FAFP2 Pharmaceutical care II

Lecture:

Obesity and its drug management

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Metabolic syndrome

- based on the pathophysiology of insulin resistance

➢ **Abdominal obesity** (waist circumference)	men > 102 cm women > 88 cm
➢ **Triglycerides**	> 2 mmol / l
➢ **HDL cholesterol**	Men < 1 mmol/l Women < 1.3 mmol/l
➢ **Blood pressure**	130/85 mmHg
➢ **Fasting blood glucose**	> 6 mmol / l

Postprandial metabolic disorders

- **postprandial concentrations** of Glc and TG correlated with **CV risk** better than their concentration in the fasting state

- **excessive glc ↑ and ↑ TG** leads to:
  - free radicals --- **oxidative stress**
  - endothelial dysfunction
  - vasoconstriction
  - atherosclerosis
  - hypercoagulation
  - sympathetic hyperactivity

Risks of obesity

- **Mechanical load**
  - joints
- **Hypoventilation syndrome**
  - sleep apnea
- Disruption own **self-regulation physiological functions**
  - CV disease
  - reproduction
  - cancer
  - gastrointestinal
    - hiatal hernia, reflux disease, hepatic steatosis
  - venous and lymphatic system
  - trophic skin

Risk of cancer

- mechanism of action: insulin resistance and chronic hyperinsulinemia

- **Endometrial cancer**
  - risk factors - obesity, nuliparity
  - **endogenous estrogens**
    - aromatase of adipose tissue converts androgens to estrogens → endometrium is exposed to increased estrogen exposure

- **Gallbladder cancer** - biliary stones

- **Esophageal adenocarcinoma** – reflux
  - problem of frequent underdosing of chemotherapy

Pharmacotheraphy in obesity

- **Sibutramine**
- **Orlistat** (Xenical®, Alli®)
- **Phentermine** (Adipex retard®)
- **Rimonabant** (Acomplia®)

Sibutramine

- mechanism of action:
  - **reuptake inhibitor** of **5-HT** and **NA** in the CNS, to a lesser extent of D
  - it does not affect the 5-HT and D receptors
  - it does not affect cholinergic, H1 and BDZ receptors
- evoking **a sense of satiety**

- clinical experience:

  - reduction energetic income (fats)
  - reduction in body weight (by 6.9 kg for placebo – by 12.9 kg for sibutramine)
  - decrease in blood glucose, insulinaemia, TAG, VLDL
  - increase in HDL-cholesterol

- drug interactions: MAO inhibitor

- recommendations for patients:

  Do not use sibutramine if you have taken an MAO inhibitor in the last 14 days.

  Serious, life threatening side effects can occur if you use sibutramine before the MAO inhibitor has cleared from your body.

- contraindications for sibutramine:
  - severe or uncontrolled hypertension (high blood pressure)
  - an eating disorder (anorexia or bulimia)
  - a history of coronary artery disease (atherosclerosis)
  - a history of heart disease (congestive heart failure, heart rhythm disorder)
  - a history of heart attack or stroke
  - taking stimulant diet pills – e. g. caffeine + ephedrine ("Elsinorské pills")

Sibutramine was withdrawn from many european markets in previous years from safety reasons !

Orlistat

- mechanism of action:

  - **blocking the enzyme lipase - prevents fat absorption**
  - reduces cholesterol absorption

- indication:
  - obese patients with an initial body mass index (BMI) of **30 kg/m^2 or greater**
  - or **27 kg/m^2** in the presence of **other risk factors** (hypertension diabetes, or dyslipidemia)
- must be used **together with a reduced-calorie diet and increased physical activity !!**
  - orlistat is only part of a complete program of treatment that also includes diet, exercise, and weight control
  - avoid a diet that is high in fat
    - high-fat meals taken in combination with orlistat can increase risk of unpleasant side effects stomach or intestines
- for use **only in adults that are overweight or obese**

Information how to take orlistat

- usually taken **3 times per day with each main meal that contains some fat** (no more than 30 % of the calories for that meal)
  - the fat content of daily diet should not be greater than 30 % of total daily caloric intake
    - for example, if you eat 1200 calories per day, no more than 360 of those calories should be in the form of fat
- take the medicine either **with meal** or **up to 1 hour after eating**
- if **meal is skipped**, or **meal that does not contain any fat**, **skip the dose** of the medicine

- **decreased absorption of** fat-soluble vitamins

  - vitamin and mineral supplement may be needed
  - take the supplement at bedtime, or at least 2 hours before or after taking orlistat

High-risk co-medication:

cyclosporine:	take 3 hours before or after this drug, measure cyclosporine levels
levothyroxine:	take at least 4 hours before or after this drug, monitor thyroid function

Contraindications for orlistat

- you are not overweight
- chronic malabsorption syndrome
- gallbladder problems
- pregnancy
  - weight loss is not recommended during pregnancy, even if patient is overweight!
- status after organ transplant
- taking cyclosporine

Substantial weigh loss can increase the risk of **cholelithiasis**

Hepatotoxicity:

- immediately report **signs and symptoms of hepatic dysfunction:**
  - itching, yellow eyes or skin, dark urine, or loss of appetite
  - severe, continuous abdominal pain

Side effects:

- flatulence
- diarrhea
- oily stools

Information for brestfeeding women:

Taking orlistat can make it harder for your body to absorb fat-soluble vitamins.

Vitamins are important if you are nursing a baby - vitamin and mineral supplement may be needed.

Rimonabant

- mechanism of action:

  - **canabinoid-receptor antagonist**
  - **selectively blocking CB1 receptors in the brain and in peripheral organs important in glucose and lipid (or fat) metabolism, including adipose tissue, the liver, gastrointestinal tract and muscle**
    - switches off the same brain circuits that make people hungry when they smoke cannabis

- effect of action:
  - reduces weight
    - **reduction of the weight** and a very large range of regulation of **plasma lipids**
  - reduces lipid concentrations
    - very significantly **increases HDL**-cholesterol and **decreases C-reactive protein**
  - aid to **smoking cessation**

Ribonamant was withdrawn from US and many european markets in previous years (EMEA - 2009) from safety reasons !

- *due to the risks of dangerous psychological side effects (depression), including suicidality*

Future treatment options in obesity

1. **CNS and neurotransmitters**

- substances related to today's anorectics and antidepressants

2. Central ring of action of **leptin and insulin**

- leptin analogs
- ciliary neurotrophic factor (Axokine)
- neuropeptide Y

3. **GIT** - **cholecystokin**n analogues, drugs affecting **GLP-1**, **ghrelin** analogues

4. **Energy expenditure**

- β3-agonists
- thyroid receptor agonists
- drugs affecting uncoupling proteins

5. Inducing **apoptosis of fat cells**

Chirurgical options in obesity

Bariatric procedures

Weight-loss surgery

- very effective is so-called **gastric banding**
- surgical method
- even after the surgery the slimming diet is needed!