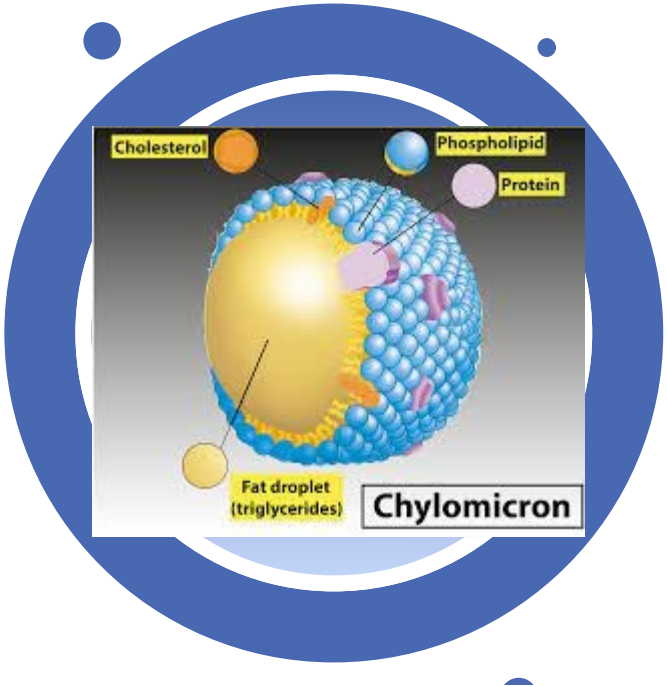
Multifactorial Chylomicronemia Syndrome



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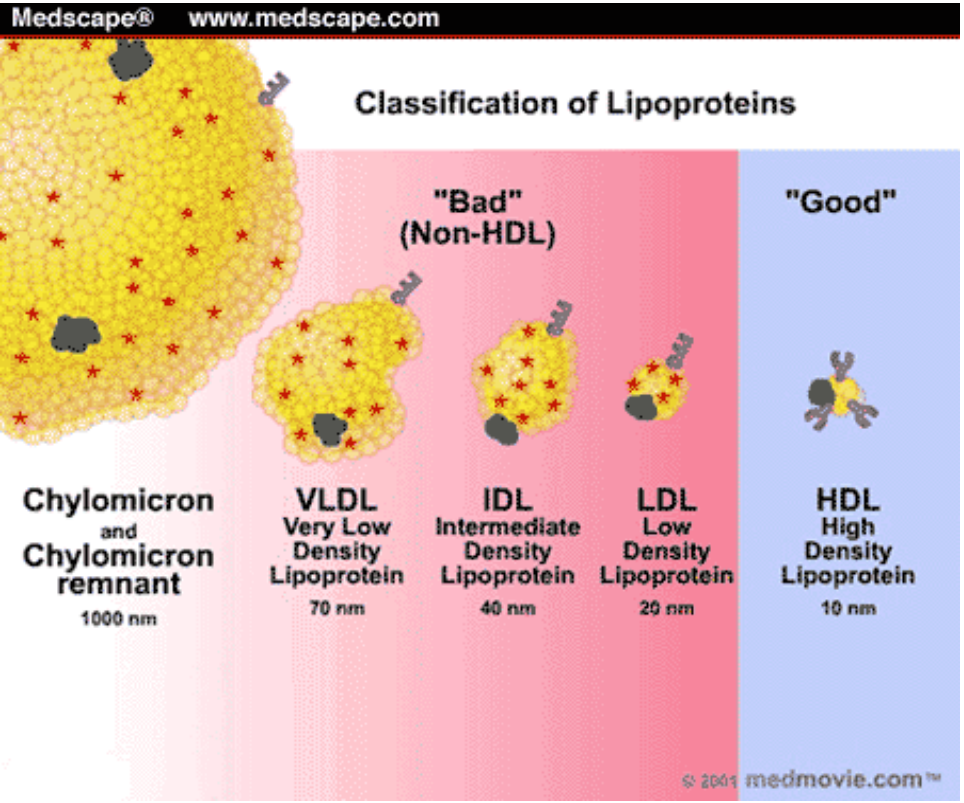
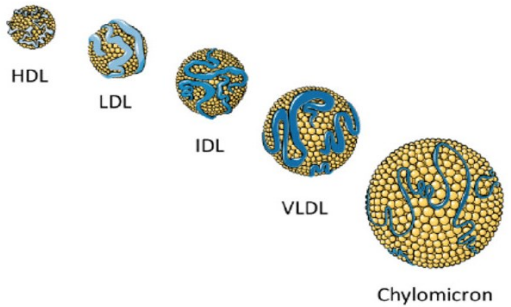
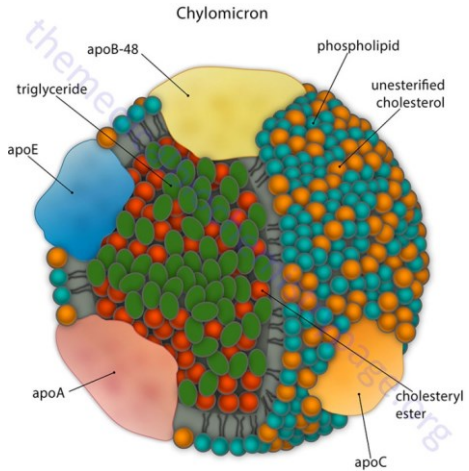
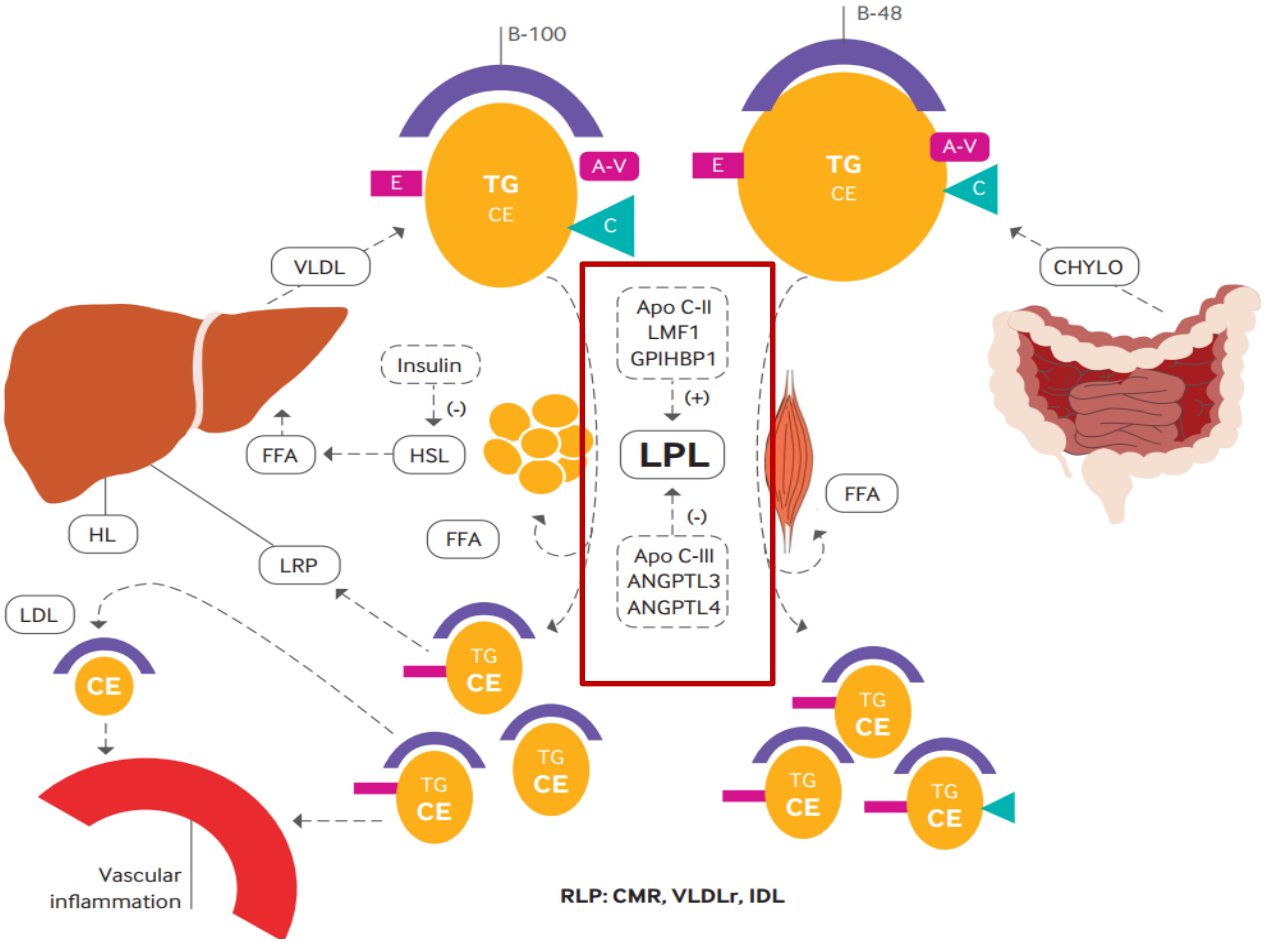
Chylomicrons are large triglyceride-rich lipoproteins produced in enterocytes from dietary lipids





LDL, IDL, VLDL, and Chylomicrons are all apoB containing lipoproteins





BMJ 2020;371

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Hyperlipoproteinemia phenotype

	WHO ICD number	Fredrickson hyper-lipoproteinaemia phenotype	OMIM number	Main lipid change	Primary lipoprotein change	Genetics
Familial hyperchylomicronaemia	E78.3	Type 1	238600	↑Triglyceride	↑Chylomicrons	Monogenic; autosomal recessive due to two mutant alleles of *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, or *GPD1*; presentation mainly paediatric or early adulthood
Familial hypercholesterolaemia	E78.0	Type 2A	143890	↑Total cholesterol	↑LDL	Monogenic; autosomal codominant; heterozygous form results from one mutant allele of *LDLR*, *APOB*, or *PCSK9*; homozygous form results from two mutant alleles of these genes or of *LDLRAP1*
Combined hyperlipoproteinaemia	E78.2, E78.4	Type 2B	144250	↑Total cholesterol, ↑triglyceride	↑VLDL, ↑LDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes; high GRS for LDL cholesterol
Dysbetalipoproteinaemia	E78.2	Type 3	107741	↑Total cholesterol, ↑triglyceride	↑IDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes; *APOE* ε2/ε2 homozygosity, or heterozygous rare mutation in *APOE*
Primary or simple hypertriglyceridaemia	E78.1	Type 4	144600 and 145750	↑Triglyceride	↑VLDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes
Mixed hypertriglyceridaemia	E78.3	Type 5	144650	↑Total cholesterol, ↑triglyceride	↑VLDL, ↑chylomicrons	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes, with higher burden of risk alleles than for hyperlipoproteinaemia type 4

GRS was created by unweighted tallying of risk alleles from single nucleotide polymorphisms associated with increased plasma concentrations of triglyceride and hypertriglyceridaemia. Adapted from Hegele (2009).[33] ICD=International Classification of Diseases. OMIM=Online Mendelian Inheritance in Man database. VLDL=very low-density lipoprotein. GRS=polygenic genetic risk score. IDL=intermediate-density lipoprotiein.

Lancet Diabetes Endocrinol 2014;2:655-66.

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Secondary causes of hypertriglyceridemia

- Obesity
- Metabolic syndrome with triglyceride levels > 1.7 mmol/L
- A diet with a positive energy-intake balance and a high fat or high glycemic index content
- Insufficient physical activity
- Alcohol consumption
- Diabetes mellitus, particularly type 2
- Renal disease, especially uremia or glomerulonephritis
- Hypothyroidism*
- Pregnancy: physiological triglyceride concentrations double during the third trimester
- An autoimmune disorder, such as a paraproteinemia or systemic lupus erythematosis
- Any of several types of medications, including
  - Corticosteroids
  - Estrogens, especially those taken orally
  - Tamoxifen
  - Antihypertensives: e.g., noncardioselective β-blockers, thiazides
  - Isotretinoin
  - Bile-acid-binding resins
  - Cyclophosphamide
  - Antiretroviral regimens, especially for HIV infections
  - Psychotropic medications: phenothiazines, second-generation antipsychotics

Atenolol, Propranolol, Metoprolol

CMAJ 2007;176:1113-20.

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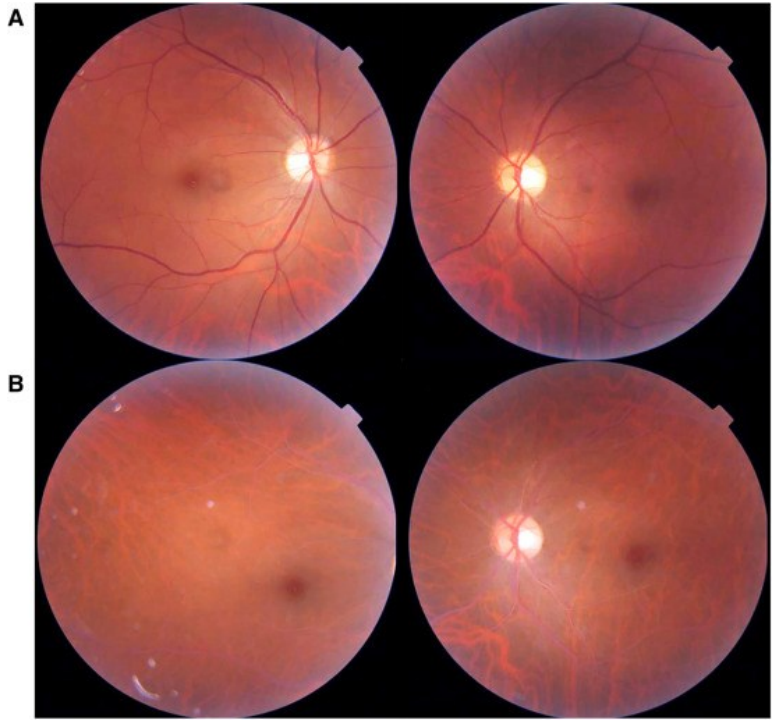
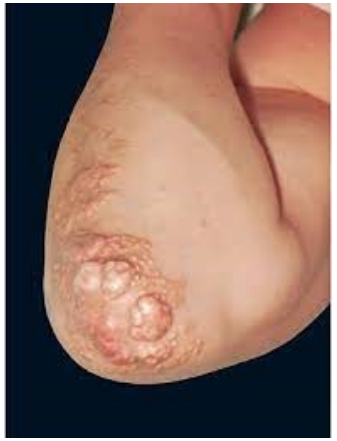
Hypertriglyceridemia



Lipemia retinalis

Eruptive xanthoma



Tuberous xanthoma

Palmar xanthoma

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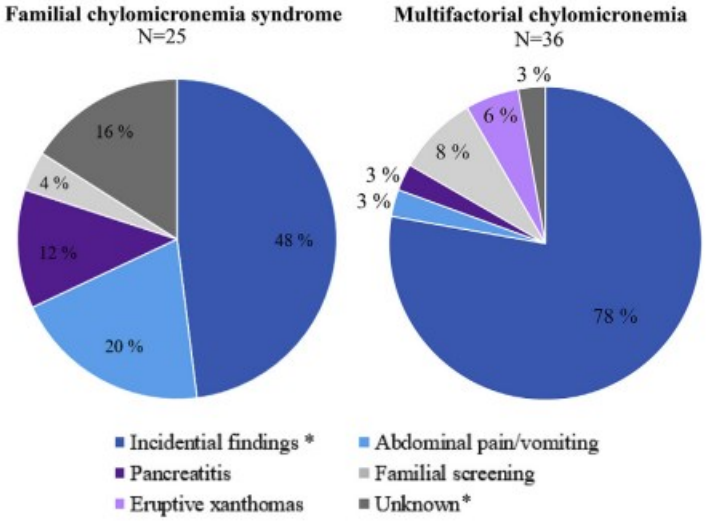
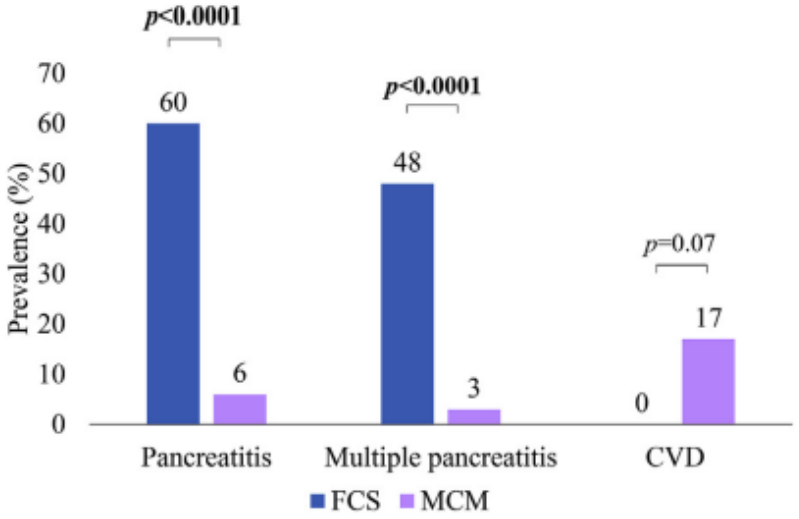
Chylomicronemia syndrome

is characterized by severe hypertriglyceridemia and fasting chylomicronemia → predisposes affected individuals to acute pancreatitis.

- Familial Chylomicronemia Syndrome (FCS) : monogenic mutations (very rare) in the genes encoding the enzyme, lipoprotein lipase (LPL), or its regulators, APOC2, APOA5, GPIHBP1, and LMF1
- Multifactorial Chylomicronemia Syndrome (MCS) : a cluster of minor genetic variants causing polygenic hypertriglyceridemia, which is exacerbated by conditions or medications

Familial CS (FCS) versus Multifactorial (MCS)





FCS → higher prevalence of abdominal pain, pancreatitis and multiple pancreatitis

MCS →higher CVD and metabolic syndrome features

Atherosclerosis 2019:137–142

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Chylomicronemia syndrome: treatment

Dietary fat restriction + Weight reduction + Triglyceride lowering medications such as fibrates, high dose omega 3 fatty acids and niacin.

Recommended fat intake is restricted to 10%–15% of total energy intake (about 15-20 g/d), with reductions in saturated, unsaturated and trans fats. Avoid refined carbohydrates.

Several new pharmacotherapeutic agents are being tested that are likely to considerably improve treatment of hypertriglyceridemia

	LDL-C	HDl-C	TG	Evidence
Statins	↓18-55%	↑5-15%	↓7-30%	++++++
Bile acid resins	↓15-30%	↑3-5%	↑0-15%	++
CAI*	↓18-20%	↑3%	↓8%	++
Nicotinic acid	↓5-25%	↑15-35%	↓20-50%	++
Stanol Esters	↓5-14%	No change	No change	++
Fibrates	↓5-20%	↑10-20%	↓25-50%	+++
Omega-3 fatty acids	↑2-5%	No change	↓30-40%	+

*CAI=Cholesterol Absorption Inhibitors

Adult Treatment Panel III of the National Cholesterol Education program. *JAMA*. 2001;265:2486-2497.

Katan MB, et al. *Mayo Clin Proc.* 2003;78965-978.

Chylomicronemia syndrome: treatment

New Pharmacotherapeutic Approaches

LPL Gene Replacement Therapy : the effect was transient and further development was discontinued in 2017.

APOC3 Inhibition: Volanesorsen is an antisense oligonucleotide that binds to APOC3 mRNA preventing APOC3 translation

ANGPTL3 Inhibition: The monoclonal antibody evinacumab that blocks the action of ANGPTL3 has been found to lower triglyceride levels up to 80% in patients with mild to moderate HTG and also lowers LDL-C.

Take home messages

- The presence of the Chylomicronemia Syndrome (CS) increases the risk of HTG-induced pancreatitis in proportion to the duration and severity of the HTG, and is the third most frequent cause of pancreatitis.
- Molecularly defined familial and multifactorial CS represent 2 distinct clinical entities as proved by a different genetic architecture and long-term outcomes.
- FCS patients presented a higher frequency of pancreatitis than multifactorial CS patients.
- FCS patients presented less metabolic abnormalities than multifactorial CS patients.

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