
## Introduction

- Triglycerides form the major portion of fats in the body, which indicates their importance and how vital their functions are to the body
- They are found in foods from plant and animal sources while cholesterol is mostly sourced from foods of animal origin.
- Sources of vegetable origin include vegetable oils such as sunflower and peanut oil, which stay liquid at room temperature.

## Introduction

- Sources of animal origin include meat and dairy products, which are solid or semisolid at room temperature
- VLDL is the lipoprotein which contains the highest amount of triglycerides

## Function Of Triglycerides

Provide energy

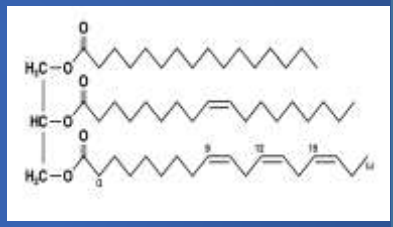
Provide insulation

Provide nutrition

Cell membranes

# Chemical structure

- TGs are tri esters of fatty acids and glycerol.
- Formed by combining glycerol with three fatty acid molecules.
- Alcohols have a hydroxyl (HO–) group. Organic acids have a carboxyl (–COOH) group.
- Alcohols and organic acids join to form esters.
- The glycerol molecule has three hydroxyl (HO–) groups. Each fatty acid has a carboxyl group (–COOH).
- In triglycerides, the hydroxyl groups of the glycerol join the carboxyl groups of the fatty acid to form ester bonds.



Example of an unsaturated fat triglyceride Left part: glycerol; right part, from top to bottom: palmitic acid, oleic acid, alpha-linolenic acid.

# Chemical structure

- There are many different types of triglyceride, with two main subtypes; saturated and unsaturated.
- Saturated fats are "saturated" with hydrogen — all available places where hydrogen atoms could be bonded to carbon atoms are occupied.
  - These have a higher melting point and are more likely to be solid at room temperature.
- Unsaturated fats have double bonds between some of the carbon atoms, reducing the number of places where hydrogen atoms can bond to carbon atoms.
  - These have a lower melting point and are more likely to be liquid at room temperature.

## Definition of hypertriglyceridemia

- The definition of different categories for elevated fasting TG levels seems to be slightly variable in different guidelines and recommendations.
- According to the EAS consensus document, mild to moderate HTG is defined as TGs 150 mg/dL, while 880 mg/dL defines HTG as severe.
- Age/gender, race/ethnicity and lifestyle are modulating factors at the population level for serum TGs.

## Definition of hypertriglyceridemia

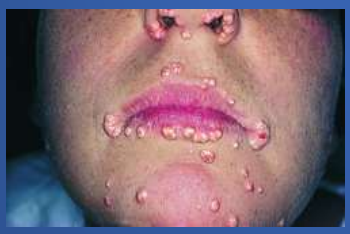
- In the Copenhagen general population 27% had TGs more than (150 mg/dL)
- Severe HTG is rare and is typically associated with monogenic mutations.
- Severe HTG is associated with an increased risk for pancreatitis.
- Signs and symptoms :

Modestly elevated triglyceride levels do not lead to any physical symptoms.

Higher levels are associated with lipemia retinalis(white appearance of the retina) , Eruptive xanthomas (small lumps in the skin, sometimes itchy)

# Definition of hypertriglyceridemia






# Importance of hypertriglyceridemia

- High TG levels are often associated with low HDL-C and high levels of small dense LDL particles.
- In a number of meta-analyses, TG level has been shown to be an independent risk factor.
- Large prospective studies have reported that non-fasting TGs predict CAD risk more strongly than fasting

**2016 ESC/EAS Guidelines for the Management of Dyslipidaemias**

# Importance of hypertriglyceridemia

- Recent data from genetic studies utilizing a Mendelian randomization design have consistently linked both non-fasting TG levels as well as remnant cholesterol to increased risk of CVD events and all-cause mortality
- For general screening and risk evaluation, non-fasting TGs can be used

**Varbo et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013**

# Causes of hypertriglyceridemia

| |
|---|
| Genetic predisposition |
| Obesity |
| Type 2 diabetes |
| Alcohol consumption |
| Diet high in simple carbohydrates |
| Renal disease |
| Hypothyroidism |
| Pregnancy (physiological triglyceride concentrations double during the third trimester) |
| Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus |
| Multiple medications including:<br>• Corticosteroids<br>• Oestrogens, especially those taken orally<br>• Tamoxifen<br>• Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides<br>• Isotretinoin<br>• Bile acid-binding resins<br>• Ciclosporin<br>• Antiretroviral regimens (protease inhibitors)<br>• Psychotropic medications: phenothiazines, second generation antipsychotics |

# Causes of hypertriglyceridemia

## Genetic causes of hypertriglyceridaemia

- The genetic aetiology for HTG seems to be very complex
- Moderate elevation of TG levels is caused by the polygenic effect of multiple genes influencing both VLDL production and removal.
- Monogenic severe HTG causes pancreatitis and lipid deposits.

# Causes of hypertriglyceridemia

- These mutations are inherited as an autosomal recessive trait and are rare.
- A profound defect in the catabolism of chylomicrons and VLDL results in chylomicronemia and TG levels (1000 mg/dL).
- Recently, gene therapy for LPL deficiency has been developed and tested in clinical trial

**Gaudet et al. safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoproteinEfficacy lipase deficiency: an open-label trial. Gene Ther 2013**

# hypertriglyceridemia and total CV risk estimation

**Table 7 Recommendations for lipid analyses in cardiovascular disease risk estimation**

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| TC is to be used for the estimation of total CV risk by means of the SCORE system. | I | C |
| LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm. | I | C |
| TG adds information on risk and is indicated for risk estimation. | I | C |
| Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG. | I | C |
| ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG. | IIa | C |
| Lp(a) should be considered in selected cases at high-risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk. | IIa | C |
| The ratio apoB/apoA1 may be considered as an alternative analysis for risk estimation. | IIb | C |
| The ratio non-HDL-C/HDL-C may be considered as an alternative but HDL-C used in HeartScore gives a better risk estimation. | IIb | C |

# hypertriglyceridemia and dyslipidemia management

**Table 8 Recommendations for lipid analyses for characterization of dyslipidaemias before treatment**

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| LDL-C has to be used as the primary lipid analysis. | I | C |
| It is recommended to analyse HDL-C before treatment. | I | C |
| TG adds information about risk, and is indicated for diagnosis and choice of treatment. | I | C |
| Non-HDL-C is recommended to be calculated, especially in subjects with high TG. | I | C |
| When available, apoB should be an alternative to non-HDL-C. | IIa | C |
| Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD (**see Box 7**). | IIa | C |
| TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment. | IIb | C |

# Treatment of hypertriglyceridemia

- A level of fasting TGs ≤ 150 mg/dL is desirable.
- The first step is to consider possible causes of HTG and to evaluate the total CV risk.
- The primary goal is to achieve the LDL-C level recommended based on the total CV risk level.
- The evidence on the benefits of lowering elevated TG levels is still modest, and is primarily derived from subgroup or post hoc analyses.
- However, recent evidence of TGs as a causal risk factor may encourage TG lowering

# Treatment of hypertriglyceridemia

**Table 10 Treatment targets and goals for cardiovascular disease prevention**

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|---|---|
| **Smoking** | No exposure to tobacco in any form. |
| **Diet** | Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish. |
| **Physical activity** | 2.5–5 h moderately vigorous physical activity per week or 30–60 min most days. |
| **Body weight** | BMI 20–25 kg/m², waist circumference <94 cm (men) and <80 cm (women). |
| **Blood pressure** | <140/90 mmHg[a] |
| **Lipids LDL-C is the primary target[f]** | **Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). |
| | **High-risk: LDL-C <2.6 mmol/L (100 mg/dL)** or a reduction of at least 50% if the baseline[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL). |
| | **Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).** |
| | Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively. |
| | HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk. |
| | TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. |
| **Diabetes** | HbA1c: <7% (<53 mmol/mol). |

# Treatment of hypertriglyceridemia

Diet control

- A high monounsaturated fat diet significantly improves insulin sensitivity compared with a high saturated fat diet. This goes in parallel with a reduction in TG levels, mostly in the post-prandial period

- Intake of sugars should not exceed 10% of total energy (in addition to the amount present in natural foods such as fruits and dairy products); more restrictive advice concerning sugars may be useful for those needing to lose weight or with high plasma TG values

# Treat of hypertriglyceridemia

- Alcohol intake has a major impact on TG levels. While in individuals with HTG even a small amount of alcohol can induce a further elevation of TG concentrations, in the general population alcohol exerts detrimental effects on TG levels only if the intake is excessive

- Weight reduction improves insulin sensitivity and decreases TG levels. In many studies the reduction of TG levels due to weight reduction is between 20–30%.

# Treatment of hypertriglyceridemia

| Recommendations | Class [a] | Level [b] | Ref [c] |
|---|---|---|---|
| Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL). | IIa | B | 261, 262 |
| Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia. | IIb | B | 263, 264 |
| In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins. | IIb | C | 261–264 |

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# Treatment of hypertriglyceridemia

## Statins

- Since statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels.
- More potent statins (atorvastatin, rosuvastatin and itavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TGs.
- In subgroup analyses from statin trials, the risk reduction is the same in subjects with HTG as normotriglyceridaemic subjects.

# Treatment of hypertriglyceridemia

## Fibrates

- Fibrates have good efficacy in lowering fasting TG levels as well as post-prandial TGs and TG-rich lipoprotein (TRL) remnant particles. The HDL-C raising effects of fibrates are modest.
- The clinical effects of fibrates are primarily illustrated by five prospective RCTs, where fenofibrate was added to statin therapy:
  - Helsinki Heart Study (HHS),
  - Veterans Affairs Highdensity lipoprotein Intervention Trial (VA-HIT),
  - Bezafibrate Infarction Prevention (BIP) study,
  - Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and
  - Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,

**Chapman et al. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther 2010**

# Treatment of hypertriglyceridemia

## Adverse effects and interactions

- Myopathy, CK, liver enzyme elevations and cholelithiasis.
- The risk of myopathy has been reported to be 5.5-fold greater with fibrate use as a monotherapy compared with statin use.
- The risk of myopathy is greater in patients with CKD.
- Gastrointestinal disturbance in less than 5%.
- Skin rashes in 2%.
- In the FIELD study, small but significant increases in the incidence of pancreatitis and pulmonary embolism.
- Fibrates have been reported to raise both serum creatinine and homocysteine

# Treatment of hypertriglyceridemia

Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

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| A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided. |
| If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated. |

# Treatment of hypertriglyceridemia

Nicotinic acid

- Decrease fatty acid influx to the liver and the secretion of VLDL by the liver.
- Nicotinic acid effectively reduces not only TGs, but also LDL-C.
- Nicotinic acid increases apoA1-containing lipoproteins, reflected in increases of HDL-C and apoA.
- At a daily dose of 2 g it reduces TGs by 20–40% and LDL-C by 15–18% and increases HDL-C by 15–35%

# Treatment of hypertriglyceridemia

## n-3 fatty acids

- n-3 fatty acids [eicosapentaenoic acid (EPA) and DHA] are used at pharmacological doses to lower TGs. n-3 fatty acids (2–4 g/day)
- The administration of n-3 fatty acids appears to be safe and devoid of clinically significant interactions.
- The antithrombotic effects may increase the propensity to bleed, especially when given in addition to aspirin/clopidogrel

# Treatment of hypertriglyceridemia

## Actions to prevent acute pancreatitis in severe Hypertriglyceridaemia

- HTG is the cause of 10% of all cases with pancreatitis.
- Any factor that increases VLDL production can aggravate the risk of pancreatitis.
- The patient should be admitted to hospital if symptomatic

## Treatment of hypertriglyceridemia

- Restriction of calories and fat content (10–15% recommended) in the diet and alcohol abstinence are obligatory.
- Fibrate therapy, with n-3 fatty acids (2–4 g/day) as adjunct therapy or nicotinic acid. Lomitapide may also be considered in severe cases
- In the acute setting, plasmapheresis is able to rapidly lower TG leve