

Expert Perspective

Management of High Triglycerides: What Non-Specialists in Lipids Need to Know

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It is well established that low density lipoprotein (LDL) is the main atherogenic lipoprotein. LDL-cholesterol is therefore the primary target for lipid lowering therapy.¹ Moreover, high density lipoprotein (HDL) is protective and HDL-cholesterol levels are inversely associated with the incidence of vascular disease.¹ Thus, every effort should be made to raise HDL-cholesterol levels.²

In contrast to LDL and HDL, the role of triglycerides (TGs) as an independent risk factor for vascular disease has been a matter of debate.^{3,4} Earlier analyses did not find a consistent association of TGs with mortality from coronary heart disease (CHD).⁵ One reason may be that TG assessment is subject to greater measurement variability compared with other lipids, because of both laboratory factors and biological variation (including fasting and non-fasting state). Furthermore, TG levels are often inversely related to HDL-cholesterol levels.^{3,4} Therefore, any relationship between vascular disease and TGs may be lost if HDL-cholesterol levels are included in multivariate analyses. However, accumulating evidence indicates that elevated fasting TG levels are an independent risk factor for vascular disease.⁶⁻⁹

In the Prospective Cardiovascular Munster (PROCAM) study⁶ (n=4,849 men, follow-up 8 years) fasting TGs were an independent risk factor for CHD events irre-

spective of HDL- or LDL-cholesterol levels. A meta-analysis⁷ of 17 population-based studies (average follow-up 8.4 years in men [n=46,413] and 11.4 years in women [n=10,864]) showed that an increase of about 90 mg/dL (1 mmol/L) in fasting TGs is associated with a 32% and 76% increase in the risk for CHD in men and women, respectively. After adjustment for HDL-cholesterol levels and other risk factors, this relationship remained significant at 14% and 37%, respectively.⁷

TGs may work in concert with the other lipid variables to increase vascular risk. In the Physicians' Health Study⁸ the risk of myocardial infarction was greatest among men with the highest tertile for both TGs and total cholesterol/HDL-cholesterol ratio. In the Helsinki Heart Study (HHS)⁹ CHD risk was highest in the cohort with TGs >200 mg/dL and an LDL-cholesterol/HDL-cholesterol ratio >5.0.

When are serum TG levels considered high?

The classification of serum TG levels according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)¹ is shown in table 1. TG levels >200 mg/dL are considered high. Moreover, TGs >500 mg/dL are considered very high; in this case the risk of acute pancreatitis increases and TGs should be the main target of treatment.¹

Table 1. Classification of triglycerides according to the National Cholesterol Education Program Adult Treatment Panel III.

Normal triglycerides	< 150 mg/dL
Borderline-high triglycerides	150 - 199 mg/dL
High triglycerides	200 - 499 mg/dL
Very high triglycerides*	≥ 500 mg/dL

* Triglycerides should be given priority of treatment because of the increased risk of acute pancreatitis

It should be noted that serum TGs >150 mg/dL is one of the diagnostic criteria for the metabolic syndrome (MetSyn).^{10,11} This also holds true for the new definition of MetSyn that was recently proposed by the International Diabetes Federation.¹²

Are raised TG levels common?

In patients with established CHD, data from 8,500 men screened for the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT)¹³ suggested that the prevalence of TGs >200 mg/dL was 33%. The incidence of elevated TGs is also high in the general population. Data from the Third National Health and Nutritional Survey (NHAVES III)¹⁴ (n=8,814 US adults) showed that 30% of participants had TG levels >150 mg/dL.

How do raised TG levels increase vascular risk?

The possible mechanisms by which high TGs increase vascular risk include:

a. High levels of TGs reflect the presence of elevated TG-rich lipoprotein concentration. Some of these TG-rich lipoproteins—for example, very low-density lipoprotein (VLDL) remnants and intermediate-density lipoprotein (IDL)—are small enough to penetrate the arterial wall and promote atherosclerosis.^{15,16} On the other hand, large TG-rich lipoprotein particles (e.g. chylomicrons and large VLDL) cannot pass through the endothelial barrier.

b. As already stated, high TGs are often associated with low levels of HDL-cholesterol, which in turn raises vascular risk.^{1,3,4}

c. Elevated serum TGs and low HDL-cholesterol are often combined with the presence of increased small, dense LDL particles that are highly atherogenic.¹⁷ This combination is also known as atherogenic dyslipidaemia or the “lipid triad” and is common in patients with type 2 diabetes or the MetSyn.¹⁸

d. The postprandial lipaemia that often accompanies hypertriglyceridaemia may also have deleterious effects on the vascular wall.³

e. High levels of TGs may promote atherothrombosis, since they are often associated with increases in fibrinogen, blood viscosity and clotting factors VII and X.¹⁹

What are the causes of elevated TGs?

Table 2 summarises the most common causes of raised TGs. Secondary causes should first be ruled out before making a diagnosis of a familial disorder.

Table 2. Aetiology of hypertriglyceridaemia.

I. Primary hypertriglyceridaemia
<ul style="list-style-type: none"> • Type I hyperlipidaemia (chylomicronaemia) <ul style="list-style-type: none"> – lipoprotein lipase deficiency – apolipoprotein C-II deficiency • Type IIb hyperlipidaemia (familial combined hyperlipidaemia) • Type III hyperlipidaemia (familial dysbetalipoproteinaemia) • Type IV hyperlipidaemia (familial hypertriglyceridaemia) • Type V hyperlipidaemia (familial hypertriglyceridaemia plus fasting chylomicronaemia)
II. Common secondary causes of hypertriglyceridaemia
<ul style="list-style-type: none"> • Alcohol (excessive intake) • Drugs: beta-blockers, thiazide-type diuretics, estrogens, oral contraceptives, tamoxifen, corticosteroids, retinoic-acid derivatives, resins, interferon, protease inhibitors • Renal disease (e.g. nephrotic syndrome) • Diabetes mellitus • Metabolic syndrome • Obesity • Smoking • Hypothyroidism • Pregnancy • Liver disease • Systemic lupus erythematosus • Monoclonal gammopathy, multiple myeloma, lymphoma • Infections

Non-HDL-cholesterol, a secondary target in patients with TGs >200 mg/dL

In patients with fasting TGs >200 mg/dL, non-HDL-cholesterol levels (non-HDL-cholesterol = total cholesterol - HDL-cholesterol) should be determined.¹ Non-HDL-cholesterol includes all atherogenic lipoproteins –atherogenic TG-rich lipoproteins (VLDL, IDL and the remnants) and lipoprotein (a)– in addition to LDL-cholesterol.

When TGs range between 200 and 499 mg/dL, then non-HDL-cholesterol levels become a secondary target after LDL-cholesterol level. The goal for non-HDL-cholesterol levels is the one set for LDL-cholesterol plus 30 mg/dL.¹ For example, if the goal for the LDL-cholesterol is <100 mg/dL, then the goal for non-HDL-cholesterol is <130 mg/dL. When TGs are >500 mg/dL then the main target is lowering TGs because of the risk of acute pancreatitis.¹

Do we need to treat elevated TGs?

As already stated, when TGs are very high the primary target of treatment is lowering TGs because of the risk of acute pancreatitis.¹ But what should we do when TGs are in the range of 200 (or even 150) to 499 mg/dL? There are no intervention trials specifically targeting TG reduction but the closest answer comes from studies with fibrates, which primarily lower TGs.

The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)²⁰ showed less angiographic CHD progression and reduced CHD events with bezafibrate, which substantially lowered plasma TGs but not the LDL-cholesterol level. In the Bezafibrate Infarction Prevention (BIP) trial 3,090 patients with CHD were randomised to receive either bezafibrate (400 mg/day) or placebo. In a post hoc analysis, bezafibrate significantly ($p=0.03$) reduced by 40% the incidence of primary end-points in patients ($n=458$) with baseline TG levels >200 mg/dL.²¹ Subgroup analysis of the HHS⁹ suggested that gemfibrozil exerted its most beneficial effect in patients with moderate hypertriglyceridaemia and an LDL-cholesterol/HDL-cholesterol ratio >5.0. In the VA-HIT,²² the combination of lowering TGs by 24% and increasing HDL-cholesterol by 7.5% with gemfibrozil was associated with a 22% decrease in the incidence of CHD, without changing LDL-cholesterol levels. In the Diabetes Atherosclerosis Intervention Study (DAIS),²³ 418 patients with type 2 diabetes and coronary atherosclerosis were randomly assigned to either micro-nised fenofibrate (200 mg/day) or placebo for at least 3

years. Coronary lesions, assessed by coronary angiograms, progressed significantly less ($p=0.02$) in the fenofibrate group compared with the placebo group. The trial was not powered to assess clinical end-points, but there were fewer events in the fenofibrate group than in the placebo group (38 vs. 50). Similarly, in the Lipid Coronary Angiography Trial (LOCAT) gemfibrozil therapy retarded the progression of coronary atherosclerosis and the formation of bypass-graft lesions after coronary bypass surgery in men with low HDL cholesterol as their main lipid abnormality.²⁴

How can we lower elevated TGs?

Raised TGs may be decreased by lifestyle changes as well as by drug treatment.²⁵ Management of the secondary causes of hypertriglyceridaemia (Table 2) will facilitate TG lowering.

Therapeutic lifestyle changes

These include smoking cessation, weight loss, healthy diet and increased physical activity.^{11,18} These interventions are expected to have modest but additive effects. For example, for every 4.5 Kg of stable weight reduction, TG levels are reduced by 6 mg/dL.²⁶ Patients should limit total fat intake to <30% of total calories as well as the intake of simple carbohydrates.¹ Aerobic exercise, independent of weight loss, can modestly decrease TGs in a dose-dependent fashion.²⁷ A decreased alcohol intake is of paramount importance in TG lowering.

Drug therapy

Statins

Statins cause a modest fall in TGs (7 to 30%) and a rise in HDL-cholesterol (about 5%). However, high doses of the more potent statins may further reduce TGs, especially in patients with high baseline levels.^{25,28}

Fibrates

Fibrates effectively lower TGs by 20-50% and raise HDL-cholesterol levels by 10-20%.²⁹

Nicotinic acid

Nicotinic acid lowers TGs by 20-50% and raises HDL-cholesterol levels by up to 35%.³⁰

Omega-3 fatty acids (fish oils)

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) in doses of 3 to 5 g/day consistently decrease fasting and postprandial TGs by 20-30%.³¹ In the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarcto miocardico (GISSI)-Prevenzione trial,³² treatment with n-3 PUFA (1 g daily for 3.5 years) in patients who had a myocardial infarction significantly reduced total and cardiovascular death. However, this benefit is unlikely to be due to any change in TG levels since the dose of n-3 PUFAs was "low".

Ezetimibe

Ezetimibe, a selective inhibitor of intestinal cholesterol absorption, can be both safely and effectively combined with a statin in order to achieve further LDL-cholesterol lowering.³³ Moreover, it exerts a modest favourable effect on TG (-7%) and HDL-cholesterol (+3%) levels. Preliminary evidence suggests that combining ezetimibe with a fibrate is a safe option.³⁴

Combination drug therapy to lower TGs

The following drug combinations may be used:^{35,36} i) statin + nicotinic acid (a single-tablet combination of niacin extended release and lovastatin is available in the US); ii) statin + fibrate (this combination should be administered with caution because of a potentially increased incidence of myositis and rhabdomyolysis); and iii) statin + n-3 PUFAs.

Conclusions

While LDL-cholesterol is currently the main treatment target, it is clear that other lipoprotein abnormalities, such as low HDL-cholesterol, elevated TGs, and especially their combination, are important modifiable vascular risk factors. Once LDL-cholesterol targets are achieved, clinicians should consider low levels of HDL-cholesterol and elevated TGs.³⁶ These patients should be encouraged to stop smoking, lose weight, adopt a healthier diet and increase their physical activity. Moreover, all secondary causes of hypertriglyceridaemia should be addressed. In high-risk subjects, pharmacological treatment to lower TGs should be considered. Specific clinical trials to investigate the effect of lowering TGs on the incidence of CHD events are needed. In this context, the ongoing Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study³⁷ will establish the role of fenofibrate treatment

in reducing vascular events in patients (n=9,795) with type 2 diabetes. There is also a need to assess the diagnostic value of postprandial hypertriglyceridaemia.³⁸ However, such research is difficult to carry out because of a lack of standardised procedures.³⁸

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