Hypertriglyceridemia

How Big is the Problem?

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What are triglycerides?

Triglycerides (TGs) in the body serve as depots of energy. The primary source of TGs is the fat consumed in the daily diet. TGs are major components of chylomicrons and of very-low-density lipoprotein (VLDL) particles. Particles of TGs are also related to the metabolism of other lipoproteins, including high-density lipoprotein (HDL).

The U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III classified levels of TGs as listed in Table 1.

What causes hypertriglyceridemia?

Hypertriglyceridemia results from either an overproduction of TGs and/or lipoproteins, or a defect in the enzymes involved in metabolizing TGs in TG-rich lipoproteins. Certain physiologic conditions are also associated with hypertriglyceridemia, such as the normal postprandial state and pregnancy. Hypertriglyceridemia may be caused by genetic conditions (Table 2), or may be acquired (Table 3).

Mike's case

Mike, 45, is seeking medical advice for bouts of abdominal pain suffered during the past two months.

- Family history: Father has hypertension, mother is healthy
- Smokes 10 cigarettes/day
- Drinks two alcoholic drinks/day
- Body mass index: 27
- Blood pressure: 124/80 mmHg
- Numerous small, yellow papules (eruptive xanthomata) noted on the extensor surface of the forearms and back
- Lipid profile: Total cholesterol 8.7 mmol/L; high-density lipoprotein: 0.80 mmol/L; triglycerides: 28.5 mmol/L.; plasma has a milky appearance

What is your diagnosis?

What further investigations would you order?

What treatment would you suggest?

For the answers, go to page 92.

Table 1
U.S. National Cholesterol Education Program TG classification

ATP III classification for serum TGs	TG level mmol/L
Normal TGs	< 1.7
Borderline high TGs	1.7-2.3
High TGs	2.3-5.6
Very high TGs	> 5.6

ATP: Adult treatment panel
TGs: Triglycerides

Is hypertriglyceridemia a risk factor?

In 1959, Albrink et al. found an association between elevated TG levels and coronary artery disease (CAD).[1] Subsequently, Zilversmit proposed that TG-rich lipoproteins, abundant in the course of postprandial hyperlipidemia, are atherogenic.[2] However, the question as to whether hypertriglyceridemia is an independent risk factor for the development of atherosclerosis remains a controversial topic. This is partly

Table 2
Genetic conditions associated with hypertriglyceridemia

Type of hypertriglyceridemia	Genetic conditions
Chylomicronemia (type I HLP)	• Deficiency of lipoprotein lipase or apolipoprotein C-II • Fasting chylomicronemia • Triglyceride levels of 11.3-50 mmol/l • In heterozygotes, normal fasting TG that increase after fatty meals • Recurrent pancreatitis
Mixed hypertriglyceridemia (type V HLP)	• Fasting chylomicronemia, elevated VLDL • Creamy plasma supernatant • Triglyceride levels of 5.6 to 34 mmol/l • Hepatosplenomegaly, eruptive xanthomatosis
Remnant hyperlipidemia (type III HLP, familial dysbetalipoproteinemia)	• Autosomal recessive trait • Binding defect of apoliproprotein E • Chylomicron and VLDL accumulation • Tuberoeruptive xanthomas • Premature CHD and peripheral vascular disease
Familial hypertriglyceridemia (type IV HLP)	• Autosomal dominant overproduction of VLDL • Isolated hypertriglyceridemia • Triglyceride levels of 2.3 to 5.6 mmol/l • Often associated with metabolic syndrome
Familial combined hyperlipidemia	• Hypercholesterolemia or hypertriglyceridemia or both • Increased family risk of premature atherosclerosis

HLP: Hyperlipoproteinemia
VLDL: Very-low-density lipoprotein
CHD: Coronary heart disease

due to the complexity of the metabolism of TGs, which play an important role in energy metabolism. The serum TG levels do not always reflect their metabolism in the tissues. Moreover, it has been argued that the non-lipid risk factors of obesity, diabetes, insulin resistance, and hypertension associated with hypertriglyceridemia are the real culprits behind increased CAD risk.[3]

Avins and Neuhaus[4] performed secondary analyses of data from the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Coronary Primary Prevention Trial, and the Lipid Research Clinics Prevalence and Mortality Followup Study. The predictive value of the following variables were assessed: fasting TGs, total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and fasting blood glucose. Age, blood pressure, cigarette smoking, body mass index, and post-menopausal estrogen use were also assessed. Analytic methods included Cox proportional hazards models, calculation of stratified crude incidence rates, and measurement of the area under the receiver operating characteristic curve. The outcome variables were fatal and non-fatal myocardial infarctions (MI). The authors concluded that in men, the assessment of TG levels did not improve the risk prediction based on evaluation of standard lipid profile. In women, there was a marginal improvement of risk assessment when high TGs were taken in consideration, but the number of events was small.

Some prospective studies have shown the association between TGs and CAD, however, when these studies were adjusted for other lipoproteins, TG level lost significance as an independent risk factor for CAD.[5]

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Table 3
Causes for acquired hypertriglyceridemia

Type of influence	Conditions
Metabolic influences	• Diabetes mellitus • Obesity • Hyperuricemia • Glycogen storage disease
Hormonal influences	• Insulin • Estrogen • Thyroxine
Nutritional influences	• High carbohydrate intake • Alcohol consumption
Disease states	• Nephrotic syndrome • Renal failure • Paraproteinemias
Drugs	• Beta blockers • Diuretics • Estrogen replacement • Tamoxifen • Glucocorticoids

Elevated levels of TG are most likely doing more harm than good.

On the other hand, a meta-analysis of 17 population-based prospective trials including both men and women, showed that an increase in plasma TG levels of 1 mmol/L was associated with a 32% increase in risk of cardiovascular disease in men and a 76% increase in women. After adjustment for HDL cholesterol and other risk factors, the risk was attenuated, but remained statistically significant.[6]

In the Prospective Cardiovascular Münster (PROCAM) study performed on 19,698 subjects, elevated TG level emerged as a significant and independent risk factor for major coronary events, even after adjustment for LDL and HDL cholesterol levels, age, systolic blood pressure, cigarette smoking, diabetes mellitus, and family history of MI and angina pectoris.[7] High serum TGs are often accompanied by high plasma levels of small, dense LDL cholesterol and low levels of HDL cholesterol. Recent assessment of this issue by Austin et al.[8] and Assmann et al.[9] suggests that raised TGs are in fact independent risk factors for the development of CAD and atherosclerosis in general.

Thus, we can conclude that elevated levels of TGs are most likely doing more harm than good, but the evidence is much weaker than that relating to high LDL levels or total cholesterol/HDL ratio.

What are some types of hypertriglyceridemia?

Familiar combined hyperlipidemia

In everyday clinical practice, what we encounter most frequently is the familial combined hyperlipidemia. This type of hyperlipidemia occurs in about 2% of the general population and in about one-third of those surviving a MI. The presence of Achilles tendon xanthoma, subperiosteal and tendon xanthomata on the dorsum of the hand should raise suspicion of this type of hyperlipidemia. In this condition, TG levels are usually only moderately elevated (between 2 mmol/L

and 5 mmol/L). As a rule, there is an inverse relationship between the TG and HDL levels in the blood. Statins, omega-3-fatty acids, fibric acid derivatives, and niacin (alone or in combination) are the therapeutic options in this type of dyslipidemia.

Type III familial dysbetalipoproteinemia

A rare disorder of TG metabolism is the type III familial dysbetalipoproteinemia. Striate palmar xanthoma and tuberoeruptive xanthomata on the arm are frequent cutaneous manifestations. Total cholesterol and TG levels are usually > 10 mmol/L. These patients should be referred to specialized lipid clinics for further diagnostic workup and therapy.

Chylomicronemia

Chylomicronemia is a serious condition characterized by high and very high TG levels (between 10 mmol/L and up to > 50 mmol/L). These patients have frequent abdominal pain, hepatosplenomegaly, and eruptive xanthomas. There is a close association between severe hypertriglyceridemia and acute pancreatitis. The risk of pancreatitis increases beyond fasting plasma TG concentration above 11 mmol/L, but most patients are symptomatic when the concentration exceeds 22 mmol/L.

What should you be looking for?

The diagnostic workup of patients with hypertriglyceridemia should assess the presence of associated conditions, which could contribute to changes in the lipid profile. These are:

- obesity, in particular abdominal obesity, which is usually a part of the metabolic syndrome (increased fasting glucose, insulin resistance, hypertension, low HDL, and elevated TGs);
- Type 2 diabetes;
- nephrotic syndrome;
- hypothyroidism;
- excess alcohol consumption; and
- high carbohydrate intake.

Some drugs can raise the TG levels as well. Examples include tamoxifen, beta blockers, glucocorticoids, cyclosporin, protease inhibitors, and, to some extent, thiazide diuretics.

A followup on Mike

Mike has hyperchylomicronemia (type V phenotype) and his abdominal pain is most likely caused by pancreatitis. Both TGs and very-low-density lipoproteins (VLDL) are normally cleared from the plasma by lipoprotein lipase. In this patient, the lipoprotein lipase would be deficient, hence the raised TGs and VLDLs. The high cholesterol level is caused by increased concentration of the VLDL particles.

Hyperchylomicronemia is frequently secondary to increased alcohol consumption, diabetes, and obesity. Therefore, it would be necessary to check Mike's blood glucose level. Therapeutic interventions would include a low-fat and low-refined carbohydrate diet, plus fibrates and salmon oil capsules.

Take-home message

What do I need to know?

- Hypertriglyceridemia is a risk factor for CAD.
- Hypertriglyceridemia can be caused by genetic conditions, or it can be acquired.
- All patients with hypertriglyceridemia should be examined for the presence of associated conditions.
- Mild to moderate hypertriglyceridemia should be treated by diet and lifestyle changes and, if necessary, treated pharmacologically.
- Severe hypertriglyceridemia (TG above 5.6 mmol/L) must be treated pharmacologically; drugs of choice are nicotinic acid and fibrates.

How is hypertriglyceridemia treated?

The first step is to evaluate whether there is an identifiable primary cause for this type of dyslipidemia. If so, this cause should be addressed first.

The American Heart Association recommends an intake of 2-4 g of LCn-3 fatty acids per day for those with elevated TGs

Lifestyle counselling should be given to all patients (*e.g.*, appropriate diet, regular exercise, restriction of alcohol, and refined carbohydrates). Fish oil containing long-chain omega-3 (LCn-3) fatty acids, a non-pharmacologic treatment, has been proven to have cardioprotective properties. The American Heart Association recommends an intake of 1 g of LCn-3 fatty acids per day for persons with existing cardiovascular disease, and 2 g to 4 g per day for those with elevated TGs.[10]

Drugs of choice for the treatment of hypertriglyceridemia include nicotinic acid and fibrates, such as bezafibrate, fenofibrate, and gemfibrozil. Dx

References
1. Albrink MJ, Man EB: Serum triglycerides in coronary artery disease. AMA Arch Intern Med 1959; 103(1):4-8.
2. Zilversmit DB: Atherogenesis: A postprandial phenomenon. Circulation 1979; 60(3):473-85.
3. Grundy SM: Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. Am J Cardiol 1998; 81(4A):18B-25B.
4. Avins AL, Neuhaus JM: Do triglycerides provide meaningful information about heart disease risk? Arch Intern Med 2000; 160(13):1937-44.
5. Austin MA: Plasma triglyceride and coronary heart disease. Arterioscler Thromb 1991; 11(1):2-14.
6. Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996; 3(2):213-9.
7. Assmann G, Schulte H, von Eckardstein A: Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol 1996; 77(14):1179-84.
8. Austin MA, Hokanson JE, Edwards KL: Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998; 81(4A):7B-12B.
9. Assmann G, Schulte H, Funke H, et al: The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J 1998; 19 (Suppl M):M8-14.
10. Kris-Etherton PM, Harris WS, Appel LJ: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. American Heart Association. Nutrition Committee. Circulation 2002; 106(21):2747-57.

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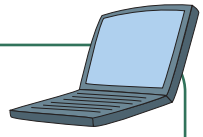

1. Heart and Stroke Foundation of Canada: *www.heartandstroke.ca*
2. The American Heart Association: *www.americanheart.org*
3. National Heart, Lung, and Blood Institute: *www.nhlbi.nih.gov*