Hyperlipidemia

Definition and overview
Diabetic arthropathy
Charcot arthropathy: definition

- Charcot neuroarthropathy (CN) is a chronic and progressive disease of bone and joints, characterised by painful or painless bone and joint destruction in limbs that have lost sensory innervation.
- Affected joints exhibit synovitis, instability, subluxation, and destruction.
- Although not often recalled, trauma is thought to be an important initiating factor.
Neurotraumatic theory

Exaggerated expression of proinflammatory cytokines theory

Clinical course

• Acute active phase
  – With normal x-ray
  – With deformity and radiological changes
  – Characteristics: unilateral erythema and oedema, temp difference 2°C

• Chronic stable phase
Combination of:
- lack of sensation
- limited joint mobility
- autonomic dysfunction resulting in dry skin
- repetitive high pressure

*callus formation*

increase the foot pressure

plantar ulceration at the site of maximum pressure

Sudomotor dysfunction

- impairment of the sympathetic innervation of cutaneous sweat glands
  “autosympathectomy”
- reduction/loss of sweating - anhidrosis
- primarily on the lower extremities
- dryness of the skin – may lead to fissure formation, cracks

Infectious ulcers

Hyperlipidemia

- **Definition** — increased concentration of plasma lipoproteins.
- One or more classes of lipoproteins may accumulate in their blood stream because of increased production or secretion into the circulation or because of decreased clearance or removal from the circulation.
Hyperlipidemia

• Diagnosis:
  Total cholesterol $\geq 200\text{mg/dl}$
  LDL-cholesterol $\geq 100\text{mg/dl}$
  TG $\geq 150\text{mg/dl}$
  HDL-cholesterol $\leq 40\text{mg/dl}$
<table>
<thead>
<tr>
<th>Type</th>
<th>Predominant elevated plasma lipoprotein</th>
<th>Predominant plasma lipid</th>
<th>Plasma appearance</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Triglycerides</td>
<td>Cream layer, clear</td>
<td>LPL deficiency</td>
</tr>
<tr>
<td>Ila</td>
<td>LDL</td>
<td>Cholesterol</td>
<td>Clear</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>IIb</td>
<td>VLDL+LDL</td>
<td>Triglycerides and cholesterol</td>
<td>Turbid</td>
<td>Familial combined hyperlipidemia</td>
</tr>
<tr>
<td>III</td>
<td>Remnants(β-VLDL)</td>
<td>Triglycerides and cholesterol</td>
<td>Turbid</td>
<td>Type III hyperlipoproteinemia</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Triglycerides</td>
<td>Cream layer, turbid below</td>
<td>Familial hypertriglyceridemia</td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons+VLDL</td>
<td>Triglycerides and cholesterol</td>
<td>Cream layer, turbid below</td>
<td>Apo-CII deficiency</td>
</tr>
</tbody>
</table>
MAJOR PLASMA LIPID ABNORMALITY

Primary disorders:

• Familial hypercholesterolemia
• Familial defective apo-B100
• Polygenic hypercholesterolemia
• Familial combined hyperlipidemia
• Type III hyperlipoproteinemia
• Familial hypertriglycerideridemia
• LPL deficiency
• Apo-CII deficiency
MAJOR PLASMA LIPID ABNORMALITY

Secondary disorders:
• Hypothyroidism
• Nephrotic syndrome
• Diabetes mellitus
• Alcoholic hyperlipidemia
• Pregnancy
• Estrogen therapy
• Glucocorticoid therapy
• Hepatitis, cholestasis
• Acute porphiria
Main classes:

- **Total cholesterol**: level of esterified and free cholesterol in blood
- **LDL-cholesterol** = esterified chol which is transported by LDL to tissues (artery)
- **HDL-chol** = cholesterol transported by HDL from tissues to liver
- **Col-LDL** = total-chol-HDL-COL-Tg/5 (mg/dl)
- **Triglycerides**
Lipoproteins

- **Chylomicrons**: transport of triglycerides and exogenous chol from intestin to blood flow
- **VLDL**: very low density lipoproteins - transport endogenous lipids to tissues
- **IDL**: intermediate density lipoproteins - transports triglycerides and esterified chol to tissues
- **LDL**: low density lipoproteins - major form of esterified chol
- **HDL**: high density lipoproteins - transports chol from tissues (artery) to liver
Lipoproteins

- **Apoproteins**: protein cover of lipoproteins. Apo is ensuring the stability for lipoprotein and induces the linkage with specific receptors and enzymatic activity.
- Apo A = from HDL - antiatherogenic effect
- Apo B = FROM LDL - aterogenic
- Lipoprotein Lp(a): aterogenic and thrombogenic (inhibits the fibrinogen). It has Apo(a)
- Fatty acids: cholesterol esterification
Main metabolic ways

- **Sources**: exogenous and endogenous
- Transport mechanism of lipids in blood: by lipoproteins
- **Cholesterol synthesis**: in liver → hydroxyacetate → HMG-CoA-reductase = cholesterol

Chol catabolism: in liver → biliary acids → intestine elimination → reabsorption for cholang and biliary acids → liver
Lipoprotein receptors

- Polypeptides which are linking lipoproteins
- The linkage is done after recognizing some apoproteins:
  - LDL receptors for Apo 100 in LDL, and ApoE from IDL
  - Receptors for chilo-remnants linking of ApoE
  - Receptors for HDL linking to ApoA1
- Specific enzymes:
  - Hepatic lipase
  - LCAT: Lecitin-Cholesterol-Acyltransferase: Esterifying Chol
Clinical forms

• Polygenic hypercholesterolemia (apoE and B)
  - moderate hypercholesterolemia
  - in obese, persons with CV disease, xanthelasma, lipid corneean arch

• Familial hypercholesterolemia: LDL-receptors disorder
  - severe hypercholesterolemia
  - severe CV risk
  - widespread xantomas, lipid corneean arch

• Mixed moderate and severe hyperlipidemia type III (ApoE, Lipoprotein-lipase)
  hyper-Tg and hyper-chol palmar xantomas
Clinical forms

- **Moderate and severe (type V) hypertriglyceridemia:**
  - severe hypertriglyceridemia
  - lipaemia retinalis, widespread xantomas, hepatosplenomegaly, risk of acute pancreatitis

- **Chylomicronic syndrome:**
  hypertriglyceridemia due to increased values of chylomicrones (decreased value of lipoprotein-lipase)
  - abdominal pains due to recurrent pancreatitis lipaemia retinalis, widespread xantomas, hepatosplenomegaly

- **Isolated decreasing of HDL**
TREATMENT

• STATINS
• INHIBITORS OF CHOLESTEROL ABSORPTION
• FIBRATES
• NICOTINIC ACIDS
• RESINES
• OMEGA-3 ACIDS
STATINS

• Mechanism of action:
  - inhibitor of HMG-CoA-reductase
  - decreases LDL and VLDL
  - decreases Tg level
  - moderate increasing of HDL
  - stability of atheromatosis plaque
  - antithrombotic and antiinflammatory effects

ATORVASTATIN;
SIMVASTATINE;
FLUVASTATINE;
LOVASTATINE;
PRAVASTATINE,
ROSUVASTATINE

• SIDE EFFECTS:
  - increased transaminase
  - miopathy

Contraindications:
  - chronic or active hepatitis
  - miopathy, chronic renal failure
  - pregnancy, breast feeding
Fibrates

• Mechanism of action:
  stimulating nuclear receptors (PPARα):
  - decreases synthesis and accelerates elimination of triglycerides
  - increases catabolism of LDL, VLDL
  - decreases post-prandial hyperlipidemia

• Side effects:
  - increases transaminase level and digestive troubles

• Contraindication:
  - liver disease
  - chronic renal failure
  - billiary lithiasis
  - pregnancy, breast feeding

Fenofibrate, bezafibrate, gemfibrosil
Nicotinic acid

- **Mechanism of action**
  - inhibits FFA delivery from adipose tissue:
  - decreases liver synthesis of VLDL and Tg
  - distroyance of ApoA1

- **Contraindications:**
  - Chronic liver disease
  - Pregnancy
  - Severe goute,
  - Association with peripheral vasodilators
Inhibitors of cholesterol absorption

EZETIMIBE

- **Mechanism of action:**
  - selective inhibition of cholesterol absorption in intestine
  - increases plasmatic clearance of chol

- **Contraindication:**
  - pregnancy
  - breast feeding
Obesity
BENEFITS OF 5-10% WEIGHT LOSS

• DECREASES > 20% GENERAL MORTALITY (ESPECIALLY FOR DIABETICS)

• INCREASES PHYSICAL EXERCISE TOLERANCE WITH 33%

• DECREASES RISK FOR DIABETES WITH 50%

• DECREASES LDL CHOLESTEROL WITH 15%

• DECREASES TRIGLICERIDES WITH 30%

• INCREASES HDL CHOLESTEROL WITH 8%

• Neuroregulation of appetite and eating

• Peripheral signals mediating the central regulation of food intake
Eating is regulated by 2 hypothalamic areas:
- Ventromedial hypothalamic nucleus (VMN) = orexigenic
- Ventrolateral hypothalamic nucleus (VLN) = anorexigenic

Circulating satiety hormone
➢ Interaction between circulating factors and neuronal pathways in the hypothalamus
➢ Monoaminergic pathways and appetite regulation
Peripheral signals mediating the central regulation of food intake

- **Glucagon-like peptides (GLP-1 and GLP-2)**
  - are secreted as a response to nutrients
  - Reduces plasma glucose and appetite through multiple effects on gastric emptying

- **Cholecystokinin**
- **Bombesin**
- **Gastric Inhibitory Peptide**
- **Enterostatin**
- **PYY**
Obesity classification:

- WHO: using BMI = KG/M²
- SUBPONDERAL: <18,5
- NORMAL: 18,5-24,9
- OVERWEIGHT: 25-29,9
- STAGE Ia: 30-34,9
- STAGE Ib: 35-39,9
- STAGE III >40
INDEX FOR OBESITY

- WAIST CIRCONFERENCE:
  MALE < 95 cm → more than 104
  Female < 80 cm → more than 88

Calculation of body weight:
Lorentz:
Ideal weight = H - 100 - (H - 150) cm

MLI:
Ideal weight = 50 + 0.75(H - 150) + (age - 20)/4
INDIVIDUAL AND BIOLOGIC SUSCEPTIBILITY

DIET AND PHYSICAL ACTIVITY

ENERGETIC BALANCE

INPUT

Fats
Carbohydrates
Proteines

OUTPUT

Physical activity
TEF
MB
Obesity management = weight loss + weight maintenance + reducing risk factors

- Behavioural management
- Diet
- Physical activity
- Drug and surgical therapy
Strategies of behavioural management

- Self-monitoring
- Eating behaviour control
- Realistic goal setting
- Stress management
- Relapse prevention
Dietary messages for managing weight

- Low fat, especially saturated fat
- Increase whole grain high fiber carbohydrates
- Fruits and vegetables
- Portion sizes
Combined treatment of obesity

Weight loss

BMI >30 or 28 risk factors
Diet, life style
Increase 3-6 kg (>10%)

Maintain

>5 kg weight loss
Drug treatment

<5 kg weight loss
Stop drug treatment
Other treatments

Dupa Royal College of Physicians, 1998
Pharmacological treatment for obesity

Hungry sensation decrease

Increase satiety

muscle

Adipose tissue

liver

GI Tract

Kopelman et co
Pharmacological treatment of obesity

Drugs that act:
- on the gastrointestinal system (pancreatic lipase inhibitors)
Pancreatic lipase inhibitor

ORLISTAT:
- inhibits pancreatic and gastric lipase
- Decreases ingested triglyceride hydrolysis