

OBESITY: BASIC PRINCIPLES

- Body mass index
 - $BMI = \frac{\text{Body mass (kg)}}{\text{Height (m)}^2}$
- In western countries the body mass increases typically 10-20 kg between 20 and 60 years of age
- In industrial countries the prevalence is 25%, but it reaches 36% in the USA
- Strong genetic determination and abnormal homeostatic mechanisms
- Easily attainable food, lack of physical activity, social, cultural and psychological factors
- Delayed satiation after fatty meals

OBESITY: GRADES OF SEVERITY

BMI	Grades
<18.5	underweight
18.5-25	normal weight
25-30	overweight
30-35	obesity
35-40	severe obesity
40-45	pathological obesity
>45	super obesity

OBESITY: CONSEQUENCES

- **Risk increased by abdominal obesity**
 - **Type II diabetes**
 - **Cardiovascular complications (hypertension, myocardial infarction, stroke)**
 - **Steatosis**
 - **Elevated LDL**
 - **Hormone-dependent and other cancers**
 - **Sleep apnoea**
 - **Heartburns, reflux disease**
 - **Osteoarthritis**
 - **Hyperuricemia**
 - **Male hypogonadism**
 - **Social stress, psychological damage**
- **Metabolic syndrome**

OBESITY: GENETIC FACTORS

- Genetic factors are responsible for 50-90% of body mass regulation
- **Genetic factors** determine **susceptibility** for obesity
- **Environmental factors** influence mainly the **manifestation** of the disease
- Genes of leptin receptor, POMC, ghrelin, melanocortin 4 receptor, CB₁, D₂, 5-HT_{2C}, β_3 und glucocorticoid receptors are involved
- Obesity is most probably a **polygenic disease** that is affected by **epigenetic factors**

OBESITY: DISORDER OF ENERGY HOMEOSTASIS

- **Leptin resistance**
- **Elevated TNF- α level in the adipose tissue**
- **Insulin resistance**
- **Decreased function of adrenergic β_3 receptors in brown adipose tissue**
- **Dysfunctional UCP-2 in adipocytes**
- **Disturbed function of PPAR receptors**

OBESITY: THERAPEUTIC OPTIONS I

- Obesity can only be treated successfully with **limited calory intake** (1000-1500 kcal/day)
- If the body mass goal is achieved, calorie intake should be increased to 1800-2000 kcal/day
- **Elevated Hunger** and **basal metabolic rate** can be problematic
- A loss of 0.5-1 kg/week is optimal

OBESITY: THERAPEUTIC OPTIONS II

- **Physical exercise** can **elevate basal metabolic rate** and help with the maintenance of reduced body weight
- It reduces muscle mass loss, as well
- Decreased calorie intake, sport activity and pharmacotherapy should **always** be **combined**
- BMI $>30 \text{ kg/m}^2$ or $>29.9 \text{ kg/m}^2$ with comorbidity indicates pharmacotherapy if non-pharmacological procedures remain ineffective after 6 months ($<5\%$ weight loss in 3-6 months)

AIM OF THE TREATMENT

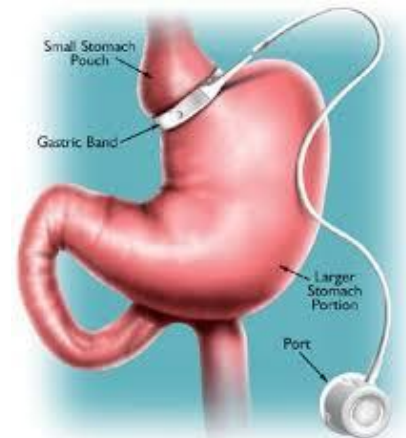
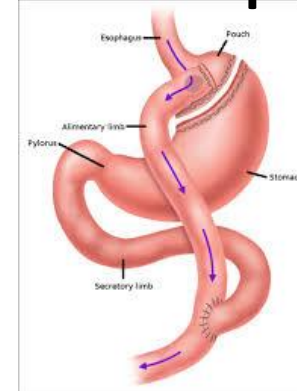
- **Maximum 4-8% total weight loss is realistic**
- **At least 2 kg weight loss should occur in the first 2 months**
- **At least 4-5% weight loss should be achieved between 3-6 months**
- **Some weight gain is normal upon ending the pharmacotherapy**

OBESITY: DIETARY TREATMENT

- Abdominal fat is lost first during diet
- The small initial weight loss already significantly reduces risks
- **Weight loss lowers basal metabolic rate** and increases appetite
- It is difficult to maintain the achieved body weight, 90% of patients fall out
- Success rate is better if medical consultations are frequent, initial weight loss is large, the patient participates in sport, sticks to the diet and checks his weight regularly

OBESITY: BARIATRIC SURGERY I

- Bariatric surgery is the **most effective** therapy of obesity today
- It is more effective than lifestyle adjustment alone and provides the best long-term outcome
- Roux-en-Y gastric bypass (RYGB)
- Reduces absorption



OBESITY: BARIATRIC SURGERY II

- **Laparoscopic adjustable gastric band (LAGB)**
- **Reduces gastric volume**
- **Nausea, dehydration**
- **Alcohol dependence, suicide**
- **Intragastric balloon**
- **Endoscopic procedure**
- **Deflation, migration, erosion, obstruction**

CONTRAINDICATIONS OF PHARMACOTHERAPY

- **Pregnancy, breastfeeding**
- **Uncontrolled chronic disease**
- **Unstable psychiatric disease in the history**
- **Eating disorder in the history**
- **Substance dependence**

LIPASE INHIBITORS I

- **Orlistat** (tetrahydrolipstatin)
- Some forms are available OTC
- Forms covalent bonds with serine amino acids of **gastric and pancreas lipase** leading to **irreversible inhibition**
- Gastric emptying and GIT-hormones might be affected, too
- Mostly (97%) excreted with the feces, 83% unmetabolized
- Fecal excretion of fat increases from 4% to 30%

LIPASE INHIBITORS II

- **Decreases LDL and cardiovascular more than explained by the weight loss**

Adverse effects

- **Gastrointestinal** – The predominant side effects of [orlistat](#) therapy are gastrointestinal, including intestinal borborygmi and cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge [\[29\]](#). In a meta-analysis of nine clinical trials, these side effects occurred at frequency rates of 15 to 30 percent [\[36\]](#) and tended to occur early and to subside as patients learned how to avoid these problems by avoiding high-fat diets and sticking to the recommended intake of no more than 30 percent fat. There was no evidence of an increased risk of gallstones, renal stones, or cardiovascular or central nervous system events.
- **Bloating, abdominal pain**
- **Frequent bowel movements, steatorrhea**
- **Despite „accidents” is compliance good**
- **Malabsorption lipid-soluble vitamins** (increased effect of coumarins)
- **Vitamin supplementation**

LIPASE INHIBITORS III

- Rarely hepatotoxicity
- Acute oxalate nephropathy (elevated intestinal absorption of oxalate due to lack of Ca^{2+})
- Side effects enforce low-fat diet
- Absorption of oral contraceptives and ciclosporin is reduced
- Contraindicated in pregnancy, chronic malabsorption, oxalate stones

INDIRECT SYMPATHOMIMETICS

- Phentermine, benzphetamine, phendimetrazine, diethylpropion
- Dexfenfluramine, fenfluramine (selective for 5-HT)
- **Appetite suppressants**
- Short duration of effect due to **tolerance**
- **Dependence, pulmonary hypertension**
- Should only be used for limited time (**maximum 12 weeks**) at the beginning of the treatment to facilitate a breakthrough

ANTIDEPRESSANTS I

- SSRI drugs induce weight loss, but are not licenced for the indication
- **Sibutramine**
- **Appetite suppressant** and increases satiety without antidepressive effect
- Stimulates sympathetic thermogenesis and energy consumption
- Selective serotonin and noradrenaline reuptake inhibitor
- Withdrawn due to hypertension, tachycardia and **elevated cardiovascular mortality**

ANTIDEPRESSANTS II

- **Naltrexone + bupropion**
- Bupropion is a noradrenaline and dopamine reuptake inhibitor
- Naltrexone reduces positive reinforcement effect of food uptake
- Smoking cessation

ANTIDEPRESSANTS III

- **Naltrexone + bupropion**
- No first line drug due to side effects and unknown cardiovascular risk
- Increased heart rate and blood pressure
- Nausea, vomiting, constipation, dizziness and dry mouth
- **Suicidal thoughts**
- Contraindicated in case of uncontrolled hypertension, epilepsy, cerebral tumor and alcohol or drug withdrawal

GLP-1 RECEPTOR AGONISTS I

- **GLP-1 increases satiety and inhibits food intake**
- **Antidiabetic GLP-1 analogues exenatide and liraglutide induce weight loss**
- **Subcutaneous liraglutide is licenced for the treatment of obesity**
- **Longer effect than that of GLP-1**

GLP-1 RECEPTOR AGONISTS II

- **Larger doses than in diabetes**
- **Cardiovascular risk decreases**
- **Side effects are nausea, antibody formation, nephrotoxicity and pancreatitis**
- **Thyroid cancer was detected in rodents (contraindication)**

LORCASERIN

- Not licensed in Europe and recently withdrawn in the US
- **5-HT_{2C} receptor agonist**
- Appetite suppressant
- Can be used in case of diabetes, hypertension, dyslipidemia
- Hypoglycemia might occur in diabetic patients
- Combinations with serotonergic drugs are contraindicated due to risk of serotonin syndrome
- Withdrawn after elevated risk of colorectal, pancreatic and lung cancer was detected

PHENTERMINE + TOPIRAMATE I

- Not licensed in Europe
- Only for the treatment of **men** and **postmenopausal women** (teratogenic effect)
- If no cardiovascular disease is present (indirect sympathomimetic)
- If other drugs are not tolerated
- More effective, but comes with more side effects

PHENTERMINE + TOPIRAMATE II

- Tachycardia
- Gallstones, kidney stones
- Depression, anxiety, attention deficit, **sucidal thoughts**
- Hyperchloremic metabolic acidosis and elevated creatinine (topiramate inhibits carbonic anhydrase)
- **Teratogenic** (orofacial cleft)
- Withdrawal of **topiramate** might induce seizures

CANNABINOID RECEPTOR ANTAGONISTS

- **Rimonabant**
- **CB1 receptor antagonist**
- Originally developed as smoking cessation aid
- Leads to significant weight loss
- Risk of **depression** and **suicide** is elevated
- Withdrawn
- Taranabant was withdrawn, too

METRELEPTIN I

- Methionyl leptin
- For the therapy of **lipodystrophy**, but not for that of obesity
- Reduced subcutaneous adipose tissue, but fatty degeneration of skeletal muscles and the liver
- **Insulin resistance, hyperlipidemia**
- Berardinelli-Seip-syndrome, Lawrence-syndrome and Barraquer-Simons-syndrome
- Administered s.c. daily

METRELEPTIN II

- **Successfully treats insulin resistance and fatty degeneration**
- **Subcutaneous adipose tissue is not regenerated**
- **Frequent side effects**
- **Hypoglycemia**
- **Weight loss**

CHITOSAN

- Dietary supplement, neither evidence-based nor accepted
- **Polycationic carbohydrate** produced out of chitin by deacetylation
- Reduces fat absorption in the intestine by **adsorbing** it
- No steatorrhoea or disturbed absorption of lipid-soluble vitamins were reported