Obesity
Disorders of Nutrition

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Nutrition

- Provision of energy to organism (in the form of chemical energy)
  - 1 kcal – 4,186 kJ

nutrient	kJ/g
proteins	17,2
lipids	38,9
saccharides	17,2

- Provision of organic and anorganic substancies for the body development

2

Energy expenditure

- Basal metabolism – basal metabolic rate
  - energy expended daily at rest (transport mechanisms, biosynthesis, thermoregulation, functioning of the vital organs)
  - 5 900 – 8 400 kJ/day

organ	% of BMR
liver	26%
brain	18%
hearth	9%

- Meatbolism during physical activity

activity	kJ/h
watching TV	250
cleaning	1090
cleaning of the windows	1130
sex	1600
swimming	2800
running	3750

- Thermogenesis

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Necessary food components

- saccharides
- lipids
- proteins

- vitamins
- minerals - Na, K, Ca, Cl, Mg, P
- trace elements - Fe, Zn, Cr, Cu ...
- fibre
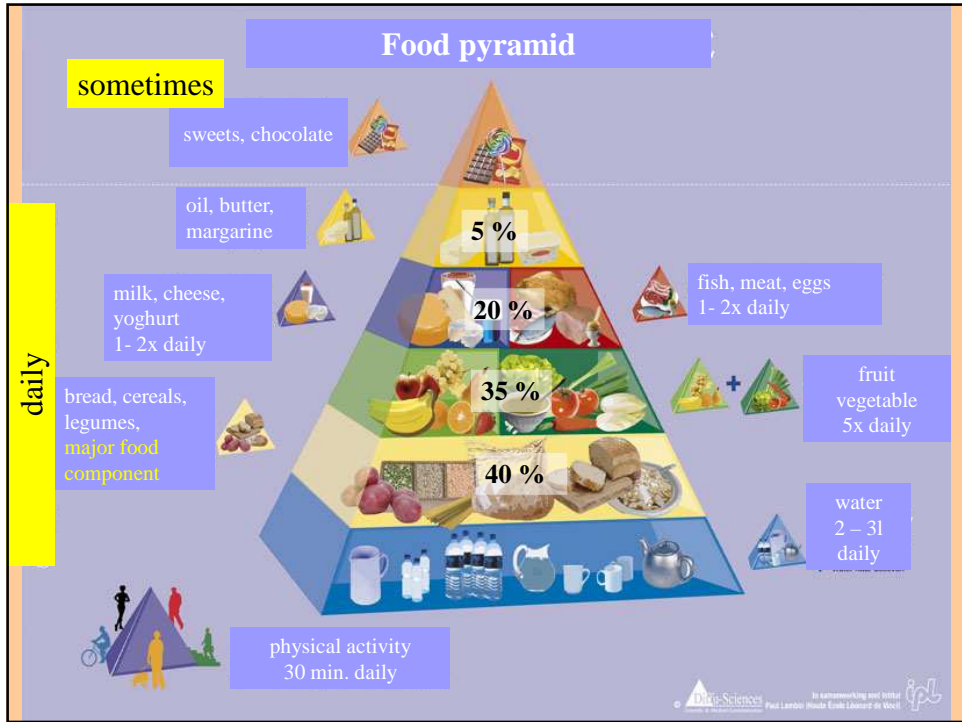- water

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Optimal nutrition

- Optimal energy intake
  - Depends on age, gender, lifestyle (intensity of physical activity at work, at home, in free time), health state (body size, healthy vs. acute/chronic disease, reconvalescence...) other factors (intensive growth period, pregnancy, lactation, climate...)

- Optimal basic nutrients ratio – proteins, lipids ($\uparrow$ PUFA, $\downarrow$ cholesterol), carbohydrates
- Optimal intake of fibre (25-35 g/day)
- Optimal intake of vitamins and minerals (3-5 portions of fruits a 3-5 portions of vegetable/day)
- Lower intake of salt (3 - 5g/day)

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Recomended energy intake

55 - 60 %   -   saccharides

max. 30 %   -   lipids
    cca 10 %   -   saturated fatty acids
    cca 10 %   -   monounsaturated fatty acids
    cca 10 %   -   polyunsaturated fatty acids
      (n-6 and n-3 polyunsaturated FA)
    lower than 300 mg/day - cholesterol

10 – 15 %   -   proteins

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Food pyramid

sometimes

sweets, chocolate

oil, butter, margarine

5 %

milk, cheese, yoghurt
1- 2x daily

20 %

fish, meat, eggs
1- 2x daily

daily

bread, cereals, legumes, major food component

35 %

fruit vegetable
5x daily

40 %

water
2 – 3l daily

physical activity
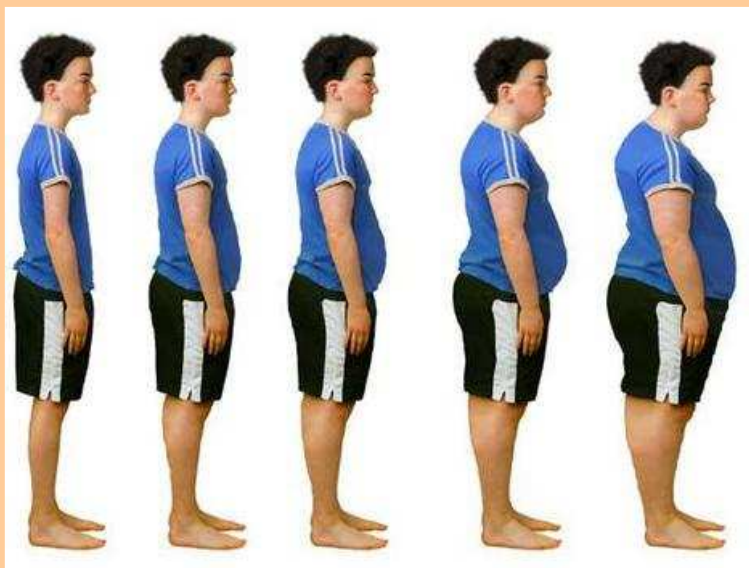30 min. daily

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Disorders of nutrition

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Inadequate nutrition
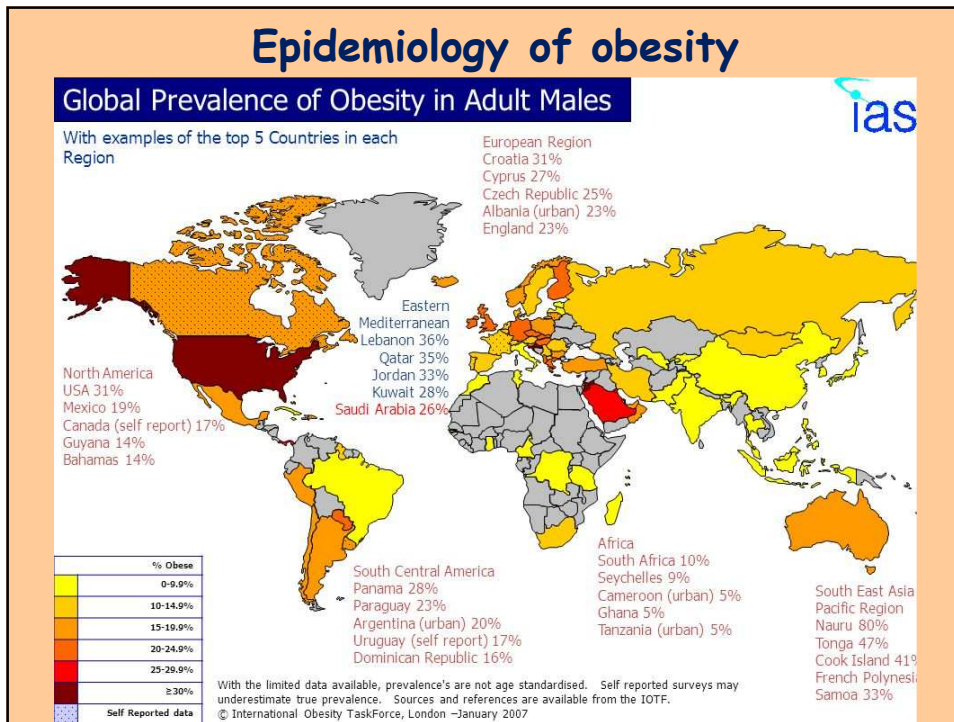
- Overnutrition
  – obesity (adiposity)
  – vitamin excess

- Undernutrition
  – quantitative - starvation
  ‎   - chronic undernutrition
  – qualitative - kwashiorkor
  ‎   - vitamin deficiency
  ‎   - trace elements deficiency

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Obesity

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Epidemiology of obesity

Global Prevalence of Obesity in Adult Males

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THE 10 MOST OBESE COUNTRIES ON EARTH
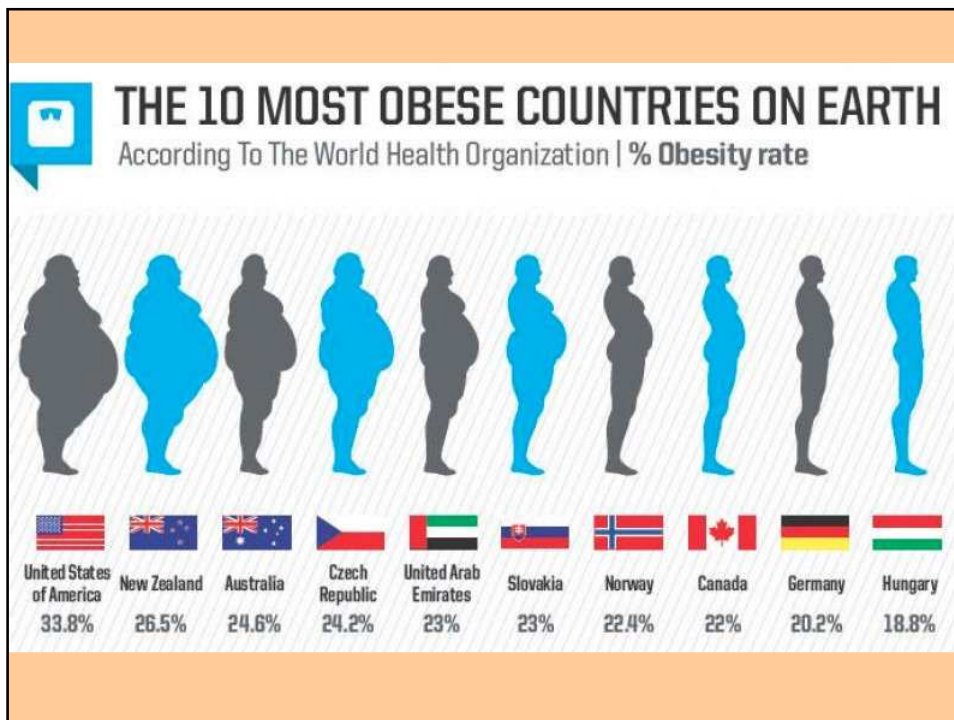According To The World Health Organization | % Obesity rate

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Definition

Obesity (adiposis, fatness) is a complex, multifactorial metabolic disorder defined as an excess of fat mass with an impact on health.

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Definitions

- Obesity: adiposity – accumulation of fat tissue

- Overweight: weight increased above the normal values

(BMI increased – fat, but also muscles, water, baby...)

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Etiology of obesity

1. Disequilibrium between energy intake and expenditure

 – High calorie diet
 - WHO – average energy intake
 - 1963 – 9660 kJ
 - 1971 – 10 250 kJ
 - 1992 – 11 420 kJ
 - 2010 – 12 200 kJ

 – Sedentary lifestyle

2. Obesogens

– chemical compounds that have effect to lipid metabolism and accumuation, and can lead to obesity

 – drugs (steroids [glucocorticoids], antidiabetics, antiepressants, antiepileptics, antihistamines, contareceptives)

 – substances occurring naturally in certain foods (e.g. phytoestrogens such as genistein found in soya)

 – substances added to foods (glucose-fructose syrup),

 – substances released into foods from plastics (phthalates),

 – pesticides (e.g. tributyltin)

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Etiology

3. Endocrine diaseases
 – rare
 – Cushing's syndrome,
 – hypothyreodism,
 – hypogonadism,
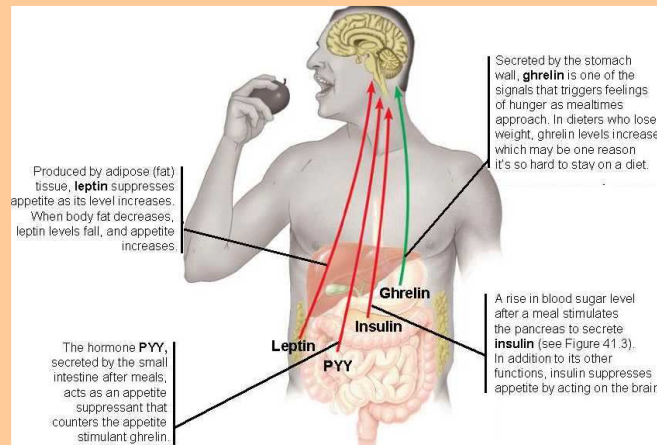 – growth hormone deficiency,
 – insulinoma
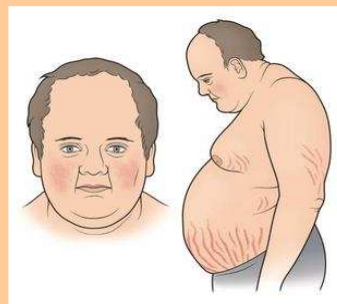
Cushing's syndrome

4. Hypothalamic obesity
 – weight gain after hypothalamic damage
 – rare in humans

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Hormones affecting energy bilance	
Hormone	Function in obesity pathogenesis
Leptin	Reduces appetite, increases energy expenditure
Ghrelin	Stimulates the feeling of hunger and increases food intake, affects GIT activity and insulin secretion
Orexin	Increases appetite, reduces the feeling of satiety
Cortizol	In excess causes increased fat storage
T3, T4	Deficiency reduces energy expenditure independent of physical activity
Insulin	Stimulates fat storage

Produced by adipose (fat) tissue, **leptin** suppresses appetite as its level increases. When body fat decreases, leptin levels fall, and appetite increases.

Secreted by the stomach wall, **ghrelin** is one of the signals that triggers feelings of hunger as mealtimes approach. In dieters who lose weight, ghrelin levels increase, which may be one reason it's so hard to stay on a diet.

The hormone **PYY**, secreted by the small intestine after meals, acts as an appetite suppressant that counters the appetite stimulant ghrelin.

A rise in blood sugar level after a meal stimulates the pancreas to secrete **insulin** (see Figure 41.3). In addition to its other functions, insulin suppresses appetite by acting on the brain

Ghrelin
Insulin
Leptin
PYY

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Etiology

5. Other factors
- – Easy availability of food
- – Social, economic, cultural, psychical factors
- – Ethnicity

Race and obesity in USA (2002 – 2007)				
	White	Black	Hispanic	Asian
Average BMI	27	28.6	27.6	24
% of obese	24.5	36	28.6	7

- – Eating disorders – binge eating, night binge eating
- – Stress
- – Virus infection – adenoviruses (by affecting adipocyte growth and differentiation, glucose uptake by cells, and inhibiting leptin production by adipose tissue)
- – Sleep deprivation (reduction of leptin production and increase of ghrelin and orexin levels, leading to appetite stimulation, increased food intake, and subsequent obesity).

6. Inherited obesity ???

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Monogenic obesity

- Obesity caused by single gene mutation
- Extremely rare
- Mutations of genes of the leptin/melanocortin axis → abnormality in foot intake regulation
- Severe obesity, early onset

Examples
- Mutation of leptin gene
- Mutation of leptin receptor gene
- Mutation of proopiomelanocortin gene
- Mutation of proconvertase 1 gene
- ...

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Leptin

- Hormon produced mainly by white adipose tissue
- Encoded by the Ob(Lep) gene on ch7
- Receptor LEP-R located mainly in hypothalamus

- Leptin is produced by adipose tissue (much adipose tissue - much leptin) → binding to receptors in hypothalamus → inhibits hunger and increases basal metabolism and spontaneous physical activity → reduction of adipose tissue
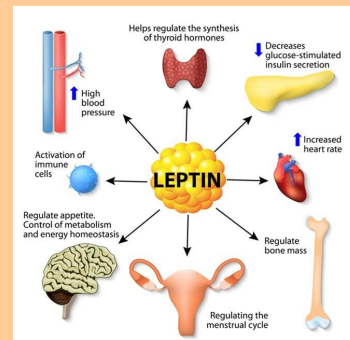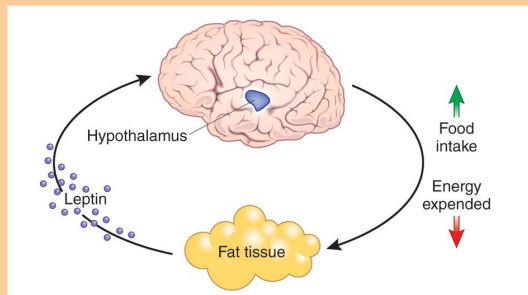
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Leptin
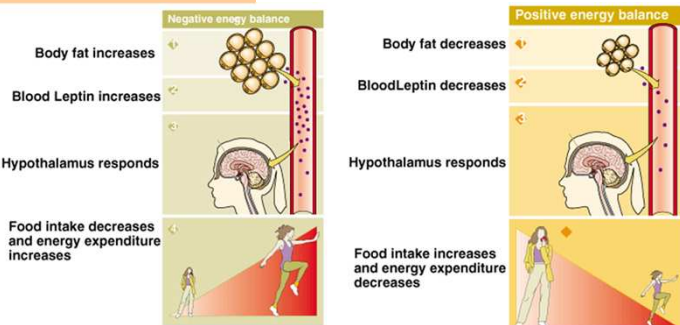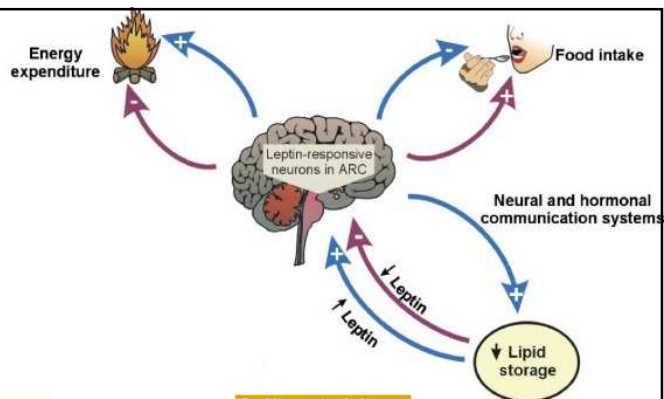
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Syndromic obesity

- Obesity associated with genetic syndromes
- Can be monogenic or chromozomal syndromes
- Very rare
- Severe obesity associated with additional phenotypes (mental retardation, dysmorphic features, organ abnormalities...)

Examples
- Prader-Willi syndrome
- Bardet-Biedl syndrome
- Cohen syndrome
- Alström syndrome
- Fragile X syndrome
- ... other more than 100 syndromes (Down sy., Turner sy., Klinefelter sy.)

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Prader-Willi syndrome

- Genetic disease that affects hypothalamic-pituitary axis

Causes
- > 75% - deletion of long arm of paternal chromosome 15
- < 25% – uniparental disomia of maternal ch15, defect of imprinting

Signs
- Obesity
- Hypotonia
- Hypogonadism
- Mild intelectual disability
- Prominent nasal bridge, small hands and feet with tapering of fingers, soft skin, which is easily bruised, thin upper lip, downturned mouth

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Bardet-Biedl syndrome

- Genetic disease that affects many organ systems
- Frequency 1:150 000

Causes
- AR inherited mutation of one from BBS genes (14 genes)
- Damage of structure or function of cilia

Signs
- Obesity + insulin resistance, hypertension, hypercholesterolemia
- Retinitis pigmentosa – night blidness, loss of vision, strabismus, cataract
- Polydactyly – sometimes brachydactyly, syndactyly
- Hypogonadism + renal failure, defects of urinary tract
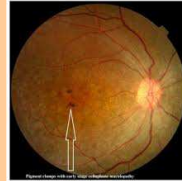
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Genetics of common obesity

- Polygenic – genetic predisposition + environmental factors
- Majority of obesity

Examples of candidate genes
- FTO gene
- MC4R, TMEM18, KCTD15 ...   ...and many many other

FTO gene
- Fat mass and obesity-associated gene - chromosome 16
- Protein alpha-ketoglutarate-dependent dioxygenase
- Function in regulation of food intake – satiety, apetite, overeating
- Increased risk of obesity – heterozygotes weigh on average 1.2 kilograms more than people with no copies, homozygotes weigh 3 kilograms more
- Incerased risk of diabetes mellitus type 2, metabolic syndrome, dyslipidemia, Alzheimer's disease

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Thrifty gene hypothesis

- The **thrifty gene hypothesis** - connections between low quality fetal and infant growth followed by diabetes mellitus type 2 and metabolic syndrome caused by poor nutrition during early childhood, produces permanent effects in glucose-insulin metabolism.
- Genes which predispose to diabetes (called 'thrifty genes') were historically advantageous, but they became detrimental in the modern world. Thrifty genes are genes which enable individuals to efficiently collect and process food to deposit fat during periods of food abundance.
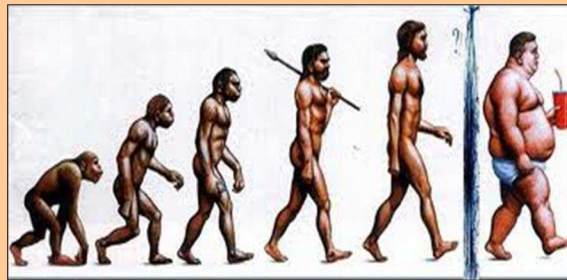
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Classification of obesity

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Classification of obesity
(according to localization ofsubcutaneous adipose tissue)

"Apple" vs. "Pear"

Above the waist
Below the waist

More weight above waist
More weight below waist

Apple shape   Apple shape   Pear shape

Abdominal obesity
- Belly fat, central obesity, android obesity, apple type, men type
- Much frequent visceral obesity

Gynoid obesity
- Lower body obesity, gluteal-femoral obesity, pear type, female type

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Adipose tissue
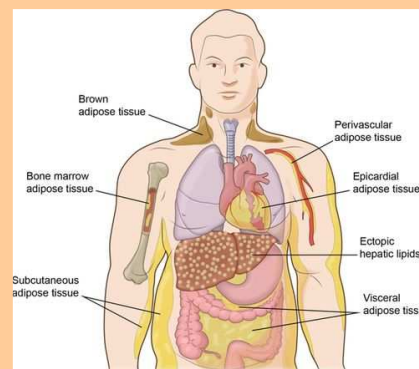
- Fat tissue, type of connective tissue

- Structure
  – Adipocytes, vascular endothelial cells, fibroblasts, adipocyte progenitors, leukocytes, macrophages

- Localisation
  – Subcutaneous – 80 % (abdominal, gluteo-femoral)
  – Between muscular fibres
  – Visceral - around the digestive organs (mesenteric and omental) and the retroperitoneal depot (kidney)
  – In bone marrow

Brown adipose tissue
Bone marrow adipose tissue
Subcutaneous adipose tissue
Perivascular adipose tissue
Epicardial adipose tissue
Ectopic hepatic lipids
Visceral adipose tissue

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Adipose tissue

- Types od adipose tissue
    - White adipose tissue
    - Brown adipose tissue
    - Beige adipose tissue
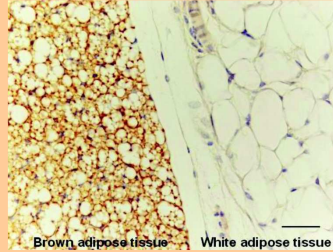
- Function
    - Energy storage
    - Body insulation
    - Termoregulation
    - Endocrine function - production of adipokines and cytokins
        - Insulin resistence and diabtes mellitus
        - Metabolic syndrome
        - Chronic inflammation
        - Cancer

Brown adipose tissue   White adipose tissue

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Types of adipose tissue
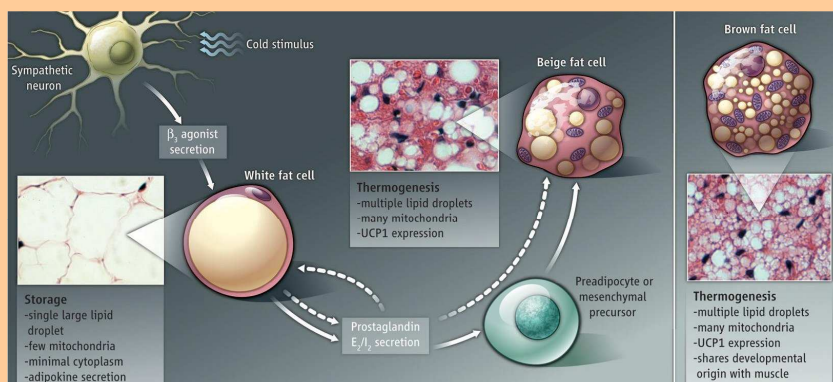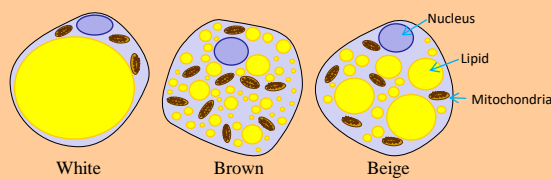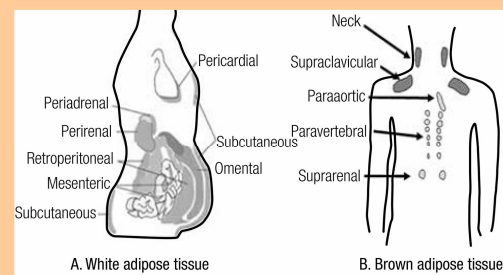

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Types of adipose tissue

- **White**
  - Function
    - fat storage
      - increased body weight
      - decreased energy expenditure
      - decreased insulin sensitivity
  - Location
    - Subcutaneous, visceral

A. White adipose tissue   B. Brown adipose tissue

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Types of adipose tissue

- **Brown**
  - Function
    - Thermogenesis
    - Whole-body energy and glucose homeostasis
      - Increased energy expenditure
      - Decreased body weight
      - Increased insulin sensitivity
  - Location
    - Newborn - interscapular, perirenal area
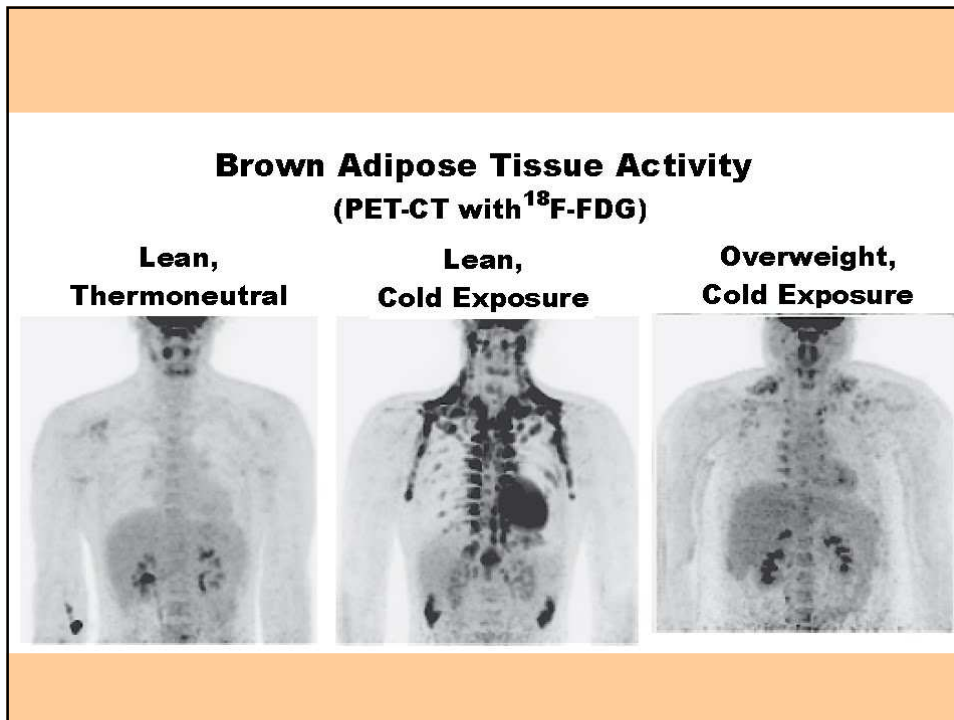   - Adult – cervical, subclavicular, axillary, paravertebral, suprarenal area
- **Beige**
  - Function
    - As brown adipose tissue
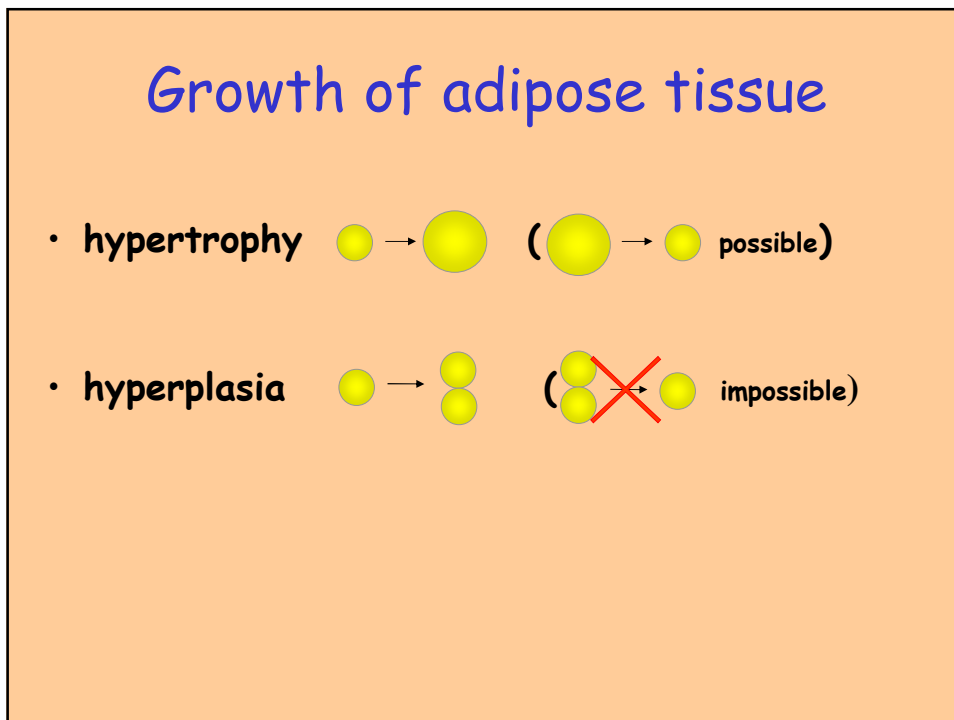 - Location
    - In subcutaneous white adipose tissue

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Brown Adipose Tissue Activity
(PET-CT with ^{18}F-FDG)

Lean, Thermoneutral · Lean, Cold Exposure · Overweight, Cold Exposure

Growth of adipose tissue

- **hypertrophy** ○ → ◯ (◯ → ○ possible)

- **hyperplasia** ○ → ◦◦ (◦◦ ⤬ ○ impossible)

Localisation of adipose tissue

- Subcutaneous
- Visceral

subcutaneous fat
abdominal muscle layer
visceral fat
intestines

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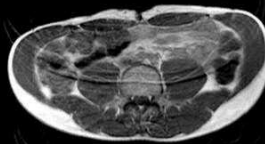# Visceral fat

- Intraabdominal white adipose tissue

Amount of visceral fat and subcutaneous/visceral fat ratio depends on:

- Genetic predisposition
- Gender
  - Men in any age (testosteron)
  - Women after menopause
- Age
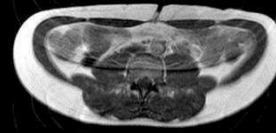 - Older people
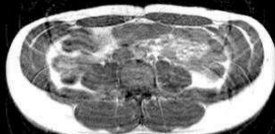- Total amount of fat in organism
- Energy intake

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Visceral fat

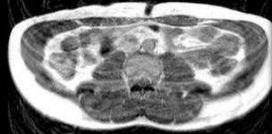Variation in visceral fat content in men with the same waist circumference.

Visceral fat = 0.5 L
Visceral fat = 1.1 L
Visceral fat = 1.2 L
Visceral fat = 1.3L
Visceral fat = 1.7 L
Visceral fat = 1.8 L
Visceral fat = 4.2 L
Visceral fat = 4.3 L
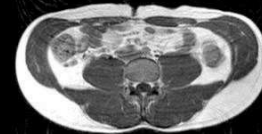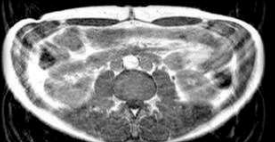
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„Metabolic obesity"

- Metabolically obese, normal-weight (MONW) people
    - Normal BMI, suffer from metabolic complications found in obese people

- Metabolically healthy obese (MHO) people
    - BMI > 30 kg/m^2, without metabolic complications typical for obese people

The main risk factor of metabolic complications is visceral fat

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Why is visceral fat risky?

- Increased lipolytic activity – leads to hyperlipidemia
- Causes hyperinsulinemia and insulin resistance
- Produces hormons and cytokins

consequently

- Visceral fat is risk factor of:
    - Cardiovascular diseases
    - Diabetes mellitus type 2
    - Some cancers – cancer of endometrium, prostata...

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Hormons produced by adipose tissue

- Leptin
    - regulation of adipose tissue mass through central hypothalamus mediated effects on hunger, food energy use, physical exercise and energy balance
    - contraregulation hormon is ghrelin („hunger hormon"), hormon produced by ghrelin cells in stomach when stomach is empty
- Adiponektin
    - regulates glycemia, and oxidation of fatty acids
    - enhances energy metabolism and fatty acid oxidation by activating peroxisome proliferator-activated receptor (PPARγ)
    - promotes fatty acid combustion and promotes insulin sensitivity by activating AMP-activated protein kinase
    - decreased in obesity, type-2 diabetes, and coronary artery disease
    - increased in anorexia
- Estrogens
- Angiotenzinogen – promotes the development of hypertension in obese people (produced mainly in liver)

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Adipokines and cytokines

Secretory cells of adipose tissue

Cytokine and cytokine-like proteins
TNFα
IL-6
MCP-1
Resistin
Progranulin

Proteins of the fibrinolytic system
PAI-1
Tissue factor

Complement and complement-related proteins
Adipsin
Complement factor B
ASP
CTRPs

- Adipocytes
- Precursor cells
- Endothelial cells
- Macrophages
- Foam cells
- Neutrophils
- Lymphocytes
- Fibroblasts
- Others

Adipokines
Leptin
Adiponectin
Visfatin/Nampt/PBEF
Vaspin
RBP4
FGF21
BMPs
Nesfatin-1
Cathepsins
Apelin
Omentin
Lipocalin
and hundreds more

Proteins of RAS
Angiotensinogen

Endocannabinoids and other lipids
Anandamide
2-AG
Free fatty acids

Enzymes
DPP-4

Lipid transport
Apolipoprotein E
Cholesterol ester transfer protein
Lipoprotein lipase

TRENDS in Pharmacological Sciences

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Metabolic syndrome

metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes.
It affects one in five people, and prevalence increases with age.

Signs and symptoms

➢ Fasting hyperglycemia — diabetes mellitus type 2 or impaired fasting glucose, impaired glucose tolerance, or insulin resistance
➢ High blood pressure
➢ Central obesity
➢ Decreased HDL cholesterol
➢ Elevated triglycerides

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Metabolic syndrome

New classification - Berlin 2005

At least three of the following signs:

+ Abdominal obesity
  waist circumference
      men > 94 cm
      women > 80 cm

+ Elevated triglycerides
      TAG > 1,7 mmol/l

+ Reduced HDL-cholesterol
      men < 0,9 mmol/l
      women < 1,1 mmol/l

+ Elevated blood pressure
      > 130/85 mmHg
      or use of medication for hypertension

+ Elevated fasting glucose
      > 5,6 mmol/l
      or use of medication for diabetes

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Measurement of obesity

- **Body mass index**

$$BMI = \frac{mass\ in\ kg}{(height\ in\ m)^2}$$

Classification	BMI Category (kg/m2)	Risk of Developing Health Problems
Underweight	< 18.5	Increased
Normal Weight	18.5 – 24.9	Least
Overweight	25.0 – 29.9	Increased
Obese		
Class I	30.0 – 34.9	High
Class II	35.0 – 39.9	Very High
Class III	≥ 40.0	Extremely High

- **Brocc´s index** (old)
  Normal weight = height in cm – 100
  Ideal weight = (height in cm – 100) – 10-15%

- **Skin fold**
  (biceps, triceps, subscapular, suprailiacal...)
  Fat: men   10 – 20% of body weight
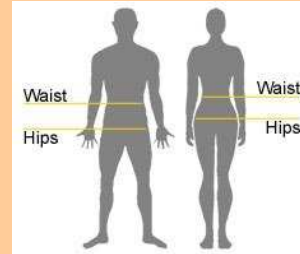   women 20 – 30% of body weight

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Measurement of obesity

- **Waist to hip ratio** (WHR)

  WHR > 1,0 in men

      > 0,8 in women   abdominal obesity


- **Waist circumference**

  Men > 94 cm, women > 80 cm   - increased risk

  Men > 102 cm, women > 88 cm   - very increased risk

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Other methods

- Bioelectric Impedance (BIA)
- Underwater Weighing (Densitometry)
- Air-Displacement Plethysmography
- Dilution Method (Hydrometry)
- Dual Energy X-ray Absorptiometry (DEXA)
- Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI)

(A) T-score -2.0   Fat   Lean   Bone   (B) T-score -1.2
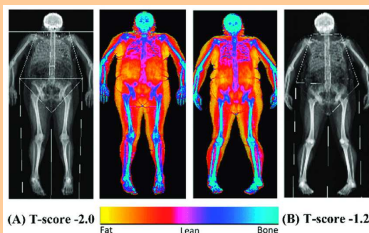
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Complications of obesity

- Metabolic complications
  - Insulin resistance – hyperinsulinemia – DM type 2
  - dislipidemia
  - hyperuricemia...
- Endocrine disesases
  - hypogonadism
  - Hyposecretion of growth hormone...
- CVS diseases
  - hypertension
  - ICHS
  - arrhytmias
- Respiratory diseases
  - Pickwick syndrome
  - Sleep apnoea syndrome...

- GIT and liver
  - gastroezofageal reflux
  - cholelitiasis
  - pankreatitis
  - liver steatosis...
- Gynekologic complications
  - oligomenhorhea
  - complications during pregnancy...
- Onkologic complications
  - Kolorectal ca...
- Psychosocial complicaytions
  - social discrimination
  - depression
  - eating disorders
- Other

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Malnutrition

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Causes

- exogenous
  - inadequate intake of nutrients (starvation, loss of appetite, mental anorexia)
- endogenous
  - disorders of digestion
  - disorders of absorption
  - disorders of metabolism
  - increased nutrient requirements (hyperthyroidism, gravidity, lactation, convalescence...)
  - loss of body fluids (bleeding)
  - loss of proteins (nephrotic syndrome)
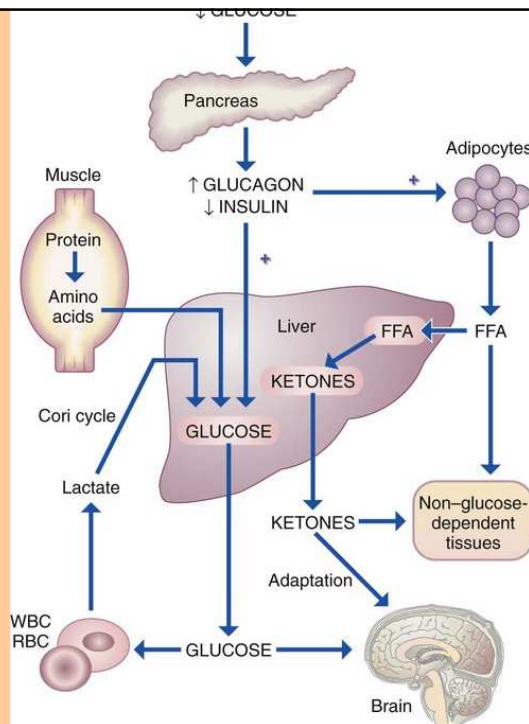
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Higher risk of malnutrition

- poor people
- sucklings and children
- adolescents in period of accelerated growing
- old people
- people on radical diet
- vegetarians
- alcoholics a people on drugs
- patients with AIDS
- patients with chronic GIT, liver, kidney diseases

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Starvation

Metabolic changes during starvation

The body mobilizes reserves

- The stores of glycogen are converted to glucose (12 - 24 h)
- Glucose is produced by gluconeogenetic pathway in liver
- ↓ concentration of glucose
  ↓
- ↓ concentration of insulin, ↑ concentration of glucagon
  ↓
- ↑ lipolysis a b-oxidation of fatty acids
  ↓
- Hyperlipidaemia, ketoacidosis
- After using of fatty stores – catabolism of proteins

Protein Energy Malnutrition
PEM

Marasmus

- inadequate intake of all nutrients
- cause: poorness, psychic disease, starvation...

Clinical signs
- in children: weight loss, muscle atrophy, weakness, fatigue, decreased immune function, anaemia, delayed wound healing
- in adults: cachexia

Kwashiorkor

- protein malnutriotion (adequate energy suply - saccharides)

- signs: oedema, growth retardation, weight loss, skin and hair depigmentation thin and sensitive skin, diarhea, anaemia, apatia, muscle atrophy, immunodeficiency
  low serum protein concentration

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Cachexia

- extreme thinness, extreme skinny
- Wasting syndrome

Causes
- Undernutrition (marasmus, anorexia...)
- Cancers
- AIDS
- Chronic diseases – COPD
- …

Mechanisms
- Not fully understood
- Changes in metabolism (cytokines e.g. TNF)
- Changes in apetite regulation (leptin)

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Specific (qualitative) malnutritions

- protein deficiency - kwashiorkor
- iodine deficiency – endemic goiter
- vitamin A deficiency – xerostomia, xeroftalmia
- Fe, folic acid, vit. B_{12} deficiency – anaemias
- vitamin D, Ca, Mg, P deficiency – osteopaties (rickets, osteomalacia, osteoporosis)
- tiamin deficiency - beri-beri
- riboflavin deficiency – oral cavity inflammation
- niacin deficiency - pelagra
- vitamin C - scurvy

Eating disorders

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- Mental anorexia (anorexia nervosa)
- Mental bulimia

- Causes

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Mental anorexia

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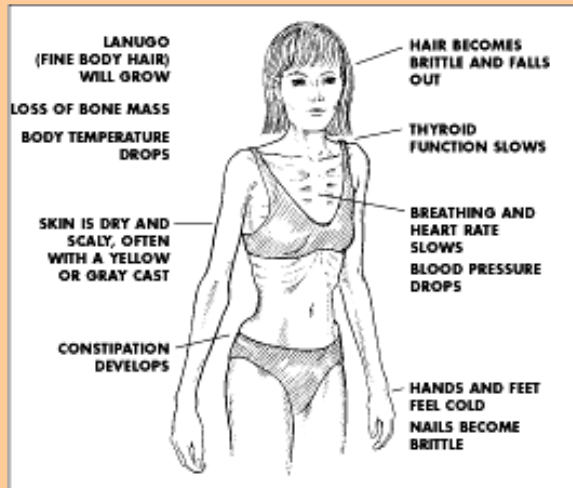

Anorexia (gr.) - lack of desire to eat

- Anorexia nervosa - eating disorder characterized by extreme weight control

Diagnostic criteria
- obsessive fear of gaining weight, control body weight through voluntary starvation, excessive exercise, diet pills...
- pathological fear of being obese
- amenorrhoea in women

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Symptoms

LANUGO (FINE BODY HAIR) WILL GROW

LOSS OF BONE MASS

BODY TEMPERATURE DROPS

SKIN IS DRY AND SCALY, OFTEN WITH A YELLOW OR GRAY CAST

CONSTIPATION DEVELOPS

HAIR BECOMES BRITTLE AND FALLS OUT

THYROID FUNCTION SLOWS

BREATHING AND HEART RATE SLOWS

BLOOD PRESSURE DROPS

HANDS AND FEET FEEL COLD

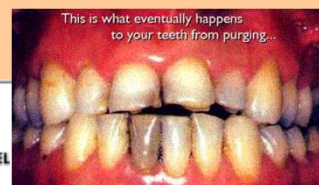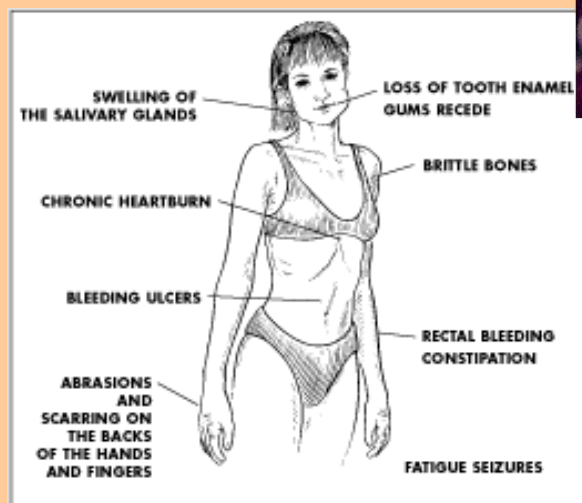NAILS BECOME BRITTLE

Mental bulimia

- Mental bulimia – eating disorder characterized by repeated episodes of overeating followed by exaggerated weight control

Diagnostic criteria
- strong desire to eat (big amount and strange combination)
- to avoid being fat – vomiting, laxatives abuse, diuretics abuse, episodes of starvation,
- pathological fear to be obese

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Symptoms

This is what eventually happens to your teeth from purging...

SWELLING OF THE SALIVARY GLANDS
LOSS OF TOOTH ENAMEL
GUMS RECEDE
BRITTLE BONES
CHRONIC HEARTBURN
BLEEDING ULCERS
RECTAL BLEEDING CONSTIPATION
ABRASIONS AND SCARRING ON THE BACKS OF THE HANDS AND FINGERS
FATIGUE SEIZURES

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Other eating disorders

Binge eating, an eating disorder with episodes of uncontrollable eating. During these episodes, a person rapidly consumes an excessive amount of food.
They try to hide this behaviour from others, and often feel ashamed about being fat or depressed about their overeating. Eating binges can be followed by so-called compensatory behaviour: purging, fasting and heavy exercising.

Night eating syndrome, an eating disorder, parasomnia, characterized by a pattern of late-night binge eating.

Thank you!

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