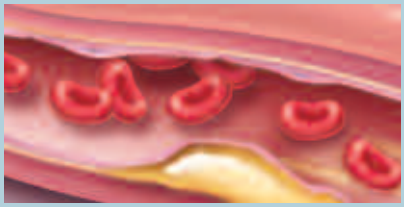
abstract



Several lines of evidence suggest that triglyceride-rich lipoproteins contribute significantly to the development of atherosclerosis. However, the relationship between cardiovascular disease and plasma levels of triglyceride remains complex due to the presence of two major confounders: (1) the inverse relationship between plasma triglyceride levels and high-density lipoprotein-cholesterol and (2) the heterogeneity in triglyceride-rich lipoprotein size, number, and composition between individuals. Plasma apo-B measurement is recommended for patients with high triglyceride levels to identify their risk category. The goals of lipid-modifying therapy for these patients are to reduce the atherogenic lipoprotein number and to increase HDL particle number.

Clinical Significance and Treatment of Hypertriglyceridemia

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Introduction

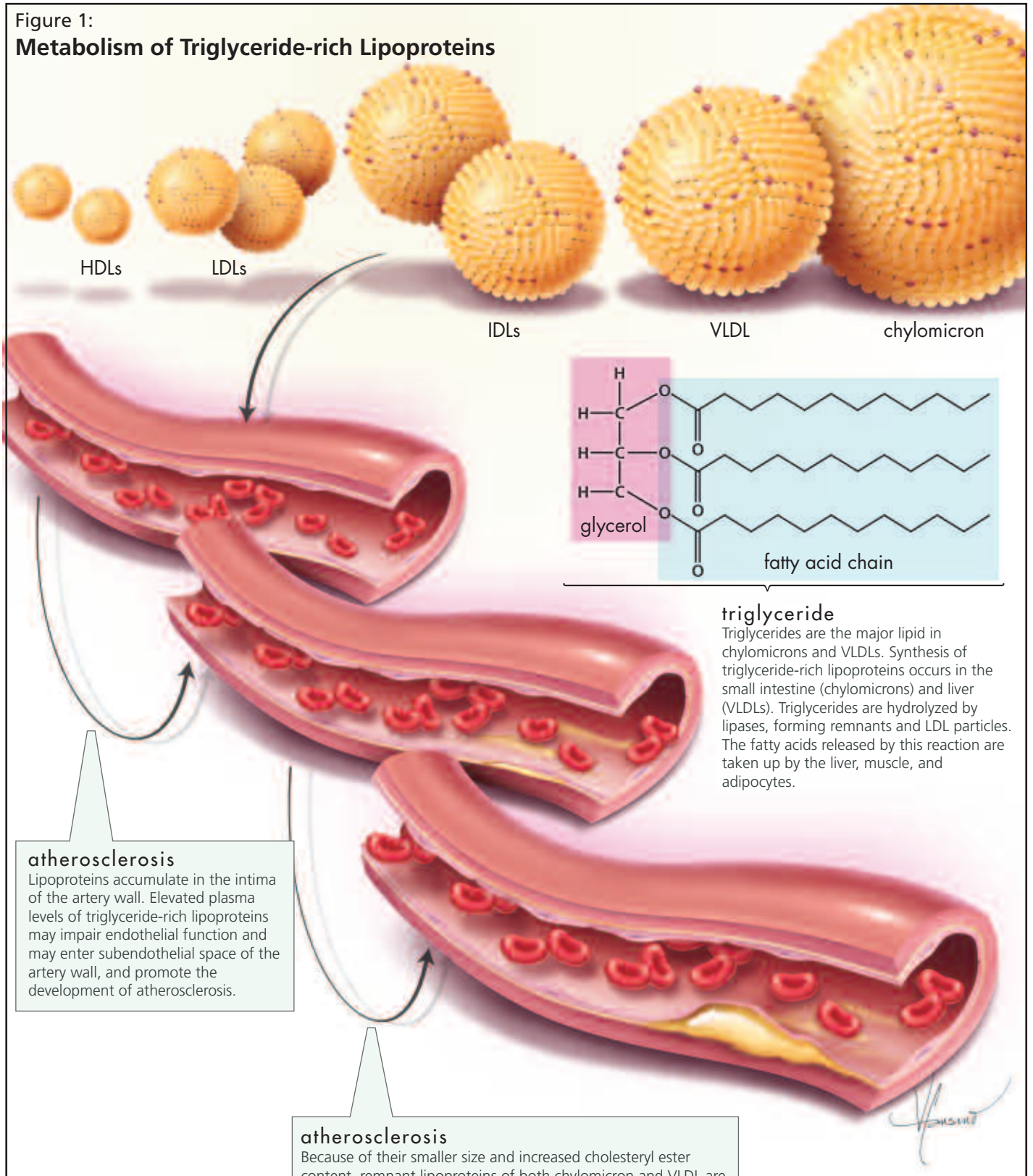
Over the past several decades, basic research and clinical studies have led to a better understanding of the atherosclerotic process. It appears that lipoproteins, particularly apolipoprotein-B (apo-B)–containing lipoproteins, first accumulate in the intima of the artery wall. As these lipoproteins become modified, they induce the production of local cytokines, adhesion molecules, and chemoattractants stimulating transendothelial migration of monocytes and their subsequent transformation into macrophages and foam cells. Smooth muscle cells and lymphocytes have also been shown to accumulate in the growing atherosclerotic plaque, which then become vulnerable to fissuring and rupturing.[1] Despite the fact that LDL particles play a central role in the development of atherosclerosis, several lines of evidence suggest that triglyceride-rich lipoproteins contribute significantly to this process. For example, it is well established that type 2 diabetic individuals have elevated plasma levels of triglyceride-rich lipoproteins that may impair endothelial function, enter subendothelial space of the artery wall, and promote the development of atherosclerosis.[2] It is therefore of considerable interest to review briefly the metabolism of triglyceride-rich lipoproteins to understand better the relationship between plasma triglyceride levels and cardiovascular risk.

Metabolism of Triglyceride-rich Lipoproteins

Synthesis of triglyceride-rich lipoproteins occurs in the small intestine and the liver in the form of chylomicrons and very low density lipoprotein (VLDL), respectively. Triglyceride is the major lipid in chylomicrons and VLDL and serves as energy substrates in the liver and peripheral tissues, particularly muscle. Once in the plasma, the vast majority of triglyceride molecules in chylomicrons and VLDL are hydrolyzed by the action of lipases (lipoprotein and hepatic lipases), leading to the formation of smaller, denser, triglyceride-rich lipoproteins (called remnants) and ultimately to LDL particles in the case of apo-B-100–containing lipoproteins. The fatty acids released by these reactions are taken up by liver, muscles, and adipocytes. Because of their smaller size and increased cholesteryl ester content, remnant lipoproteins of both chylomicron and VLDL are considered more atherogenic than their respective precursors. At the artery wall, remnant lipoproteins of both VLDL and chylomicron have the potential to interact with endothelial cells, causing changes that may enhance transendothelial passage of the remnants and circulating monocytes into the intima, leading to an acceleration of the development of atherosclerosis.[2-4]

The relationship between cardiovascular disease and plasma levels of triglyceride is complex. In part, this is related to the presence of two major confounders: (1) the inverse relationship between plasma triglyceride levels and high-density lipoprotein (HDL)-cholesterol and (2) the heterogeneity in triglyceride-rich lipoprotein size, number, and composition between individuals. HDL-cholesterol is widely accepted as being protective against car-

Figure 1:
Metabolism of Triglyceride-rich Lipoproteins



triglyceride

Triglycerides are the major lipid in chylomicrons and VLDLs. Synthesis of triglyceride-rich lipoproteins occurs in the small intestine (chylomicrons) and liver (VLDLs). Triglycerides are hydrolyzed by lipases, forming remnants and LDL particles. The fatty acids released by this reaction are taken up by the liver, muscle, and adipocytes.

atherosclerosis

Lipoproteins accumulate in the intima of the artery wall. Elevated plasma levels of triglyceride-rich lipoproteins may impair endothelial function and may enter subendothelial space of the artery wall, and promote the development of atherosclerosis.

atherosclerosis

Because of their smaller size and increased cholesteryl ester content, remnant lipoproteins of both chylomicron and VLDL are considered more atherogenic than their respective precursors. At the artery wall, remnant lipoproteins of VLDL and chylomicron interact with endothelial cells enhancing transendothelial passage of the remnants and circulating monocytes into the intima, leading to an accelerated development of atherosclerosis.

Table 1: Risk Categories and Treatment Targets

Risk Level	10-year CAD risk	Recommendations
High	≥20%	Treat when apo-B ≥ 0.85 or TC/HDL-C ≥ 4.0
Moderate	10–19%	Treat when apo-B ≥ 1.05 or TC/HDL-C ≥ 5.0
Low	<10%	Treat when apo-B ≥ 1.20 or TC/HDL-C ≥ 6.0

Source: McPherson R et al., 2006;[24] used with permission.

diovascular disease and plays a crucial role in the reverse cholesterol transport pathway by delivering cellular cholesterol to the liver for excretion. Several lines of evidence indicate that increased levels of triglyceride-rich lipoproteins stimulate the exchange of their triglyceride for cholesterol in HDL, a process mediated in plasma by cholesterol ester transfer protein.[5] In humans, triglyceride enrichment of HDL has been shown to enhance the metabolic clearance of HDL particles, leading to reduced HDL-cholesterol concentrations.[6] Variability in physical and biochemical properties of triglyceride-rich lipoproteins is another important reason for the difficulty in linking plasma triglyceride levels to the risk of cardiovascular disease. In particular, size, number, and cholesterol content of these lipoproteins can greatly vary among individuals. For instance, the very large triglyceride-rich lipoproteins found in patients with familial hyperchylomicronemia cannot easily pass into the subendothelial space to promote atherosclerosis, in contrast to the relatively small cholesteryl ester-enriched VLDL found in type 2 diabetic patients. A large number of triglyceride-rich lipoproteins as well as an elevated cholesterol content of triglyceride-rich lipoproteins are also associated with an increased risk of cardiovascular disease.[7] In populations or cohorts having similar plasma triglyceride levels, it appears that size, number, and cholesterol content of triglyceride-rich particles are responsible for variations in the risk of cardiovascular disease.

Triglycerides as a Risk Factor for Coronary Heart Disease

A substantial body of evidence indicates that triglycerides are an independent risk factor for coronary heart disease. A meta-analysis of population-based studies on plasma triglycerides and cardiovascular disease showed that each 1 mmol/L elevation in plasma triglycerides increased cardiovascular disease risk by 32% in men and 76% in women. However, after adjustment for HDL-cholesterol and other risk factors, these risks were reduced to 14% in men and 37% in women but remained statistically significant.[8] Furthermore, several prospective epidemiological studies have revealed that plasma triglyceride levels and LDL particle size predict coronary heart disease in Caucasians.[9-11] In fact, plasma triglyceride levels have been shown to be negatively correlated with LDL particle size, meaning that patients with higher triglyceride levels have smaller, denser, and more atherogenic LDL particles. Smaller LDL particles enter the arterial wall more easily, have greater affinity for the glycoproteins of the arterial wall, and greater propensity for oxidation.[12,13] Finally, clinical trials in which plasma triglycerides were reduced by a therapeutic agent also support the role of triglycerides in the development of atherosclerosis. These studies, however, should be interpreted with caution since LDL-cholesterol and HDL-cholesterol were also modulated by pharmacologic interventions.[14,15]

Are Triglycerides Atherogenic?

It is important to emphasize that individuals with the highest plasma triglyceride levels (>15 mmol/L) are not at particular risk of developing cardiovascular disease but rather pancreatitis. Severe hypertriglyceridemia is secondary to massive accumulation of chylomicrons and very large VLDL in plasma, and these particles are unable to pass through the endothelial barrier to promote atherogenesis. The lack of cardiovascular complications in patients with complete lipoprotein lipase deficiency often having plasma triglyceride levels greater than 20 mmol/L supports this concept. In fact, this observation suggests that triglycerides per se may not be atherogenic but that some of the lipoprotein classes carrying triglycerides or associated abnormalities in triglyceride metabolism are atherogenic.

Utility of apo-B Measurements in Hypertriglyceridemic Patients

Each VLDL, intermediate-density lipoprotein (IDL), and LDL particle contains one molecule of apo-B-100, and each chylomicron and chylomicron remnant contains one molecule of apo-B-48. Total plasma apo-B, which corresponds to the sum of the total apo-B-100 and apo-B-48 lipoprotein particles, is the best current estimate of total atherogenic particle number. Clinical assays currently available measure both apo-B-100 and apo-B-48. The relationship between plasma LDL-cholesterol and total plasma apo-B levels is largely influenced by plasma triglyceride concentrations.[16] In fact, at any LDL-cholesterol level, patients with higher plasma triglyceride levels have a greater number of smaller, denser, and more atherogenic LDL particles than patients with lower triglyceride levels. This relationship is the consequence of two metabolic processes: first, the overproduction of small, dense LDL derived from the progressive hydrolysis of larger, triglyceride-rich lipoproteins and second, the overproduction of triglyceride-enriched LDL particles. Triglycerides of these lipoproteins are then hydrolyzed by lipoprotein and hepatic lipases, leading to the formation of small, dense LDL with less cholesterol per particle and therefore a lower choles-

terol/apo-B ratio. Apo-B has been shown to be superior to LDL-cholesterol in predicting the risk of cardiovascular events and the progression of cardiovascular disease in a series of prospective epidemiological studies. These include the 4S,[17] AFCAPS/TexCAPS[18] and LIPID[19] studies as well as the Nurses' Health Study,[20] the Northwick Park Heart Study[21] and the 5- and 13-year reports of the Quebec Cardiovascular Study.[22,23]

Therapeutic Approaches

The goals of lipid-lowering therapy for patients with hypertriglyceridemia are to reduce the atherogenic lipoprotein number and to increase HDL particle number. Therefore, plasma apo-B measurement is recommended for patients with plasma triglyceride levels greater than 1.5 mmol/L to identify their risk category and is a useful marker of the adequacy of reducing the number of atherogenic particles. Following global risk assessment, goals of treatment for plasma apo-B should be based on the Canadian recommendations for the management of dyslipidemia and the prevention of cardiovascular disease (Table 1).[24] An optimal level of apo-B in a patient at high, moderate, or low risk of coronary artery disease is less than 0.85, 1.05, and 1.20 g/L, respectively. These apo-B values represent the 15th, 50th, and 75th percentiles for the Canadian population.[25]

Nonpharmacologic Therapies

First-line therapy consists of lifestyle changes that focus on weight reduction and regular physical activity. Restriction of alcohol and refined carbohydrates as well as increased intake of monounsaturated and polyunsaturated fats, including omega-3 fatty acids, are particularly helpful in patients with high triglyceride and low HDL-cholesterol levels.[26] A diet rich in vegetables, fruit, and whole-grain cereals is also strongly recommended. Patients should be encouraged to perform 60 minutes of light, 30–60 minutes of moderate, or 20–30 minutes of vigorous activity four to seven days per week.[24] A waist circumference of less than 94 cm for men and 80 cm for women as well as a body mass index of less than 25 kg/m^2 are optimal.

Pharmacologic Therapies

When drugs are required, the HMG-CoA reductase inhibitors (statins) could be the first choice for therapy, given their efficacy in lowering apo B levels and their modest effects on triglyceride and HDL-cholesterol (Table 2). Fibrates have variable effects on apo B levels and should be used in first instance only if fasting triglyceride levels exceed 8 mmol/L. Bile acid sequestrants (resins) are not recommended for monotherapy because they tend to increase triglyceride concentrations. Ezetimibe, a selective inhibitor of intestinal cholesterol absorption, has virtually no effect on triglyceride and HDL-cholesterol levels but could be used in combination with a statin to lower apo-B levels. The combination of a statin with niacin is very effective to reduce the number of atherogenic lipoproteins and increase HDL-cholesterol and has been shown to reduce cardiovascular events significantly in the HDL-Atherosclerosis Treatment Study.[27] Nonsteroidal anti-inflammatories, including acetylsalicylic acid, usually attenuate the vasodilatory effects (flushing) of niacin. Particular attention should be given, however, to hepatic transaminases and blood glucose in patients treated with niacin. A combination of a statin and a fibrate may be used in patients who are not candidates

Table 2: Currently Available Lipid-lowering Medications

Generic Name	Trade Name	Recommended Dose Range
*Statins**		
Atorvastatin	Lipitor	10 mg–80 mg
Fluvastatin	Lescol	20 mg–80 mg
Lovastatin	Mevacor	20 mg–80 mg
Pravastatin	Pravachol	10 mg–40 mg
Rosuvastatin	Crestor	5 mg–40 mg
Simvastatin	Zocor	10 mg–80 mg
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	(generic)	2 g–24 g
Colestipol	Colestid	5 g–30 g
Ezetimibe	Ezetrol	10 mg
Fibrates†		
Bezafibrate	Bezalip	400 mg
Fenofibrate	Lipidil Micro/Lipidil Supra/Lipidil EZ	100 mg, 145 mg, 160 mg, 200 mg
Gemfibrozil††	Lopid	600 mg–1200 mg
Niacins§		
Nicotinic acid	(generic cystalline niacin)	1 g–3 g
	Niaspan	0.5 g–2 g

*Use lower dose ranges in persons of South and East Asian origin. †In patients with renal insufficiency (creatinine clearance between 20 mL/min and 100 mL/min), fibrates should be initiated at the lowest available dose and increased only after re-evaluation of renal function and lipid parameters. ††Do not use gemfibrozil in combination with a statin. §In patients with diabetes or glucose intolerance, initiate therapy at 500–1000 mg/day and monitor glycemic control.
Source: McPherson R et al., 2006;[24] used with permission.

Key Points

- Although LDL particles play a central role in the development of atherosclerosis, several lines of evidence suggest that triglyceride-rich lipoproteins contribute significantly to this process.
- The relationship between cardiovascular disease and plasma levels of triglyceride is complex, partly due to the presence of two confounders—(1) the inverse relationship between plasma triglyceride levels and high-density lipoprotein (HDL)-cholesterol and (2) the heterogeneity in triglyceride-rich lipoprotein size, number, and composition between individuals.
- In populations having similar plasma triglyceride levels, it appears that size, number, and cholesterol content of triglyceride-rich particles are responsible for variations in the risk of cardiovascular disease.
- Evidence indicates that triglycerides are an independent risk factor for coronary heart disease.
- Individuals with the highest plasma triglyceride levels (>15 mmol/L) are not at particular risk of developing cardiovascular disease but rather pancreatitis.
- Total plasma apo-B, which corresponds to the sum of the total apo-B-100 and apo-B-48 lipoprotein particles, is the best current estimate of total atherogenic particle number.
- Apo-B has been shown to be superior to LDL-cholesterol in predicting the risk of cardiovascular events and the progression of cardiovascular disease.
- Goals of treatment for plasma apo-B should be based on the Canadian Cardiovascular Society recommendations for the management of dyslipidemia and the prevention of cardiovascular disease.
- First-line therapy consists of lifestyle therapies that focus on weight reduction and regular physical activity.
- The HMG-CoA reductase inhibitors (statins) may be the first choice when pharmacologic therapy is needed to meet optimal lipid levels based on recommendations for the management of dyslipidemia.

for niacin therapy. These patients should be carefully monitored since fibrate treatment is associated with a small but significant risk of renal impairment and pancreatitis.[28] As compared with fenofibrate, gemfibrozil is associated with a higher risk of rhabdomyolysis and should not be used in combination therapy. The addition of omega-3 fatty acid supplements (3 g daily) to statin therapy is also safe and effective to reduce triglyceride levels.[29] Finally, severe hypertriglyceridemia (fasting triglyceride levels >15 mmol/L) poses a significant risk of pancreatitis and should be treated promptly with a fibrate, fish oil, or medium-chain triglyceride (MCT) supplementation.

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