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Comprehensive Approach in Managing Hypertriglyceridemia: Integrating Pharmacological and Non-Pharmacological Strategies

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ABSTRACT:

In many instances, hypertriglyceridemia is multifactorial, caused by a combination of genetic variables and other conditions that result in increased synthesis or impaired clearance of triglyceride-rich lipoproteins (TRLPs). Triglyceride (TG) levels that are significantly elevated increase the risk of developing pancreatitis and must be reduced with medication and lifestyle modifications in addition to an analysis of the underlying cause. Even though statin medication has improved the results of atherosclerotic cardiovascular disease (ASCVD), there is still a risk. Recent studies on the outcomes of cardiovascular disease when triglyceride-lowering medications are used suggest that, while a net benefit is likely present, both relative and absolute risk reductions appear modest in comparison to the benefit of lowering low-density lipoprotein cholesterol levels with treatment. Numerous studies have demonstrated that mild to moderate hypertriglyceridemia (HTG) is an independent risk factor for cardiovascular disease (CVD) in this context of residual atherosclerotic cardiovascular disease risk; however, the data do not provide conclusive proof that the risk of CVD decreases with the treatment of hypertriglyceridemia.

1. Introduction

Triglycerides (TG) are a crucial molecule for the body's effective storage of extra energy. No matter the nutrient in excess, whether it is glucose, protein, or fat itself, we always store it as fat, which is TG. About 90% of the TG that circulates with chylomicrons (CM) and very low-density lipoproteins (VLDL) is transported through the bloodstream on lipoproteins. The latter is put together into CM together with apolipoprotein B48 (apoB48), cholesterol, phospholipids, and other substances. The CM is then secreted into the lymphatic system and subsequently into the bloodstream, where it can carry its TG-FA to adipose tissue for storage or to both skeletal and cardiac muscle for use as fuel. Adipose tissue-derived FAs, FA produced by the liver from acetylCoA (de novo lipogenesis, or DNL), and FA released from CM-R and VLDL-R TG that have evaded peripheral absorption and been removed from circulation by the liver are all used to make TG in the liver [1,2].

According to population research, roughly 25% of people have fasting plasma TG levels below 100 mg/dl, which is regarded as being quite normal. One common upper limit of normal is 150 mg/dl, which is present in about 65% of persons. The whole range of fasting plasma TG, however, is between approximately 30 mg/dl and 10,000 mg/dl (0.33-12.0 mmol/L) [3].

Energy, in the form of TG, is transported by CMs and VLDL from the small intestine and liver to adipose tissue and muscle, where it is stored or used, respectively. Therefore, increased rates of TG secretion from the small intestine and liver will occur in the presence of nutritional balance disorders, whether as a result of excessive calorie intake or inadequate energy storage [1].

There are too many triglycerides in your blood, which is a disorder known as hypertriglyceridemia. Lipids (fats) called triglycerides give your body energy. Triglycerides can be obtained from foods you eat, such as butter and oils. Additionally, your body turns extra calories into triglycerides when you ingest more than you need. Triglycerides can be used by your body later when you need energy, but having too many of them increases your risk of cardiovascular disease [3].

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A fasting plasma triglyceride reading that is higher than the 95th percentile for age and gender is referred to as hypertriglyceridemia, albeit additional quantitative or qualitative lipoprotein abnormalities may also be present [4].

Exogenous (i.e., from dietary fat) and carried in chylomicrons, and endogenous (from the liver) and carried in very-low-density lipoprotein (VLDL) particles, are the two main sources of plasma triglycerides, also known as triacylglycerol. These lipoproteins and chylomicrons are degraded into free fatty acids by lipoprotein lipase in capillaries within adipose and muscle tissue [4,5].

1.1 Etiology

The causes of hypertriglyceridemia are frequently complex. Hypertriglyceridemia is known to be caused by a combination of hereditary factors, increased production, and/or poor clearance of triglyceride-rich lipoproteins (TRLP). Syndromes with a predominance of HTG (common) or chylomicronemia (rare) are among the genetic reasons. Both familial combination hyperlipidemia (polymorphisms of apolipoprotein C-II (apoC-II), apolipoprotein C-III (apoC-III), etc.) and familial hypertriglyceridemia (excess Very Low-Density Lipoprotein but normal cholesterol) typically present with HTG [6,7].

Specific medical disorders, medications, and dietary factors are examples of secondary causes of HTG. HTG has been linked to illnesses like pregnancy, metabolic syndrome, type 2 diabetes, systemic lupus erythematosus, hypothyroidism, Cushing's syndrome, chronic renal disease, and human immunodeficiency virus. Excessive alcohol use, foods high in saturated fat, and foods with a high glycemic index are all dietary causes of HTG [7].

1.2 Pathophysiology

Triglyceride-rich lipoproteins (VLDL and chylomicrons) transport triglycerides throughout the body. The small intestine releases chylomicrons, which contain a considerable amount of TGL. Peripheral tissues hydrolyze the TGL-rich chylomicrons. Free fatty acids (FFA) are released as a result of the lipolysis. The FFA are absorbed by muscle cells, where they serve as an energy source. The FFA is kept in adipose tissue as a dormant fuel [8].

Triglycerides are transported throughout the body by triglyceride-rich lipoproteins (VLDL and chylomicrons). Chylomicrons, which are expelled by the small intestine and contain a large amount of TGL, are produced. The TGL-rich chylomicrons are hydrolyzed by peripheral tissues. The lipolysis results in the release of free fatty acids (FFA). The FFA are taken up by muscle cells and used as an energy source there. Adipose tissue preserves the FFA as a dormant fuel [9].

1.3 Diagnosis

It has long been accepted practice to measure the lipid levels in fasting blood. This strategy reflects the difficulty in interpreting postprandial variations in TG levels. Postprandial lipoproteins, on the other hand, have an atherogenic effect as well, and this makes them useful for risk assessment [10-12].

Blood drawn from patients who are fasting is a requirement for using this equation. LDL cholesterol is now, however, typically assessed directly. According to current standards, blood should be drawn from individuals who are fasting if one of the conditions listed in:

- Non-fasting triglyceride levels > 440 mg/dL (5 mmol/L)
- Known hypertriglyceridemia
- After hypertriglyceridemia-associated pancreatitis
- Before beginning medications that may cause hypertriglyceridemia
- Whenever other tests (such as those to check blood sugar levels or drug levels) call for fasting blood collection [13].

Disorders that exhibit chylomicronemia or hypertriglyceridemia are differential diagnoses. Chylomicronemia is accompanied by mutations in the glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), lipoprotein lipase impairment, Apo C II deficiency, Apo AV homozygosity, and Apo AV homozygosity [8].

Disorders that manifest as hypertriglyceridemia:

• Elevated VLDL and/or LDL are symptoms of familial combination hyperlipidemia. From isolated hypertriglyceridemia to isolated hypercholesterolemia, the phenotypic varies. In any case, elevated apo B concentrations are observed and are utilised to rule out familial hypertriglyceridemia. It has a link to cardiovascular disease that develops too early.

• Large VLDL particles are secreted more frequently in familial hypertriglyceridemia, which is typically accompanied by low levels of LDL and HDL. Increased VLDL synthesis and decreased VLDL catabolism lead to lipoprotein lipase saturation. Unless the TGL levels are really high, it is typically not linked to early cardiovascular disease but can manifest as pancreatitis.

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• A faulty Apo E is the cause of familial dysbetalipoproteinemia (type III hyperlipoproteinemia). Chylomicron accumulation and the presence of VLDL remnants are its defining features. Raising concern for this syndrome should occur when both cholesterol and triglyceride readings are elevated and are at nearly equal levels. It is linked to peripheral vascular disease and early cardiovascular disease [8].

The computed non-HDL-cholesterol concentration (total cholesterol minus HDL-cholesterol) should be included in the lipid profile together with total cholesterol, TG, HDL, and LDL cholesterol. Patients with hypertriglyceridemia frequently have elevated TG, as well as elevated total cholesterol, decreased HDL cholesterol, and normal to low LDL cholesterol values. The fact that all triglyceride-rich lipoproteins also contain cholesterol, which causes the total cholesterol level to rise, explains why total cholesterol has increased. The amount of residual or VLDL cholesterol, which is related with triglyceride-rich lipoproteins, is specified by the non-HDL-cholesterol parameter. The benefit of estimating non-HDL cholesterol is that it only requires the measurement of one parameter to estimate the content of all atherogenic lipoproteins. Given that it also comprises LDL cholesterol, non-HDL cholesterol has a stronger correlation with adverse cardiovascular events than TG. Additionally, the atherogenicity response to growing TG levels is mediated by the presence of new lipoproteins rather than by TG loading of already present lipoproteins [14].

Table 1: Target lipid values for preventing cardiovascular disease [16**]**

	Primary target level	**Grade of recommend-dation / level of evidence**	**Secondary targets**	
Cardio-vascular Risk*1	**LDL-cholesterol**		**Non-HDL-cholesterol**	**apoB**
	mg/dl		**mg/dl**	**mg/dl**
Low*2	<116	IIb/A		
Moderate*2	<100	IIa/A	<130	<100
High	<70	I/A	<100	<80
Very High	<55	I/A	<85	<65

*1Calculation of cardiovascular risk based on clinical indicators and the European Society of Cardiology risk score (10-year risk of fatal cardiovascular disease); examples include "very high risk" with evidence of atherosclerotic disease or score >20% or "high risk" with diabetes but no end-organ damage.

*2These objectives may be taken into account.

1.4 Risk Factors

• For CVD

The complexity of lipoprotein-lipid metabolism and the limitations of population-based epidemiologic studies, where multivariate analyses frequently fall short, are the root causes of the debate. Due to its function in energy metabolism, TG has significantly more daily variability in blood levels compared to LDL and HDL cholesterol, which reduces its statistical power. More significantly, HDL cholesterol levels and VLDL TG levels are adversely correlated thanks to CETP. The fact that VLDL transports both TG and a sizable amount of cholesterol makes it dubious to adjust the role of TG in CVD risk using VLDL cholesterol (which is normally computed in part from TG concentrations) [16].

• For Pancreatitis

An increased risk of acute pancreatitis and low-grade inflammation are linked to mild to severe HTG. Newer results show that pancreatitis risk increases at moderately high TG concentrations in a dose-dependent manner, contrary to the long-held belief that only severe HTG is linked to acute pancreatitis. However, it is not apparent whether the risk is the same for all TRLs or whether CMs and CM-R provide a higher risk than VLDL and VLDL-R. It is challenging to pinpoint a particular TRL as the beginning of pancreatitis because a variety of TRLs are present in the majority of severe HTG due to the struggle between VLDL and CM for LpL. The lack of a distinct cutpoint in TG concentrations and risk has complicated attempts to understand the pathophysiologic relationship between HTG and pancreatitis [16, 17].

1.5 Management

Therapeutic therapies are used to treat hypertriglyceridemia with the goal of lowering pancreatitis and cardiovascular event risk. As a result, the European medical associations have established lipid target values based on the overall risk. The target LDL-cholesterol levels for patients with hypertriglyceridemia are much the same as those for people without it. Because the existing data from randomised trials is weaker than that for LDL-cholesterol, non-HDL-cholesterol and apoB represent secondary objectives of lipid lowering. This reflects the fact that LDL-cholesterol was the primary focus of the design and

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statistical analysis of the majority of significant studies of lipid-lowering regimens [18].

• *Pharmacological Treatment*

a. Fibrates

Gemfibrozil, bezafibrate, and fenofibrate are examples of fibric acid compounds that are frequently used to treat hypertriglyceridemia. Although these percentages vary, these fibrates can lower plasma triglyceride levels by as much as 50% and increase HDL-C concentrations by as much as 20%. In addition to modulating the activity of the peroxisome proliferator-activated receptor in the liver, fibrates also promote lipolysis of plasma triglycerides while decreasing hepatic production of VLDL. Fibrates raise HDL-C and decrease the amount of tiny, dense LDL particles. Fibrates can occasionally increase plasma LDL-C levels, which calls for switching to a different medication or adding a second agent. Fibrate therapy is typically well tolerated, and there have only been a very small number of cases of it causing myositis or hepatitis [19-21].

However, the use of fibrates may be considered in patients with hypertriglyceridemia and a very high risk (for example, progression of atherosclerotic disease despite achieving target LDL levels), as analyses in subgroups of the aforementioned studies suggested potential benefits in this combination. The continuing research examining the potential benefits of combining fibrates and statins in patients with high risk and higher TG levels deserves special attention [22-24].

It should be determined on an individual basis whether fibrates are beneficial in patients with very high TG levels (>1000 mg/dL, around 10 mmol/L; pancreatitis prophylaxis). Patients should be reevaluated after 4 to 6 weeks; at which time the lifestyle changes are strictly maintained. When performing a re-evaluation, the medicine should be stopped if no clinically relevant effect (reduction >30%) is discovered. The information that is currently available does not suggest that fibrates can lower the risk of pancreatitis [23,24].

b. Omega 3 fatty acid

Polyunsaturated fatty acids (PUFAs), such as omega 3 fatty acids, play a variety of significant roles in cell physiology. They are called necessary fatty acids because the body cannot produce them on its own from tiny carbon molecules. Alpha-linolenic acid (ALA), which can be found in plant oils like flaxseed, soybean, and canola, as well as eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which must be consumed with fish and other seafood, are the two main omega 3 FAs, though small amounts can be produced by elongating ALA [25,26].

The triglyceride-lowering effect of high dosages of omega-3 fatty acids (>1.5–2 g icosapent ethyl with 1.2–1.5 g doconexent ethyl daily) is about 25–30%. Studies examining the use of low-dose omega-3 fatty acids (1 g daily) to reduce cardiovascular events have produced mixed results. Low doses of omega-3 fatty acids should not therefore be used to start treatment [27-29].

c. Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase enzyme is inhibited by statins. Higher doses of more recent statins can significantly lower triglyceride levels. However, they are not a first-line treatment when triglyceride levels are above 5 mmol/L. The overwhelming data showing a decrease in coronary heart disease end points, particularly in people with type 2 diabetes, is one benefit of statins. Statins are often well tolerated, similar to fibrates, and seldom result in myopathy or liver toxicity. The continuing action to control cardiovascular risk in diabetes (ACCORD) study is currently examining potential positive effects of the combination of a statin and fibrate in the treatment of type 2 diabetes [30-32].

d. Niacin

Niacin (nicotinic acid) intake of up to 3 g per day has been shown to lower plasma triglyceride levels by up to 45%, increase HDL-C by up to 25%, and lower plasma LDL-C by up to 20%. Older clinical research revealed a link between niacin therapy and a decrease in cardiovascular events. Niacin, however, frequently results in dizziness, skin flushing, or itching. By beginning treatment with modest doses and gradually increasing the daily dose, using acetylsalicylic acid concurrently, or using longer-acting medications like Niaspanit is possible to reduce these negative effects [33-35].

• *Emerging Treatment*

A cannabinoid-1 receptor antagonist called rimonabant lessens hunger and lowers food consumption. The Rimonabant in Obesity trials, also known as RIO-Europe, RIO-Lipids, RIO-North America, and RIO-Diabetes, each evaluated rimonabant in different patient groups and found that it successfully and persistently reduced obesity variables in the treatment groups while concurrently improving metabolic biomarkers, such as triglycerides [36-40].

The use of glitazar medicines to treat type 2 diabetes and metabolic syndrome is theoretically advantageous

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because they are dual agonists of peroxisome proliferator-activated receptors- (similar to fibrates) and - (similar to thiazolidinediones). However, a review of phase 2 and 3 trials revealed strong links between muraglitazar and myocardial infarction, stroke, and death [39].

• *Therapy for Acute Pancreatitis Associated with Hyperlipidemia*

The same initial diagnostic and treatment procedures should be followed as with other acute pancreatitis causes. All cases of acute pancreatitis should have their TG levels checked because even when the primary cause is clear (such as alcohol), significant HTG can still play a role. IV glucose should be avoided at first because it can raise TG levels even further [41].

Heparin and insulin have been used in TG-associated pancreatitis, largely based on case reports or short case series, although there is no convincing evidence of benefit. Heparin may lower TG levels and release endothelial-bound LPL[41].

For patients with significant hypertriglyceridemia (>1000 mg/dL or 11.4 mmol/L), stringent fasting and intravenous fluid replacement are the primary treatments for acute pancreatitis. A case-by-case analysis must be done in order to determine whether plasmapheresis is necessary. This method allows for the quick reduction of TG levels, which may stop the underlying pathomechanism and cause the pancreatitis to progress more slowly [42].

Patients with complicated hypertriglyceridemia, such as those who experience recurring pancreatitis episodes, should get care in specialised lipidological centres so that it can be determined whether there is a need for the application of novel therapeutic strategies [43].

• *Non-Pharmacological Treatment*

Managing lifestyle variables linked to high TG is the most crucial aspect of treating people with HTG. These include metabolic syndrome, high-fat or high-glycaemic index meals, and diets with a high positive energy-intake balance. Alcohol use is also a significant factor. Corticosteroids, thiazides, non-selective beta-blockers, oestrogen, tamoxifen, bile acid sequestrants, cyclophosphamide, antiviral medications, and second-generation antipsychotic medicines are among the medications that elevate TG. The aim is to achieve optimal blood sugar management in individuals with diabetes mellitus and weight loss in obese patients. Additionally, it's critical to remember that each person's response to lifestyle changes is quite different. The first practical step in changing one's lifestyle is to cut back on alcohol use, which people with high TG should do in all forms and in moderation. An increase in physical activity is another tenet of lifestyle advice due to its numerous extra positive metabolic and physiological consequences. The most crucial dietary rule is to cut back on net caloric consumption. According to particular dietary guidelines, foods high in refined carbohydrates, sucrose, and fructose also elevate TG significantly more than meals high in fibre and low in GI do. A dietetics consultation can be very beneficial. Limiting saturated and trans-fat intake and increasing aerobic activity can lower plasma levels of triglycerides in less severe cases of hypertriglyceridemia [44-48].

2. CONCLUSION

Genetic and epidemiological research identifies TRL and their remnants as significant causes of ASCVD. Implementing lifestyle modifications is the initial stage of treatment. Second, decreasing LDL-C with statins is advised to lower the risk of vascular disease; this is separate from statin-associated TRL lowering. Although it is likely that lower plasma triglyceride levels lower the risk of cardiovascular disease, there is less clinical trial evidence in favour of fibrate monotherapy than there is for lower plasma LDL-C levels. Previous studies with fibrates, niacin, inhibitors failed to show definitive evidence of a decrease in ASCVD in patients receiving the best cholesterol-lowering therapy. Patients who will benefit from TRL reduction may be identified using novel and emerging data, such as those on omega-3 fatty acids (high-dose icosapent ethyl) and the specific PPAR modulator pemafibrate. In addition to decreasing LDL-C, treating TRL in particular patient populations will soon become a crucial component of lipid-directed therapy.

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