

Hypertriglyceridemia

Triglycerides are fat (lipid) particles that circulate our bloodstream and serve as an energy source for our body. Because triglycerides are insoluble in blood, they are carried by proteins and combined into molecules called lipoproteins. The main lipoproteins responsible for carrying triglycerides are chylomicrons and very low-density lipoproteins (VLDL). Chylomicrons are made in our intestines from the dietary fats we consume, while VLDLs are produced by our liver. Both chylomicrons and VLDLs circulate throughout our body and release their stored triglycerides to different tissues, such as muscles for fuel or fat cells for energy storage.

Hypertriglyceridemia is a health condition characterized by elevated triglycerides in the body. Elevated levels of triglycerides and triglyceride-carrying lipoproteins have been shown to increase the risk of developing atherosclerotic cardiovascular disease (e.g., heart disease and stroke). At very high levels of triglyceride elevation (≥ 500 mg/dL), there is also an increased risk of pancreatitis, or inflammation of the pancreas that can present as severe abdominal pain, nausea, and vomiting.

Hypertriglyceridemia occurs when there is overproduction and/or impaired clearance of the triglyceride-rich lipoproteins (i.e., chylomicrons and VLDLs). This imbalance can be caused by one or a combination of genetic disorders, chronic diseases, dietary habits, and medications.

Causes of Hypertriglyceridemia

Below are some examples of causes of hypertriglyceridemia from each category:

Genetic Disorders

- Familial chylomicronemia syndrome
- Familial partial lipodystrophy
- Familial combined hyperlipidemia
- Polygenic hypertriglyceridemia

Dietary Habits

- Alcohol
- Diets high in saturated fat and sugar
- Sedentary lifestyle

Chronic Diseases

- Diabetes
- Chronic kidney disease
- Hypothyroidism

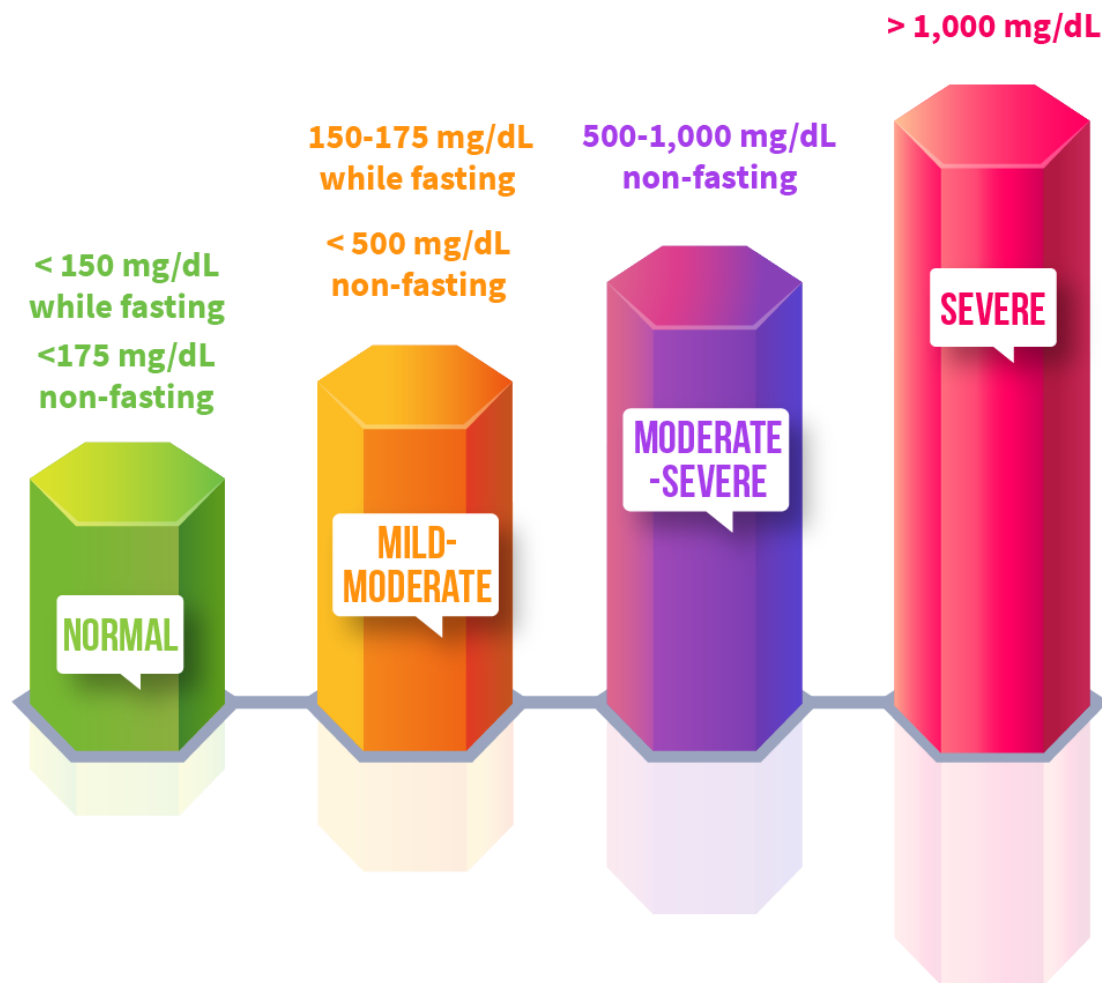
- Metabolic syndrome and insulin resistance
- Obesity
- Rheumatoid arthritis
- Systemic lupus erythematosus

Medications

- Beta blockers
- Diuretics
- Steroids
- Oral estrogen
- Chemotherapy agents (e.g., tamoxifen, cyclophosphamide)

Hypertriglyceridemia Criteria

- Normal levels of triglycerides are < 150 mg/dL while fasting (no food except water for 8-12 hours before the blood sample is collected), or <175 mg/dL while non-fasting
- Mild-moderate hypertriglyceridemia refers to those with fasting triglyceride levels <150 mg/dL (or non-fasting triglyceride levels <175 mg/dL) and < 500 mg/dL.
- Moderate-severe hypertriglyceridemia refers to triglyceride levels <500 mg/dL and <1,000 mg/dL
- Severe hypertriglyceridemia refers to triglyceride levels >1,000 mg/dL



Diagnosis of Hypertriglyceridemia

The evaluation of hypertriglyceridemia involves a blood test to measure triglyceride levels. A routine lipid screening is usually conducted when establishing care with a primary care physician. However, the exact timing and frequency of lipid screening depend on individual factors such as physical exam findings, estimated cardiovascular disease risk, and family history of lipid disorders. The decisions regarding lipid screening and follow-up intervals should be made collaboratively with a healthcare provider.

Consult with your doctor regarding whether the labs should be drawn in a fasting or non-fasting state. While non-fasting triglyceride levels can be useful in certain situations, they may need to be repeated if the triglyceride level is very elevated, or if the purpose of the lab draw is to formally diagnose hypertriglyceridemia or guide initiation of pharmacotherapy.

Additional components of the evaluation for hypertriglyceridemia include a comprehensive physical exam to check for fat deposits under the skin, also known as xanthomas, which can be present in some patients with hypertriglyceridemia. The exam also aims to assess for signs of other medical conditions associated with hypertriglyceridemia. A thorough review of the patient's past medical history, current medications, dietary and exercise habits, as well as family medical history can further inform the potential causes of or risk factors for hypertriglyceridemia.

Lifestyle Recommendations for Reducing Triglyceride Levels

Modification of dietary and exercise habits is the first-line therapy for hypertriglyceridemia.

Diet – fats

Here are some dietary recommendations for managing hypertriglyceridemia:

1. **Limit Total Fat Intake:** Keep total fat intake to less than one-third of your total caloric intake. Depending on the severity of your hypertriglyceridemia, reducing fat intake to as low as 10-15% of total calories may be necessary.
2. **Choose Healthy Oils:** When cooking with oil, reduce the use of saturated fats such as butter, lard, coconut, or palm oil. Instead, try liquid oils like olive, avocado, soybean, or canola oil, which are healthier options.
3. **Reduce Full-Fat Dairy:** Limit your consumption of full-fat dairy products like whole milk or whole milk yogurt. Instead, choose low-fat or non-fat versions of dairy products to reduce your intake of saturated fats.
4. **Prioritize Fatty Fish:** Include fatty fish as a source of dietary fat, such as salmon, anchovies, sardines, tuna, and rainbow trout. These fish are rich in omega-3 fatty acids, which can help lower triglyceride levels and promote heart health.
5. **Consider Leaner Fish:** If your triglyceride levels are very high, consider leaner fish options such as cod, tilapia, flounder, and shrimp. While these fish may not be as high in omega-3 fatty acids as fatty fish, they are still nutritious choices with lower fat content.

Diet – carbohydrates

While carbohydrates (sugars) are a different type of macronutrient compared to fats and don't themselves contain triglycerides, excess sugar consumption can lead to increased production of triglycerides from the liver. In fact, studies have shown that lower-carbohydrate / higher-fat diets are *more effective* at lowering triglyceride levels compared to higher-carbohydrate / lower-fat diets. While any level of reduction in carbohydrate consumption can help with reducing triglyceride levels, the greatest effect has been demonstrated with very low carbohydrate diets (<10% of total caloric intake)

1. **Reduce Sugar Intake:** Excess sugar consumption can lead to increased production of triglycerides in the liver. Prioritize decreasing your intake of sweets and foods with added sugars, such as candies, sodas, juices, breakfast cereals, and flavored yogurt.
2. **Check Food Labels:** To identify added sugars, check food labels under the “Total Carbohydrate” section, specifically the subsections for “Total Sugars” and “Added Sugars.” Choose products with lower added sugar content.
3. **Choose Healthier Beverages:** Replace sugary drinks and sodas with healthier alternatives like sparkling water, unsweetened tea, or coffee.
4. **Eat Whole Fruits:** Instead of fruit juices, try to eat fresh whole fruits, which provide fiber and nutrients without the added sugars found in juices.
5. **Select Fiber-Rich Grains:** If consuming bread, rice, pasta, or cereals, prioritize products labeled as “fiber-rich” and “whole grain.” These options provide more fiber and nutrients compared to refined grains.
6. **Emphasize High-Fiber Foods:** Ensure adequate fiber intake by consuming fruits and vegetables, focusing on items with a low glycemic index to help stabilize blood sugar levels. Examples include apples, pears, peaches, plums, oranges, broccoli, spinach, lettuce, cucumber, and asparagus.

Diet – miscellaneous considerations

1. **Limit Alcohol Consumption:** Alcohol can increase triglyceride production and impair triglyceride clearance, leading to elevated levels in the blood. Consider reducing or eliminating alcohol consumption entirely. If you choose to drink, pick beer or wine over cocktails/mixed drinks, as the latter often contain added sugars that can further raise triglyceride levels.
2. **Consult a Registered Dietitian:** A visit with a registered dietitian can be valuable in implementing dietary changes to manage hypertriglyceridemia. They can provide personalized guidance and support tailored to your specific health goals and preferences.

Exercise

Exercise is not only effective in lowering triglyceride levels but also plays a crucial role in improving cardiovascular health and reducing the risk of heart disease and stroke. Here are some exercise recommendations to help manage hypertriglyceridemia and promote overall well-being:

1. **Weekly Exercise Goal:** Aim for at least 150 minutes of moderate exercise or 75 minutes of vigorous exercise per week.
- **Moderate Exercise:** These are activities that increase your heart rate and allow you to talk while doing them but not sing or hold a full conversation. Examples include brisk walking, gardening, biking, swimming, or mowing the lawn.

- **Vigorous Exercise:** These are more intense activities during which you may struggle to say more than a few words before running out of breath. Examples include jogging, jump ropes, hiking, tennis, or basketball.
1. **Start Small:** If achieving the recommended exercise goal seems daunting, remember that any amount of exercise is beneficial. Even short bursts of physical activity can help improve triglyceride levels and overall health.
 2. **Incorporate Exercise into Daily Routine:** Small changes in daily habits can add up to significant improvements in physical activity levels. For example:
 - Park farther away in the parking lot to increase walking distance.
 - Prioritize taking the stairs instead of using elevators.
 - Alternate between sitting and standing frequently while at work, if possible.

Remember to consult with a healthcare provider before starting any new exercise regimen, especially if you have existing health conditions or concerns.

Weight Loss

Weight loss plays a significant role in reducing triglyceride levels and improving overall health. Aim for a weight loss of 5-10% of your current body weight. Studies have shown that this amount of weight loss can lead to a reduction in triglyceride levels by approximately 20%. Further weight loss may result in additional improvements in triglyceride levels, although the extent of this effect may vary among individuals. Consult your doctor to develop a personalized plan for weight reduction that employs a combination of dietary changes, exercise, and other lifestyle modifications.

Pharmacologic Treatment Options for Hypertriglyceridemia

Several medications are available for the treatment of hypertriglyceridemia, each working to reduce triglyceride levels through various mechanisms. These medications are typically considered when lifestyle interventions alone are insufficient in lowering triglycerides and/or when there are additional risk factors for cardiovascular disease. Here are some commonly prescribed medications for hypertriglyceridemia:

1. **Statins:** Statins not only lower triglyceride levels but also have decades of proven efficacy in preventing cardiovascular disease and reducing low-density lipoprotein cholesterol levels. They are considered first-line pharmacotherapy for lipid disorder treatment and cardiovascular disease prevention. Potential side effects may include muscle ache, stomach upset, and liver dysfunction.
2. **Omega 3 fatty acid formulations:** Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two types of omega 3 fatty acids (also known as fish oil) that can help lower triglyceride levels. Prescription formulations include icosapent ethyl, which contains EPA, or a mixture of EPA and DHA. Both have demonstrated triglyceride-lowering effects when taken at a dose of 4 grams per day. Unlike over-the-counter

fish oil supplements, prescription versions offer better purity and lower incidence of stomach upset. One notable side effect of omega 3 medications is increased risk of atrial fibrillation, an abnormal heart rhythm.

3. **Fibrates:** Fibrates are another class of medication used to reduce triglyceride levels, particularly in cases of severe hypertriglyceridemia (triglycerides \geq 500 mg/dL). While fibrates can help lower triglycerides, their impact on cardiovascular health outcomes remains under investigation. Fibrates may be considered to help reduce the risk of pancreatitis associated with very high triglyceride levels.

Before starting any medication for hypertriglyceridemia, consult a healthcare professional to discuss potential benefits and risks based on your health profile and existing medical conditions.

Finding a Specialist

Primary care providers often diagnose and manage hypertriglyceridemia. However, if triglyceride levels remain high despite initial interventions, consultation with a lipid specialist may be appropriate. To find a lipid specialist:

1. Review the provider database on your health system or insurance website.
2. Use keywords such as “lipid clinic,” “lipidology,” “prevention,” “preventive cardiology,” “cholesterol,” or “hypertriglyceridemia” to narrow your search.

Current & Future Clinical Trials for Triglyceride Lowering Therapies

Several recent and ongoing clinical trials are evaluating the safety and efficacy of various pharmacotherapies for treating hypertriglyceridemia and reducing cardiovascular disease risk. If you are interested in learning more about these trials, it is essential to consult your doctor. They can provide information on relevant trials and discuss whether participation might be suitable for you based on your individual health status and needs. Your doctor can also help you weigh the potential benefits and risks of participating in a clinical trial.

ApoC-III based therapies

ApoC-III is a protein in the liver that usually inhibits triglyceride clearance. Several medications have been developed to inhibit this molecule, with the goal of increasing triglyceride clearance and thereby lowering blood triglyceride levels. Medications developed for this purpose include:

- **Volanesorsen:** An antisense oligonucleotide that interferes with the genes responsible for ApoC-III synthesis. It travels to the nucleus of liver cells to inhibit ApoC-III production.
- **Olezarsen:** Similar to volanesorsen, olezarsen interferes with ApoC-III synthesis but is additionally modified to enhance drug delivery to the liver, where ApoC-III is produced.

- **ARO-APOC3:** A small interfering RNA that targets ApoC-III via a different mechanism, aiming to reduce its levels and consequently increase triglyceride clearance.

ANGPTL3 based therapies

ANGPTL3 is a protein that inhibits triglyceride clearance both in the liver and in endothelial cells. Medications designed to target ANGPTL3 include:

- **ARO-ANG3:** A small interfering RNA that specifically targets ANGPTL3, aiming to suppress its expression and consequently enhance triglyceride clearance.

References

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