Lipid disorders-Frederickson Classification

1) Type 1: Hyperchylomicronemia

   Lipoprotein lipase ya da ApoCII deficiency

2) Type 2: a Hypercholesterolemia without hypertriglyceridemia (FH)

   b Hypercholesterolemia with hypertriglyceridemia

3) Type 3 : ApoE protein variants (increased IDL)

4) Type 4 : Increased VLDL, CM does not change

5) Type 5 : Increased VLDL, CM ve triglycerides

Secondary lipid disorders

DRUGS	METABOLIC EFFECTS
Oestrogen replacement	Obesity
Cyclosporine	Type 2 Diabetes
Antiretroviral agents	Renal disease with proteinuria
Isotretinoin analogs	Lipodystrophy
Excess androgen in women	High energy diet with saturated fat

Secondary Lipid disorders

- Increased lipid intake, alcohol, anorexia nervosa → Increased VLDL
- Increased VLDL→mixed dyslipidemia
- Insulin resistance→ Increased VLDL

Secondary Lipid disorders

- Kidney disease with proteinurea (Increased Apo B ve VLDL)
- Hypothyroidism (Increased cholesterol)

Secondary Lipid disorders

- Paraproteinemias (Proteins make complexes with lipoproteins and therefore prevent their removal→xanthomas
- Beta blockers →Decreased clearance of TRL particles and increased TAG
- Retinoic acid analogues used for psoriasis increase VLDL production

Hypercholesterolemia

Normally,

↓5 mmol/L (Total cholesterol)

↓3 mmol/L (LDL cholesterol) is preferred.

Monogenic or polygenic…

Monogenic Hypercholesterolemia

- Familial Hypercholesterolemia
- Familial defective apoprotein B100
- Autosomal resesive hypercholesterolemia
- Mutations of genes coding Convertase subtisilin kexin tip 9
- Sitosterolemia

Familial hypercholesterolemia

- Defective LDLR mediated endocytosis
- 900 different mutations in LDLR gene (Ligand binding, internalization, ligand removal, recycling of receptor)
- Heterozygote or homozygote.
- Homozygote disease can result with premature arterial disease.

Familial Hypercholesterolemia

Familial Hypercholesterolemia

Definite familial hypercholesterolemia

Total cholesterol > 7.5 mM in adults and > 6.7 mM in children under 16 years of age

or

LDL cholesterol > 4.9 mM in adults and 4 mM in children plusone of these conditions:

The presence of tendon xanthomas

A first or second degree FH patient relative

Familial defective apoprotein B100

- Defective ApoB100
- IDL can be normally taken up by receptor.
- Homozygote form is clinically similar to FH.

Autosomal recessive hypercholesterolemia

- Recycling of receptor is defective

Mutations of Convertase subtisilin kexin type 9 gene

- This gene increases the catabolism of LDLR.
- It is not clear how it leads to hypercholesterolemia.

Sitosterolemia

- Removal of sterols from cells is defective.

- ABCG5/G8 restricts restrict the amount of cholesterol absorption from intestinal lumene by sending plant sterols and cholesterol from enterocytes back to the intestinal lumen. It is also found in the liver membrane and it has been shown that it accelerates the clearance of sterols in the liver by increasing their bile excretion. In humans, mutations of these transporters - ABCG5/ABCG8 increased cholesterol absorption and atherosclerosis susceptibility. Deficiency of ABCG5/ABCG8 results with sitosterolemia.

Polygenic or non-familial hypercholesterolemia

- Genes have not been identified for this type of hypercholesterolemia.

Hypocholesterolemia

- Cancer is associated with low cholesterol. Low blood cholesterol levels indicate low LDL cholesterol and are called hypobetalipoproteinemia. (Factors may be genetic defects leading to familial hypobetalipoproteinemia and non-heritable factors such as abetalipoproteinemia and malignancy, nutrition, intestinal malabsorbidity and liver disease).

Familial hypobetalipoproteinemia

- More than 35 mutations leading to shortened forms of ApoB100.
- Heterozygotes are asymptomatic and the risk of atheroma formation is low.
- ApoB in homozygotes is very low, CMs can not be assembled, fat malabsorption, impairment of VLDL formation.

Abetalipoproteinemia

- Rare autosomal recessive disorder
- Lipoproteins carrying ApoB can not be synthesised. CMs can not be asembled, fat malabsorption, impairment of VLDL formation.
- Deterioration of VitE absorption → retinitis pigmentosa (neurological disorder) Acanthocyte (abnormal erythrocyte membrane)

Decreased levels of blood HDL particles

- Genetic or secondary (as a result of disease).
- Insulin resistance leads to decreased endothelial LL and increased hepatic lipase.

Decreased blood HDL particles and Apoprotein A1-hereditary factors

Which metabolic defects cause this condition?

What are the clinical features?

Which diseases are characterized with low number of HDL particles?

Increased level of blood HDL particles Primary and secondary causes

Primary causes of increased level of HDL particles such as CETP deficiency, hepatic lipase deficiency and secondary causes such as primary biliary cirrhosis, chronic excessive alcohol consumption will be discussed.

Hypertriglyceridemias

- Hereditary hypertriglyceridemia
- Familial endogenous hypertriglyceridemia
- Familial combined hypertriglyceridemia
- Type 3 hyperlipidemia
- Apoprotein E polymorphisms

Familial endogenous hypertriglyceridemia

- Candidate genes are hepatic lipase, ApoC3 and ApoA5.

Familial combined hyperlipidemia

- Members are common in families with heart attacks.
- It is seen between the ages of 20-30.
- LDL or TRL or both increase.
- Cholesterol, TAG, VLDL are increased.
- Obesity and insulin resistance are accompanied by an increase in VLDL.
- Family studies have linked hypertriglyceridemia with haplotypes of certain gene clusters.

Type 3 hyperlipidemia

- It is characterized by the accumulation of IDLs. Mixed hyperlipidemia is observed. The binding of IDL to the cell surface receptor is reduced. Increased LDL is observed.