ Coronary heart disease (angina pectoris)
  ○ Congestive heart failure
  ○ Stroke
  ○ Venous thrombosis
III. Premature death
IV. Gout
  ○ Uric acid is a breakdown product of purines; uric acid nephrolithiasis
V. Endometrial, breast, prostate, and colon cancer
VI. Poor female reproductive health
  ○ Menstrual irregularities, infertility, irregular ovulation, PCOS
Malnutrition

- Primary malnutrition: one or more components of an adequate diet is missing
  - Starvation & cachexia (wasting induced by chronic illness)
  - Childhood forms (predominantly <5 yrs of age)
    - Stunting (reduced linear growth or nutritional dwarfism) [~115 M]
    - Wasting (loss of muscle and fat & physiologic abnormalities)
      - Moderate wasting [~35 M] for mechanisms see starvation /cachexia
      - Severe wasting or marasmus [~17 M]
    - Kwashiorkor („the disease of the child displaced from the breast” or nutritional edema) [~50-70% of the above]

- Secondary or conditional malnutrition
  - Decreased intake: dysphagia, anorexia
  - Malabsorption
  - Increased requirements: normal growth, pregnancy, trauma, burns
  - Special categories: total parenteral nutrition
Adaptation to starvation

Day 1
Liver glycogen stores are depleted; glucose utilization is decreased; glucose level is maintained by gluconeogenesis (glycerol, amino acids; Cori & alanine cycle)
Fat mobilization is increased (lipolysis, ketone body production)

Day 3
Lipolysis is increased by 50% - ketone body production ↑↑, ketoacidosis

Day 7
Ketone body production: 75-times increase; 70% of energy needs is covered
   Can cross blood-brain barrier – fuel for brain
   Inhibits protein breakdown from muscle
Kidney – 50% of total glucose production from glutamine
Resting metabolic rate is decreased by 1%/day; until stabilizing at about 75% of normal

The short-term hormonal regulation of starvation: insulin & glucagon
Day 14 or over

**Maximal adaptation to starvation**

- Adipose tissue provides more than 90% of fuel
- Glucose production and myofibrillar protein breakdown are at the minimum
- Diminished urea load to the kidney diminishes urine volume to 200 ml/day – minimizing fluid requirements

When fat stores are exhausted (~ 2-3 months); significant myofibrillar protein loss again becomes necessary for energy production; death occurs due to infection (secondary immunodeficiency)

Long-term regulators: GH, thyroid hormones, catecholamines, corticosteroids

! 382-day of successful fast: 207 kg → 126 kg

Cachexia:

- Release of IL-1,6,12 TNF-α (appetite, food intake ↓, muscle & fat catabolism ↑)
- Activation of ubiquitin-proteasome system (breakdown of myofibrillar proteins) & autophagy
Severe acute malnutrition

● Severe acute malnutrition (formerly: protein-energy malnutrition): marasmus & kwashiorkor
  ● Marasmus: severe starvation induced fat loss and muscle wasting
  ● Kwashiorkor: maladaptive metabolic response to high carbohydrate, low protein diet; impaired metabolism is associated with mitochondrial malfunction & ROS↑

● Inadequate dietary intake of energy, protein, or both for prolonged periods and presence or absence of chronic diseases/infections
  ○ Impaired skin, respiratory & GI mucosal barrier
  ○ Cytokines (IL-1, 6, 12, TNF-α) diminish IGF-1 → linear growth failure
  ○ Overall malfunction of the immune system (neutrophil, T-cell hyporesponsiveness)
Severe acute malnutrition

- Adrenal gland activation
- GH ↓ - stunted growth
- Muscle protein catabolism ↑
- Plasma protein normal
- Lipoprotein synthesis normal
- FFA ↑
- No fatty liver
- Hypoproteinemia
- Edema & Fatty liver

**Marasmus**

**Kwashiorkor**

**Weaning**
- Low protein:energy ratio foods (bananas, maize, root crops)
- Wet season (food shortage, frequent infections: malaria, diarrhea)
- Acute & chronic diseases, infections: TNF-α, interleukins
- Increased protein need / poor intake / increased catabolism
- Aflatoxins: liver & immune damage
<table>
<thead>
<tr>
<th>Marasmus</th>
<th>Kwashiorkor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adaptive response</strong> to chronic conditions</td>
<td><strong>Maladaptive response</strong> to acute conditions with predominant protein deficiency</td>
</tr>
<tr>
<td>(starvation, alcoholism, eating disorders)</td>
<td>(weaning, stress, under nutrition, trauma, infection)</td>
</tr>
<tr>
<td>Younger (&lt; 12 months) kids, marked depletion</td>
<td>Older (&gt; 18 months) kids, better nutrition (subcutaneous fat is maintained)</td>
</tr>
<tr>
<td>of subcutaneous fat, and muscle mass (body</td>
<td>body mass: 60-80% of normal; Edema, pot belly, fatty liver, moon face</td>
</tr>
<tr>
<td>mass: &lt; 60% of normal), loss of fat pads,</td>
<td></td>
</tr>
<tr>
<td>loose skin, monkey face</td>
<td></td>
</tr>
<tr>
<td>Loss of somatic protein compartment,</td>
<td>Visceral protein loss (liver), albumin ↓↓, edema</td>
</tr>
<tr>
<td>albumin N or ↓; no edema</td>
<td></td>
</tr>
<tr>
<td>Fatty liver – no</td>
<td>Fatty liver – yes</td>
</tr>
<tr>
<td>Dry, wrinkled skin, ulcerations, lanugo-like</td>
<td>Dyschromia (hyper/ hypopigmentation), desquamation, enamel-paint spots,</td>
</tr>
<tr>
<td>hair</td>
<td>hair with reddish tingle, dermatitis</td>
</tr>
</tbody>
</table>
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
    - Microvascular complications (eyes, kidneys, nerves)
    - Macrovascular complications (heart and blood vessels)
    - Metabolic complications/emergencies
      - Diabetic ketoacidosis
      - Non-ketotic hyperosmolar coma
      - Hypoglycemia (upon treatment of DM by insulin or insulin secretagogues)
Diabetes mellitus

- 6th leading cause of death
- Renal failure
- Blindness
- Amputation
- Nerve damage in 60% to 70% of patients
- Life expectancy ↓ 5-10 years
- Cardiovascular disease ↑ 2-4x

Diabetes is the no. 1 cause of renal failure, new cases of blindness, and non-traumatic amputations

Etiologic classification of DM

1. Type 1 DM (type 1a, 1b) (T1DM)
2. Type 2 DM (T2DM)
3. Other specific types of DM
   - Genetic defects in insulin secretion and action
     - Maturity-onset diabetes of the young (MODY) ~2% of diabetes
       - Defect in insulin secretion or glucose metabolism (6 genes are identified) with no insulin resistance
       - Inherited in an autosomal dominant pattern
     - Mutations of the insulin receptor
   - Diseases of the exocrine pancreas
   - 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
○ 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

• 4. Gestational DM (GDM) ~7% of pregnancies
  ○ Any degree of glucose intolerance in the 2\textsuperscript{nd}-3\textsuperscript{rd} 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
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: 7.0 mmol/l
- Impaired fasting glucose: 5.6 mmol/l
- Normal: 5.6 mmol/l

Oral glucose tolerance test (75 g glucose)

- 2 hr plasma glucose
  - Diabetes mellitus: 11.1 mmol/l
  - Impaired glucose tolerance: 7.8 mmol/l
  - Normal: 7.0 mmol/l
Type 1 DM

- Type 1a DM (autoimmune)
  - Lack of insulin (prone to ketoacidosis) due to autoimmune destruction of pancreatic β cells
    - Immunologic markers: autoantibodies against insulin (IA-2), glutamic acid decarboxylase (GAD65 or GAD2), or zinc transporter 8 (ZNT8)
    - Genetic markers: strong HLA-II associations (DR3-DQ2, DR4-DQ8)
  - 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 type 1a DM

Immune dysregulation

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

Accelerating factors
- Infections
- Puberty, stress, infections

Loss of 1st phase of insulin secretion

Beta cell amount

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

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

Freshly discovered T1DM

Prediabetes
- Hyperglycemia
- Symptoms

Stage I
- Autoantibodies
- Hyperglycemia
- Symptoms

Stage II
- Autoantibodies
- Hyperglycemia
- Symptoms

Stage III
- Autoantibodies
- Hyperglycemia
- Symptoms

Time

Stage I

Stage II

Stage III
○ The first manifestation of T1DM is the loss of the 1st phase of insulin response following an intravenous glucose tolerance or ↑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 or severe symptoms of hyperglycemia. This is when most people with T1DM are diagnosed (~90% of pancreatic β-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
Antigen presentation by B cells and DCs drives the activation of β-cell-specific T cells
● Type 1b DM (idiopathic form)
  ○ Strongly inherited (African, Asian ancestry), no immunological evidence for autoimmune β-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 β-cell destruction
    ■ Fulminant type 1 DM accounts for 15-20% of type 1 DM cases in Japan
Prediabetes

- Prediabetes: leads to development of type 2 DM
  - Associated with metabolic syndrome
  - Risk factors for future diabetes and CVD
  - Lifestyle changes are effective in the majority of cases
  - Conversion of prediabetes into full-blown T2DM: 7-11% per year

  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)

- 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
- HbA1c in prediabetes: 5.7-6.4% (39-47 mmol/mol)
American Diabetes Association
Type 2 DM

- The most prevalent form of diabetes - 90% with DM have type 2
- Etiology
  - Strong genetic basis (90% with family history) with complex and not clearly defined inheritance or markers
  - 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
• Type 2 DM is caused by two separate pathophysiological abnormalities.
  1. Genetic defects β-cells (~50% ↓ of β-cell function at the time of development of DM)
     ■ Impaired ability of insulin to suppress hepatic glucose output - increased glucose production (glucagon ↑)
     ■ Insulin secretion is insufficient to match the degree of insulin resistance (insulin deficiency)
  2. Insulin resistance or defect in insulin action
     ■ It is caused by genetic and environmental factors
Ten physiologic abnormalities involved in T2DM. Insulin resistance in muscle and the liver, and impaired insulin secretion by the pancreatic β-cells are the core defects.
Abnormalities of β-cells

- 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

Normal response

Insulin

Glucagon

IV glucose
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 type 2 DM – 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 type 2 DM 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**

<table>
<thead>
<tr>
<th>Genetic abnormalities may effect β-cell apoptosis, regeneration, glucose sensing, hormone synthesis etc (first degree relatives of DM, GDM, PCOS &amp; elderly)</th>
<th>Acquired factors</th>
</tr>
</thead>
</table>
| Malnutrition *in utero* and early childhood Islet cell changes in T2DM  
  • Abnormally regulated a-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  
  • Obesity and insulin resistance: factors released from adipose tissue (FFA, TNF-α, resistin, leptin) and tissue accumulation of lipids impair 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 |
α-cells secrete glucagon  
β-cells secrete insulin  
There are insulin receptors on alpha cells  
In addition, there are delta cells that make somatostatin, and pancreatic progenitor (PP) cells  

**α-cell dysfunction**: secrete inappropriately high levels of glucagon  
**Fewer β-cells (40-60% ↓)** secrete insufficient levels of insulin  
Amyloid plaques
Insulin resistance

● 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
Approximately 20% of obese patients do not have insulin resistance, while as many as 20% of thin, normal-weight people do.
Decreased phosphatidylinositol kinase-3 signaling
**Overall effect:** ↓ GLUT-4 translocation → hyperglycemia

MAP kinase pathway unaltered (or stimulated)
Mitogenic and pro-inflammatory effects
Endothelial dysfunction
**Overall effect** – enhanced atherosclerosis
● Other mechanisms contributing to the development of insulin resistance
  ○ 1. ectopic lipid accumulation in insulin-sensitive tissues (PKC activation; ceramid, DAG ↑)
  ○ Mitochondrial dysfunction (ROS↑, adiponectin↓)
  ○ Systemic inflammation
    ■ Pro-inflammatory cytokines contribute to molecular mechanisms of insulin resistance
      ■ M1 macrophages, Th1,17, CD8 ↑, Treg, Th2↓
  ○ ER stress and the unfolded proteins
Chronic consumption of lipogenic calories

Hyperinsulinemia → insulinopenia

Glucotoxicity

Glucogenolysis
Gluconeogenesis

apo(B)
VLDL-C

Atherogenic dyslipidemia
Coagulation factors↑
PAI-1, CRP ↑

Increased glucose reabsorption (SGLT2)
↑ threshold for glucose spillage into urine

↓ glucose uptake

Lipotoxicity

Lipolysis↑

FFAs

Fatty liver

Lipotoxicity

Obesity
Resistance to appetite suppressing effects of insulin, leptin, GLP-1, amylin, peptide YY
Brain DA ↓, 5HT↑

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).
The 2TDM is preventable ~ 90%

- Healthy diet
- BMI ≤ 25
- Daily physical activity for at least 30 minutes
- Avoid cigarettes, alcohol
T2DM in non-Caucasian populations

Increased genetic predisposition*

- Increased visceral obesity, BMI cutoff lower
- Lower cutoff values for waist circumference: ≥ 85, ≥ 80 cm

Cytokines substrates, hormones

- Insulin resistance

β-cell dysfunction has a key role in Asian population

Impaired glucose tolerance

Type 2 DM

*TCF7L2 gene mutation (Transcription factor 7-like 2 protein)
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.

**Insulin sensitivity (mol/kg/min)**

**Visceral abdominal fat (%)**

- Area of subcutaneous fat: 115 cm²
- Area of visceral fat: 146 cm²
- BMI: 23.1 kg/m²

- Area of subcutaneous fat: 190 cm²
- Area of visceral fat: 60 cm²
- BMI: 24.0 kg/m²
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 diabetic complications
Microvascular complications

- Microvascular complications are caused by prolonged exposure to hyperglycemia
  - Hyperglycemia damages cells that cannot down regulate glucose uptake, causing IC hyperglycemia
    - Mesangial cells: kidney
    - Neurons: retina and peripheral nerves
    - Endothelial cells: retina, kidney, peripheral nerves
- Hyperglycemia induces mitochondrial
  - Superoxide overproduction
    - Damage to endothelial barrier and IC proteins, white blood cell activation, NO levels
    - Persistent consequences of hyperglycemia-induced mitochondrial superoxide overproduction may also explain the continuing tissue damage after improvement of glycemic levels ("hyperglycemic memory")
○ decreases GAPDH activity (~66%↓) and activates five pathologic metabolic routes
  ■ 1. Increased polyol pathway flux
    □ Makes cells prone to oxidative stress
  ■ 2. Activation of hexoseamine pathway
    □ PAI-1, TGF-β ↑
  ■ 3. Protein kinase C activation
    □ Structural changes of small vessels
  ■ 4-5. Accumulation of advanced glycation end-products and receptors (IC, EC)
    □ Growth factors and cytokines

● Microvascular complications
  ○ Diabetic retinopathy, diabetic nephropathy and diabetic neuropathy
PARP – poly(ADP-ribose) polymerase
GAPDH – glyceraldehyde-3 phosphate dehydrogenase
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)
      - “Beading” of the retinal veins
      - Cotton wool spots (soft exudates)
      - Irregular, dilated, and tortuous retinal capillaries
  - Proliferative retinopathy – the final stage of retinopathy
    - Hypoxia → growth factors↑→ neovascularization with fragile new vessels, which are prone to bleeding, develop in response to ischemia leading to:
      - “Floaters”, “cobwebs”
      - Retinal detachment
      - Sudden, painless and permanent vision loss is related to a severe retinal hemorrhage
Cataract

Background or non proliferative retinopathy

Proliferative retinopathy – *retinitis proliferans*

Hemorrhages

"Cotton-wool" spots

Neovascularization

480
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 is the first sign (30-300 mg albumin/24 hrs)
  - A2 albuminuria may be reversed by ACE and angiotensin receptor blockers
- Overt nephropathy – albumin excretion > 300 mg/24 hrs accompanied by hypertension
- Development and acceleration of diabetic renal insufficiency
  - Higher blood pressure
    - SBP >135 mm Hg, DBP > 85 mm Hg
  - Neurogenic bladder leads to hydronephrosis and infections
  - Urinary tract infections and obstructions
  - Nephrotoxic drugs: NSAIDs, chronic analgesic abuse, radiocontrast 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 [see microvascular dysfunction]) 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

<table>
<thead>
<tr>
<th>Sensorimotor peripheral neuropathies</th>
<th>Autonomic neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric, distal, bilateral of upper/lower extremities (frequent)</td>
<td><strong>Gastroparesis diabeticorum</strong></td>
</tr>
<tr>
<td>Stocking glove distribution, symptoms of numbness and tingling (pins and needles paresthesias) to painful burning and stabbing</td>
<td>Early satiety, abdominal distension/bloating after meals</td>
</tr>
<tr>
<td>End result is 100% numbness with loss of protective sensation (Charcot's joints)</td>
<td>Diabetic diarrhea (during the night)</td>
</tr>
<tr>
<td>Mononeuropathies (peripheral, cranial nerves)</td>
<td>Secondary to GI stasis with an overgrowth of bacteria in the gut</td>
</tr>
<tr>
<td>Diabetic amyotrophy</td>
<td>Neurogenic bladder (detrusor paresis)</td>
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<td></td>
<td>Small, frequent voiding and may progress to urinary retention and overflow incontinence</td>
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<tr>
<td></td>
<td>Impaired CV reflex responses</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension, fixed tachycardia, continuous hypertension, respiratory sinus arrhythmia disappear</td>
</tr>
<tr>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td></td>
<td>Caused by circulatory and nervous system abnormalities (male patients)</td>
</tr>
<tr>
<td></td>
<td>Foot (neuropathic) problems</td>
</tr>
</tbody>
</table>
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

- Manifestations: of all cases of diabetes, 80% 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: > 50% of diabetics, especially women, likely to be hypertensive by age 50 (insulin resistance increases vascular resistance & sympathetic tone)
    - T1DM hypertension develops as a result of *nephropathia diabetica* (30%)
    - T2DM part of metabolic syndrome. Prevalence of hypertension is 2-3 times greater than non-diabetic. *Nephropathia diabetica* (15-20%) can occur
  - Congestive heart failure
  - Greater incidence of atherosclerosis
- SGLT2 inhibitors (gliflozins) and GIP-1 receptor agonists (incretins) may decrease adverse CV and renal outcomes
Diabetes Mellitus

- Hyperglycemia
- Excess Free Fatty Acids
- Insulin Resistance

Oxidative Stress

- Protein Kinase C Activation
- Receptor for Advanced Glycation End Product (RAGE) Activation

ENDOTHELIUM

- Nitric Oxide
- Endothelin-1
- Angiotensin II

- Nitric Oxide
- Activation of NF-κB
- Angiotensin II
- Activation of Activator Protein-1

Vasoconstriction
- Hypertension
- Vascular Smooth Muscle Cell Growth

Inflammation
- Release of Chemokines
- Release of Cytokines
- Expression of Cellular Adhesion Molecules

Thrombosis
- Hypercoagulation
- Platelet Activation
- Decreased Fibrinolysis

Atherogenesis
Diabetic ketoacidosis

- Diabetic ketoacidosis is associated with uncontrolled T1DM or less commonly in severely decompensated T2DM
- Precipitating factors leading to diabetic ketoacidosis
  - 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 diabetic ketoacidosis

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

Polydipsia

Coma, death
Non-ketotic hyperosmolar coma

- An acute, life threatening metabolic complication with a high mortality (30-50% primarily due to underlying vascular or infectious event) usually in the elderly patients with T2DM or undiagnosed DM
- Enough insulin is present to prevent ketoacidosis; acidemia & ketosis (if present) is mild
- Cardinal features
  - Severe hyperglycemia: plasma or serum osmolality (> 340 mOsm)
  - Severe dehydration: long-standing uncompensated osmotic diuresis; unbalanced fluid intake; average fluid loss is ~9 liters
  - Mild confusion, lethargy w focal neurological signs (often will mimic a cerebrovascular accident: hemisensory deficits, hemiparesis, aphasia, seizures)
  - Coma: high blood sugar level + dehydration
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

Increased EC osmolality

Water and electrolyte loss

Na⁺ and K⁺ loss

Dehydration

IC water loss

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>
</tr>
<tr>
<td>Hunger ↑</td>
<td>Parasympathetic system</td>
<td>Eating</td>
<td></td>
</tr>
<tr>
<td>&lt; 3.3</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>
</tr>
<tr>
<td>GH ↑</td>
<td>Low glucose level</td>
<td>↑ lipolysis antagonizes insulin action in muscle</td>
<td></td>
</tr>
<tr>
<td>ACTH, cortisol ↑</td>
<td>Low glucose level</td>
<td>↑ lipolysis and muscle breakdown</td>
<td></td>
</tr>
</tbody>
</table>
## Classification of hypoglycemia (< 4.1 mmol/l)

<table>
<thead>
<tr>
<th>Fasting hypoglycemia</th>
<th>Postprandial hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With low insulin level</strong></td>
<td><strong>Structural / organic</strong></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Alimentary</td>
</tr>
<tr>
<td>Endocrine deficiencies</td>
<td>Early T2DM</td>
</tr>
<tr>
<td>Liver insufficiency / failure</td>
<td></td>
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<tr>
<td>Renal insufficiency / failure</td>
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<tr>
<td>Septic shock</td>
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<tr>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Tumors</td>
<td></td>
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<tr>
<td>Inborn errors of carbohydrate metabolism</td>
<td></td>
</tr>
<tr>
<td><strong>With high insulin level</strong></td>
<td><strong>Functional or „reactive” hypoglycemia</strong></td>
</tr>
<tr>
<td>Insulin effect in diabetes patients</td>
<td>Idiopathic postprandial syndrome</td>
</tr>
<tr>
<td>Factitious hypoglycemia</td>
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<tr>
<td>Autoimmune hypoglycemia</td>
<td></td>
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<tr>
<td>Pentamidine</td>
<td></td>
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<tr>
<td>Insulinoma</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 ß cells. Following the acute injury and destruction of the ß 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
### Autonomic nervous system symptoms (glucose < 3.6 mmol/l)

<table>
<thead>
<tr>
<th>Sympathetic &amp; adreno-medullary</th>
<th>Tremor, anxiety, palpitations, pallor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic</td>
<td>Hunger, sweating (diaphoresis), paresthesias</td>
</tr>
</tbody>
</table>

### Neuroglycopenic symptoms (glucose < 2.8 mmol/l)

<table>
<thead>
<tr>
<th>Glucose &lt; 2.8 mmol/l</th>
<th>Irrational or uncontrolled behavior&lt;br&gt;Weakness, slurred speech, blurred vision, impaired cognition (lethargy, confusion) slowed reaction time ↓ concentration, extreme fatigue and somnolence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose &lt; 1.7 mmol/l</td>
<td>Completely disoriented behavior&lt;br&gt;Loss of consciousness (coma) inability to arouse from sleep&lt;br&gt;Seizures&lt;br&gt;May progress to death</td>
</tr>
</tbody>
</table>