**Metabolic syndrome and obesity**

**Body weight**
- adipose tissue
  - males ~10–20% of body weight
  - females 20–30% of body weight
- body weight *increases with age* in both genders
- it is a *continuous trait*, establishing normal range is arbitrary to certain extent
  - ideal weight is associated with the longest life-expectancy
- body weight is viewed also in the cultural, geographical and historical context
- obesity is a one of many symptoms in some diseases – especially endocrinopathies
  - hypothyreosis
  - Cushing syndrome
  - hypogonadism
- however, majority of obese subjects are affected by “common” obesity of multifactorial origin

**Overweight / obesity**
- defined as an excessive deposition of fat in the body with concurrent *hyperplasia* and *hypertrophy* of adipose tissue
- ↑ differentiation of pre-adipocytes
- ↑ deposition of lipids in adipocytes
- obesity is, first of all, consequence of abnormal long-term regulation of energy homeostasis
- criteria
  - **BMI** (body mass index)
    - malnutrition BMI <18.5
    - overweight BMI 25 – 29.9
    - obesity BMI >30 (mild 30 – 34.9, moderate 35 - 40, morbid >40)
  - WHR index (waist-hip ratio)
    - female: mild risk >0.80, high risk >0.85
    - male: mild risk >0.90, high risk >0.95
- fat distribution is more precisely reflected in **WHR** index
  - male pattern has more health-risks
- nowadays it’s common to measure just waist circumference
  - females: mild risk >80 cm, high risk >88 cm
  - males >94 and >102 cm, respectively
- thickness of skin fold
- exact measurement of body fat content
  - *adiposity* (% of body weight)
  - *fat mass* (% of body weight)
  - *fat-free mass* (% of body weight)
  - *fat percentage* (% of body weight)
  - *fat distribution* (android [male] and gynoid [female])
  - fat distribution is more precisely reflected in **WHR index** (waist-hip ratio)
- function of adipocytes
  - mechanical support / protection
  - thermoisolation
  - energy store
  - endocrine organ (~1×10^9 of cells = by far the largest!!!)
    - insulin-sensitising factors (negatively correlating with number of adipocytes)
      - few adipocytes → muscle has to be very insulin sensitive in order to utilize glucose
    - insulin-desensitising factors (positively correlating with number of adipocytes)
      - when NEFA plentiful utilization of glucose in the muscle does not need to be efficient?
    - pro-inflammatory factors (cytokines)
Fat distribution

- "brown" adipose tissue (BAT) – newborns
  - neck, back, around large vessels = thermoregulation
  - mitochondrial "uncoupling" of oxidation of FFA and ATP synthesis
- "white" (WAT) stored at
  - subcutaneous adipose tissue – aesthetic but not metabolic catastrophe
  - in obese subjects also in visceral region
    - intra-abdominally – e.g. omentum, mesentery
    - retroperitoneally
    - others
      - epicardium
      - local source of FFA?
      - possible paracrine effect of secreted factors on the heart
      - orbital, joints, synovia
  - and also intra-organ in muscles and liver
    - two important organs influencing insulin sensitivity
      - ↑ NEFA
      - ↑ adipokines

Evolution of obesity

- unlimited storage of fat is not metabolically "safe"!!!
  - as to why is not clear?
  - critically limited energy resources in adverse living conditions were likely evolutionary much more important factor than eventual consequences of affluence
    - selection of "thrifty genotype" in the hunter-gather period enabled its carriers to make the most from minimal resources and represented selective advantage
      - the very same metabolic regulatory tools preventing us from life-threatening energy depletion form basis of metabolic diseases nowadays
        - esp. insulin and leptin resistance
      - humoral products of adipose tissue actively participate in multiple regulations negatively affecting
        - carbohydrate and lipid metabolism
        - vascular homeostasis and circulation
          - ↑ ICAM, ↓ NO
        - immunity
          - ↑ pro-inflammatory cytokines and RA
        - fibrinolysis
          - ↑ PAI-1
        - reproduction

Risks connected with obesity

- cardiovascular
  - metabolic syndrome (diabetes, hypertension, dyslipidemia) → atherosclerosis
- tumors
  - ovary
  - endometrial
  - breast
  - colorectal
  - kidney cancers
- musculoskeletal system
  - arthrosis of lower limb joints
- infertility
- polycystic ovary syndrome
- biliary calculosis
- respiratory insufficiency (morbid obesity – Pickwick syndrome)
- sleep apnoea

Metabolic syndrome

- ↑ NEFA
- ↑ adipokines
**Adipocyte differentiation**

- In positive energy balance, fat tissue does not expand passively; regulation of adipocyte differentiation.
- Pluripotent mesenchymal cell (MSC) → adipoblast → pre-adipocyte → adipocyte.
- Control (transcription factors):
  - Peroxisome proliferator-activated receptor γ (PPARγ): expressed mainly in fat tissue, stimulates adipocyte differentiation, lipogenesis, and fat storage.
  - CCAAT regulatory enhancer binding protein α (CREBPα): sterol-regulatory element binding protein 1c (SREBP1c): others (Wnt signalling pathway).

**Hypertrofic, overloaded adipocyte**

- Hyperplastic but small adipocytes store fat relatively "safely".
- Limited differentiation plasticity of adipose tissue – esp. subcutaneous – leads to the hypertrophy of existing adipocytes.
- Overloaded adipocytes secrete cytokines attracting monocytes upon their differentiation into macrophages further production of pro-inflammatory cytokines affecting insulin sensitivity.
- Competition of Tyr- and Ser/Thr-kinases (signalisation of TNF-α vs. insulin for IRS-1).
- "Low-grade inflammation" responsible for the development of co-morbidities associated with obesity, esp. T2DM, atherosclerosis, carcinogenesis, ...

**Ectopic fat**

- Upon reaching maximum of saturation of WAT additional nutrients are "redirected" towards other organs not specialized for storage of lipids.
  - therefore sensitive to lipotoxicity
  - Skeletal muscle → insulin resistance
  - Myocardium → cardiomyopathies
  - arrhythmias
  - Apoptosis = systolic dysfunction
  - Liver → NAFLD/NASH
  - Pancreas (B-cells) → Apoptosis

**Lipotoxicity**

- Inability to store unlimited amount of nutrients and limited expandability of subcutaneous a. tissue leads to progressive inflammation and production of pro-inflammatory adipokines.
  - Apoptosis of hypertrophic adipocytes
  - Saturation of visceral fat
  - NEFA "spillover"
    - interferes with utilization of glucose in muscle (↓ ins. sensitivity)
  - Ectopic storage of fat in organs
    - Liver steatosis
    - Skeletal and heart muscle
    - Secondary failure of B-cells.
Lipodystrophy as an extreme example of dysfunctional subcutaneous fat tissue with metabolic consequences

- inherited (AR i AD) or acquired
  - generalized
  - localized
- similar to metabolic syndrome
  - dyslipidemia
    - hypertriglyceridemia and hypercholesterolemia, low HDL
  - impaired Glc tolerance
  - visceral obesity
  - liver steatosis
  - ...

Vascular (intraabdominal) fat tissue

- localization
  - omentum, mesenterium, retroperitoneum
- visceral adipocytes are different from s.c. !!!
  - lower LPL activity
  - higher HSL activity ≠ subcutaneous tuk
  - higher 11βHSD1 activity = higher local production of cortisol
  - different density of receptors for GC, β3 adr., Ins, ...
  - lower leptin synthesis, higher production of pro-diabetogenic adipokines (e.g. resistin and RBP)
- in summary: higher sensitivity to lipolytic effect of catecholamines and GC, lower sensitivity to antilipolytic effect of insulin and higher tendency to GC-stimulated differentiation of adipocytes
- draining by v. portae = direct effect on liver
  - glycerol is a substrate for gluconeogenesis = diabetes/IGT/IFG
  - esterification and synthesis of VLDL = dyslipidemia
  - induction of hepatic lipase - -> modification of LDL and HDL to small dense particles = atherogenesis

Ration of S and V fat tissue

- CT cross-sectional abdominal areas at umbilicus level in two patients demonstrating variation in fat distribution
  - A: Visceral type (49-yr-old female, 23.1 of BMI, visceral fat area: 146 cm², subcutaneous fat area, 115 cm²; V/S ratio, 1.27)
  - B: Subcutaneous type (40-yr-old female, 24.0 of BMI, visceral fat area: 60 cm²; subcutaneous fat area, 190 cm²; V/S ratio, 0.31)
  - cut-off of metabolic a CV risk >0.4

Cushing syndrome as an example of redistribution of s.c. into visceral

- (1) regional differences in intensity of lipogenesis vs. lipolysis between s.c. and v. adipose tissue
  - suppression of LPL in s.c.
  - activation of ATGL/HSL in bot, but more in v.
    - however results of studies are controversial (acute vs. long-term, animal vs. humane, contribution of hypeinsulinemia, ...)
- (2) preferential differentiation of v. adipocytes
  - higher availability of cortisol due to ↑ activity of 11βHSD1
- (3) lower central effect on the control of appetite
  - end-result is central obesity with all the components of metabolic syndrome
Evolution of obesity and inflammation

- Ability to store energy for periodical fasting was equally important as an ability to fight infection.
  - Biologically interconnected systems for energy storage and immune reaction developed:
    - Single system in lower organisms (e.g., fat body in insects).
    - Separate systems in higher organisms (liver, adipose tissue, bone marrow), but dynamic cooperation regulates immunity (e.g., via Toll-like receptors).
  - Interaction exists even within organs:
    - E.g., liver: hepatocytes/adipocytes/Kupffer cells.
- Two periodically changing situations required redistribution of energy:
  - Fasting (or danger) → Stress reaction → Decline of immunity
    - Glucocorticoids / Lymphocytes
  - Storage of energy → Production of humoral factors in fat tissue with pro-inflammatory effect → Removal of pathogens

Ethiopathogenesis of obesity

- Obesity develops as a consequence of long-term imbalance between:
  - Energy intake
    - Food
  - Energy expenditure
    - Basal metabolic rate (~60% of daily expenditure)
    - Thermic effect of food (~10-15%, different for various macronutrients)
  - Activity energy expenditure
    - Non-exercise activity thermogenesis (daily chores, posture, fidgeting)
- Favouring higher intake (= Positive balance) due to:
  - Relatively higher intake
  - Lower expenditure
  - Combination of both
- But why?
  - Is there any feedback loop between adipose tissue and central and peripheral organs influencing metabolism and food intake in order to prevent increase of body weight over the threshold necessary for optimal functioning of organism?

Pathogenesis of obesity

- Endogenous and exogenous factors likely contribute equally:
  - Endogenous - Genetic
  - Exogenous - Diet (amount, frequency, quality), physical activity, education, social class, psychological factors (personality), stress
- Recent change of behavioural and environmental (not genetic!) factors is responsible for the current epidemic of obesity in developed countries (and its growing prevalence in developing ones):
  - Although generic predisposition plays probably and important role it isn’t genes that would change rapidly recently!
Regulation of food intake

- food intake is a periodical event
- main stimuli regulating timing of meals are:
  - appetite respectively hunger
    - appetite = natural desire to eat which changes behaviour in order to get access to food
    - hunger = feeling of imperative need of food associated with various objective symptoms, esp. negatively perceived stomach contractions
- satiety
  - satiety = opposite of hunger, follows after adequate meal
- frequency of meals, portion size, quality, type of processing is influenced by various exogenous and endogenous factors
  - social, psychogenic, emotional, habitual, daily regimen, cost, season etc.
  - regardless these short-term physiological fluctuations energy balance should be balanced in healthy man in long-term so that energy intake equals expenditure
- however, the regulation of food intake (and body weight) is not purely homeostatic but quite a complex process involving neural and hormonal regulation
  - homeostatic regulation
    - afferent signals are so far much better understood than efferent signals
  - hedonic regulation
    - satisfaction after meal

Homeostatic regulation

- afferent signals (= appetite vs. satiety):
  - peripheral signals via systemic humoral factors (influencing appestatial mediator leptin)
  - central signals via hypothalamus
    - the most important humoral factors are:
      - GLP-1 (in gut), CCK (in gut) – postprandial release paralleling the glycemia
      - leptin – adipose tissue hormone, likely involved in long term modulation of sensitivity to peripheral "satiety" signals from GIT (cholecystokinine (CCK), glucagon-like peptide 1 (GLP-1) and peptide YY)
      - ghrelin – hormone released from stomach whose concentration rises during fasting ("hunger mediator")
    - concentration of leptin (and indirectly of insulin) is proportional to the adipose tissue mass and intensity of their signals in CNS (via their receptors) is related to their plasma levels
    - main stimuli regulating timing of meals are:
      - food intake is a periodical event
      - hunger = feeling of imperative need of food associated with various objective symptoms
      - satiety = opposite of hunger, follows after adequate meal
      - meal composition (amount of carbohydrates, proteins and lipids) is reflected in afferent signalisation – changes of insulinemia after meal containing sugar ("glycemic index)
      - frequency of meals, portion size, quality, type of processing is influenced by various exogenous and endogenous factors
      - social, psychogenic, emotional, habitual, daily regimen, cost, season etc.
- central integration of signals takes place in hypothalamic nuclei (nucleus arcuatus) by local neurotransmitters:
  - orexigenic mediators (neurotransmitters)
    - neuropeptide Y
    - ghrelin - hormone released from stomach whose concentration rises during fasting ("hunger mediator")
  - anorexigenic mediators (neurotransmitters)
    - proopiomelanocortine (POMC)
    - cocaine-amphetamine-regulated transcript (CART)
  - however, the regulation of food intake (and body weight) is not purely homeostatic but quite a complex process involving neural and hormonal regulation

Peripheral and central signalisation in regulation of food intake

- events initiated by primary centres in hypothalamus are not entirely known yet by the currently available literature cooperation
- hedonic and homeostatic regulation are largely independent
  - therefore, unfortunately, the type and amount of meal very often doesn't correspond with metabolic needs

Hedonic regulation

- = sensations connected with meal (e.g. palatability, vision, reward, ...)
- afferent signals:
  - gustatory and olfactory pathways into particular centres
    - ventral tegmental area (VTA) – dopaminergic stimulation
  - sub-cortical regions – limbic system (amygdala)
    - they mediates the "good" feeling
      - neuro-modulators are endocannabinoids binding to CB1 and 2 receptors
        - anandemid (arachidonoylethanolamid, AEA)
        - 2-arachidonoylglycerol (2-AG)
      - basal ganglia (n. accumbens and pallidum)
      - prefrontal cortex
      - homeostatic and hedonic regulation are largely independent
        - therefore, unfortunately, the type and amount of meal very often doesn't corresponds with metabolic needs
Retrograde signaling by EC

- The endocannabinoids (EC) anandamide and 2-AG are synthesized in postsynaptic target cells such as hippocampal pyramidal cells.
- Synthesis is initiated by calcium influx through voltage-gated calcium channels, or by the activation of G protein-coupled neurotransmitter receptors, including type I metabotropic glutamate receptors (mGluR) or muscarinic acetylcholine receptors (mAChR).
- The EC gain access to the extracellular space and activate CB1 cannabinoid receptors found concentrated on certain nerve terminals, e.g., of cholecystokinin-containing GABAergic interneurons in hippocampus.
- CB1 activation causes presynaptic inhibition of GABA or glutamate release by inhibiting calcium channels, interfering with vesicle release, and activating potassium channels.
- The EC are taken up into postsynaptic or presynaptic cells by the anandamide transporter (AT). The degradative enzyme FAAH is present in postsynaptic cells and monoglyceride lipase (not shown), which degrades 2-AG, is found in presynaptic terminals.

Genetics of obesity

- Candidate genes = genetic polymorphism in genes encoding products involved in:
  - Regulation appetite/satiety
    - Peripheral and central orexigenic/anorexigenic mediators and their receptors
    - Endocannabinoid system
  - Adipose tissue differentiation and metabolism
    - PPARs, enzymes, adipokines and their receptors
  - Carbohydrate metabolism
    - Insulin receptor signal cascade
    - Post-receptor sensitivity
  - Thermogenesis
    - Uncoupling proteins
- Genome-wide search for obesity genes

Environmental factors

- Lack of physical activity
- Change of diet:
  - Lipid-rich diet brings twice as much energy in the same amount compared to carbohydrates and proteins.
  - Lipids mediate the satiety much later than saccharides (→ insulin)
- National cuisine traditions
- Family habits
- Educational and social status
- Consumption of alcohol can play a role too:
  - Non-negligible energy content
### Endocrine activity of adipose tissue

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>TARGET TISSUE/ORGAN</th>
<th>PLASMA LEVELS</th>
<th>METABOLIC EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>CNS (hypothalamus), muscle, ovary</td>
<td>positive correlation with BMI</td>
<td>central – long-term ↓ of appetite and ↑ of sympathetic activity; peripheral – ↑ insulin sensitivity and lipid metabolism</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>insulin-dependent tissues (muscle!)</td>
<td>negative correlation with BMI</td>
<td>↑ of insulin sensitivity, ↑ NEFA oxidation, anti-inflammatory</td>
</tr>
<tr>
<td>Resistin</td>
<td>insulin-dependent tissues (muscle!)</td>
<td>positive correlation with BMI in rodents</td>
<td>↑ insulin resistance, pro-inflammatory</td>
</tr>
<tr>
<td>TNF-α</td>
<td>insulin-dependent tissues (muscle!)</td>
<td>positive correlation with BMI</td>
<td>interferes with insulin receptor signalling (phosphorylation of serin residues) – ↑ insulin resistance</td>
</tr>
<tr>
<td>IL-6</td>
<td>?</td>
<td>positive correlation with BMI</td>
<td>↑ (pro-inflammatory?)</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>adipose tissue (para- and autocrine action), endocrine as a part of systemic RAAS?</td>
<td>expression in adipose tissue positively correlates with BMI</td>
<td>influence adipocyte differentiation, ↑ lipogenesis, circulatory effect of obesity (systemic circulation?)</td>
</tr>
</tbody>
</table>

### Adipokines vs. insulin sensitivity

**Pro-hyperglycaemic**
- Resistin
- TNF-α, IL-6, other cytokines
- RBP4

**Anti-hyperglycaemic**
- Leptin
- Adiponectin
- Visfatin
- Omentin

### Hormones of adipose tissue

- Increased insulin resistance in muscle
- Interference of NEFA with glucose utilisation
- Insufficient inhibition of hepatic glucogen synthesis
- Lipogenesis, circulatory effect of obesity (systemic circulation?)

### Spontaneously obese strains of mouse - mutations in Ob or Db genes

- Mutations in Ob or Db genes in spontaneously obese strains of mouse.
- Activation of SNS
- Overcoming glucagon resistance
- Opposite effect on obesity
Leptin [“leptos” = lean]

- central hormone in regulation of energy homeostasis and food intake (thermogenesis?)
- central and peripheral action
- obesity is associated with hyperleptinemia
  - leptin resistance?? (parallel to insulin resistance) is hypothesised to play a role in the pathogenesis of obesity
  - endogenous highly set “adipostate” might be also a problem of relapses in obese subjects after loosing weight

Other less common causes of obesity/hyperphagia

- tumors and lesions of ventromedial hypothalamus
  - mostly craniopharyngeoma
- monogenic genetic syndromes
  - Prader-Willi syndrome
    - deletion or alteration of expression of group of genes on the proximal part of long arm of paternal chromosome 15
  - abnormally increased appetite (hyperphagia) and subsequent morbid obesity, muscular hypotonia, mental retardation, low height, hypogonadism and acromicria (small hands and feet)
    - high levels of ghrelin are common in PW patients - consequence of primary genetic defect?

How technology changes us ...