CHAPTER

39

Isolated Triglyceridemia

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Introduction

The various forms of hyperlipoproteinemia used to be designated type I to type V, depending on whether chylomicron triglyceride , VDRL triglyceride or both were elevated and whether LDL cholesterol was or not raised as well, has fallen into disuse. Now we distinguish : [1] Combined hyperlipidemia if triglycerides and LDL cholesterol are elevated. [2] Isolated moderate or severe hypertriglyceridemia if triglycerides are raised but LDL cholesterol is normal [3] High LDL cholesterol with normal triglycerides [4] Low HDL cholesterol with or without other abnormalities. By definition all patients with forms of moderate pure hypertriglyceridemia have a normal LDL cholesterol level, but that is not to say that all patients with moderate hypertriglyceridemia are the same.There are two forms :one with a normal apoB and one with an elevated apoB. The distinction is important as several studies have shown that risk is markedly increased in the latter only. Unfortunately, the two forms can not be distinguished accurately by measurement of lipid values. Thus many causes of hypertriglyceridemia exist, and not all hypertriglyceridemias are associated with increased cardiovascular risk. Clinicians have several tools to assess risk in individual patients, including non-HDL cholesterol levels, the triglyceride-to-HDL ratio, apoprotein B levels and lipoprotein particle subfractionation. Most important, however, is interpretation of triglyceride levels in the overall clinical context.[1]

Metabolic pathways and Metabolic consequences

Triglycerides enter the bloodstream via two pathways. When fat is ingested (the exogenous pathway), it is packaged into large chylomicrons in the gut. Chylomicrons are characterized by the surface presence of apoproteins B48, E and apo-CII, the latter of which is an essential cofactor for the activation of lipoprotein lipase (LPL). LPL hydrolyzes the triglycerides and makes free fatty acids available for use by organs of the body, such as muscle and adipose tissue. During hydrolysis, the triglyceride content of the chylomicron particle decreases, whereas the cholesterol content does not. The resultant chylomicron remnants are therefore cholesterol-enriched (and thus potentially atherogenic) and, because of the apo-E moiety, they are recognized by the hepatic apoB/E (i.e., LDL) receptor and removed from the circulation.

In the endogenous pathway (beginning in the liver), triglycerides and cholesterol are packaged into VLDL particles, which have apo-B100 and apo-CII on the surface. VLDL particles are also hydrolyzed by lipoprotein lipase and become progressively cholesterol-enriched, resulting in VLDL remnants,

Table 1 : Classification of Triglyceride Levels

Classification	Triglyceride Level (mg/dl.)
Normal	< 150
Borderline high	150 to 199
High	200 to 499
Very high	> 500

IDL and ultimately LDL particles, which can all be taken up by the liver. VLDL remnants and intermediate-density lipoproteins [IDL] not converted into LDL are removed by the liver. After a meal, newly synthesized TRLs are hydrolyzed by endothelial lipases into smaller remnant particles, which are cleared from the circulation mainly by receptor-mediated endocytosis in the liver . The metabolic fate of TRL particles is determined by their apolipoprotein (apo) and lipid composition, which governs their access to lipases and receptors. The structural protein apoB is an integral part of every TRL particle. Of the two forms of apoB–apoB48 (synthesized in the intestine) and apoB100 (synthesized in the liver)–only apoB100 has a specific receptor-binding site. ApoB100 and apoE are important mediators of the clearance of circulating TRLs by receptors ; apoE-mediated binding of TRLs to receptors is inhibited by members of the apoC family, in particular apoCI and apoCIII . Apolipoprotein CII is necessary for lipoprotein lipase-mediated hydrolysis of TRL particles, which is blocked by apoCIII but not apoCI. Apo CI content of postprandial TRLs is a novel independent risk factor for early atherosclerosis in normolipidemic healthy middle-aged men with possible implication for the enrichment of TRL remnant lipoproteins with cholesterol.[2]

Hypertriglyceridemia has metabolic consequences. The metabolism of triglyceride-rich lipoproteins and the metabolism of HDL particles are linked through cholesterol ester transfer protein (CETP). CETP exchanges triglycerides and cholesterol ester between triglyceride-rich lipoproteins and HDL particles, leading to triglyceride enrichment of HDL particles and a lowering of HDL cholesterol levels.

Table 2 : Fredrickson Dyslipidemia Classification

Type	Elevated Lipoprotein	Total Cholesterol Level	Triglyceride Level	Relative Frequency
I	CM*	Normal	++	< 1%
IIa (FHC)	LDL	++	Normal	10%
IIb (FCH)	LDL/VLDL	++	+	40%
III	IDL	+	+	< 1%
IV (FHT)	VLDL	Normal to +	++	45%
V	CM VLDL	+	++	5%

* CM, chylomicron; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; IDL, intermediate density lipoprotein; FHC, familial hypercholesterolemia; FCH, familial combined hyperlipidemia; FHT, familial hypertriglyceridemia.

+, Mild to moderate increase. ++, Moderate to severe increase.

Classification

The Adult Treatment Panel III of the National Cholesterol Education Program has suggested four triglyceride strata in the context of assessment of risk of cardiovascular disease: [Table-1]

An alternative scheme, the World Health Organization–supported Fredrickson system of hyperlipoproteinemia phenotypes, was a one time widely taught, but has fallen into disuse. [Table-2]

Causes of hypertriglyceridemia: Inherited disorders Four inherited conditions cause hypertriglyceridemia.[3]

The most common inherited condition is familial combined hyperlipidemia, which occurs in one in 200 patients and presents with a type IIB Fredrickson lipid profile. Familial combined hyperlipidemia is characterized by a family history of high levels of LDL and VLDL cholesterol and apolipoprotein B (ApoB) and with triglycerides ranging from 150 mg/dL to 500 mg/dL. People with this condition are at increased risk for coronary heart disease. The inheritance pattern of familial combined hyperlipoproteinemia(type 2B) is one of an autosomal dominant with variable penetrance, with a population prevalence of 2%–5%. The defining

lipoprotein abnormalities are increased VLDL and low-density lipoprotein (LDL) with depressed HDL, associated with an abnormal lipoprotein profile in at least one first-degree relative. Affected people occasionally have obligate heterozygosity for LPL or APOC3 gene mutations, but the molecular basis underlying familial combined hyperlipoproteinemia is unknown in most instances. A recently defined gene that may be causative for this disorder is USF1, which encodes an upstream stimulatory factor[4] although several other genes (including APOA5 and APOC3) have been variably claimed as causative.[5]

The second condition familial dysbetalipoproteinemia (hyperlipoproteinemia type 3) has a population prevalence of 1–2 in 20000. The main observable lipoprotein abnormality is an increase in triglyceride-rich lipoprotein remnants, also known as IDL or beta-VLDL which produce an equimolar elevation of plasma total cholesterol and triglyceride measurements. People with this disorder typically are homozygotic for the binding-defective APOE E2 isoform, which differs from the common E3 isoform by a substitution of cysteine for the normal arginine at residue 158 in the receptor-binding domain. Phenotypic expression, however, usually requires accompanying factors such as obesity, type 2 diabetes or hypothyroidism. Plasma levels of LDL are decreased because of interrupted processing of VLDL. An increased VLDL-C :triglyceride ratio and E2/E2 homozygosity are diagnostic. Affected people often have tuberous or tuberoeruptive xanthomata on the extensor surfaces of their extremities, planar- or palmar crease xanthomata and increased risk of cardiovascular disease.

The third disorder is familial hypertriglyceridemia, which is usually a type IV phenotype with high VLDL cholesterol, normal LDL cholesterol and normal ApoB. Triglycerides are usually between 250 mg/dL to 1,000 mg/dL, and the disorder is often associated with insulin resistance. Familial hypertriglyceridemia (hyperlipoproteinemia type4) is defined by an isolated elevation of VLDL, which is not as triglyceride-rich as chylomicrons are. This familial disorder has a population prevalence of some 5%–10%. Its molecular basis is still largely unknown but is likely to be polygenic, requiring a secondary factor for expression. Typically, patients with this disorder have moderately elevated plasma measurements of triglycerides, often with low levels of high-density lipoprotein–cholesterol (HDL-C). Although it was believed that these patients did not have higher than average cardiovascular risk, this view has been challenged by more recent follow-up analyses, such as those by Austin and colleagues.[6] In some of these patients, superimposed chylomicronemia leads to elevated triglyceride levels (> 1,000 mg/dL) that increase the risk of pancreatitis.

Lastly, **familial chylomicronemia** presents as extremely elevated triglyceride levels from birth (1,000 mg/dL to 10,000 mg/dL) and is caused by an LPL or ApoCII genetic defect. These patients do not have increased cardiovascular risk. Familial chylomicronemia (hyperlipoproteinemia type 1, in the Fredrickson system) and primary mixed hyperlipidemia (type 5) are each characterized by the pathologic presence of chylomicrons after a 12–14-hour period of fasting. Clinical features observed in both familial chylomicronemia and primary mixed hyperlipidemia include eruptive xanthomata, lipemia retinalis, hepatosplenomegaly, focal neurologic symptoms such as irritability, and recurrent epigastric pain with increased risk of pancreatitis. Samples of lipemic plasma develop a creamy supernatant when refrigerated overnight. Key distinguishing features of familial chylomicronemia and primary mixed hyperlipidemia include initial manifestation during childhood for the former and in adulthood for the latter; biochemically proven deficiency of lipoprotein lipase, apo CII activity or homozygous gene mutations in the former, with less severe functional deficiency and infrequent detection of gene mutations in the latter; a much lower population prevalence of the former (about 1:106) than of the latter (about 1:103); frequent presence of secondary factors in the latter; and a greater elevation of total cholesterol in the latter,

Table 3 : Secondary causes of and contributors to hypertriglyceridemia

- Obesity
- Metabolic syndrome
- A diet with a positive energy-intake balance and a high fat or high glycemic index content
- Insufficient physical activity
- Alcohol consumption
- Diabetes mellitus, particularly type 2
- Renal disease, especially uremia or glomerulonephritis
- Hypothyroidism*
- Pregnancy: physiological triglyceride concentrations double during the third trimester
- An autoimmune disorder, such as a paraproteinemia or systemic lupus erythematosus
- Any of several types of medications, including
  - Corticosteroids
  - Estrogens, especially those taken orally
  - Tamoxifen
  - Antihypertensives: e.g., non-cardioselective beta-blockers, thiazides
  - Isotretinoin
  - Bile-acid–binding resins
  - Cyclophosphamide
  - Antiretroviral regimens, especially for HIV infections
  - Psychotropic medications: phenothiazines, second generation antipsychotics

*Less common a cause of hypertriglyceridemia than elevated total cholesterol levels.

relative to that in familial chylomicronemia. In biochemical diagnosis, familial chylomicronemia features a loss of lipoprotein lipase activity in plasma collected after an intravenous dose of heparin.

Secondary hypertriglyceridemia

In contrast to primary hypertriglyceridemia, there are many secondary causes of hypertriglyceridemia. These include medical conditions such as diabetes mellitus, hypothyroidism, obesity, and nephrotic syndrome. In addition, certain medications, high carbohydrate diets, and alcohol can cause or exacerbate hypertriglyceridemia (Table-3)

Commonly, hypertriglyceridemia results from a combination of factors. For example, a patient may be found to have familial combined dyslipidemia, obesity, and high alcohol consumption.

Hypertriglyceridemia and pancreatitis

Hypertriglyceridemia is a risk factor for pancreatitis and it accounts for 1 to 4% of cases of acute pancreatitis. Although a few patients can develop pancreatitis with triglyceride levels > 500 mg/dL, the risk for pancreatitis does not become clinically significant until levels are > 1000 mg/dL.[7]

Controversial link with CHD risk

Many epidemiological studies have reported an association between serum triglyceride concentrations and the risk of coronary heart disease, but this association has not been reliably quantified.[8] The importance of serum triglycerides as a risk factor for cardiovascular diseases is controversial. Many epidemiological studies have demonstrated a univariate association between triglycerides and cardiovascular risk, particularly in relation to coronary heart disease (CHD). However, this relationship is attenuated and often becomes nonsignificant after adjustment for major cardiovascular risk factors, particularly HDL cholesterol levels

Important exceptions may be seen in women with hypertriglyceridemia and patients with diabetes. Several lines of evidence suggest that the association of plasma TGs with CAD is complex.[9-10]

In the largest and most comprehensive epidemiological assessment so far in Western populations by Nadeem Sarwar, et al , moderately strong associations were consistently observed between triglyceride concentrations and CHD risk, as well as moderately high levels of reproducibility in triglyceride values within individuals over time. These data renew the importance of further investigations to help assess the nature of any independent associations between triglycerides and CHD.[11]

Recently two large, long-term prospective cohort studies conducted in different populations by Bansal and colleagues[12] and by Nordestgaard and colleagues[13] support the role of nonfasting

Table 4 : Bansal and colleagues study on Triglyceridemia and Cardiac risk[13]

- In the prospective study, 26,509 healthy US women (20,118 fasting and 6391 nonfasting) participating in the Women's Health Study were enrolled between November 1992 and July 1995 and followed up for median of 11.4 years. Triglyceride levels were measured in blood samples obtained at time of enrolment.
- Main outcome measures were hazard ratios (HRs) for incident CV events (nonfatal MI, nonfatal ischemic stroke, coronary revascularization, or CV death).
- During median follow-up of 11.4 years, 1001 participants had an incident CV event (including 276 nonfatal MIs, 265 ischemic strokes, 628 coronary revascularizations, and 163 CV deaths), for overall rate of 3.46 CV events per 1000 person-years of follow-up.
- After adjusting for age, blood pressure, smoking, and use of hormone therapy, both fasting and nonfasting triglyceride levels predicted CV events.
- However, among fasting participants, further adjustment for levels of total cholesterol and HDL-C and measures of insulin resistance weakened this association. In contrast, nonfasting triglyceride levels maintained a strong independent relationship with CV events.
- In secondary analyses stratified by time since participants' last meal, triglyceride levels measured 2 to 4 hours postprandially had strongest association with CV events. Triglyceride levels measured within 2 hours of a meal showed no association with CV risk.

triglyceride levels as a significant risk factor for coronary heart disease (CHD) events. These two new studies provide support for the role of nonfasting triglyceride levels as a significant risk factor for coronary heart disease (CHD). Even after adjustment for other CHD risk factors, including obesity, diabetes mellitus, and other lipoproteins such as high-density lipoprotein cholesterol (HDL-C), the investigators report that triglyceride levels were still associated with an increased risk of heart disease.(Tables 4 & 5).

For now, instituting postprandial TG screening in routine cardiovascular risk stratification is probably premature; however, based on these findings, high TG levels may serve as a readily obtainable clinical indicator of risk, particularly in women.[14]

Table 5 : Nordestgaard and colleagues study on Triglyceridemia and cardiac risk[12]

- In the prospective cohort study, 7587 women and 6394 men from general population of Copenhagen, Denmark, aged 20 to 93 years, were followed up from baseline (1976 - 1978) until 2004.
- Main outcome measures were HRs for incident MI, ischemic heart disease, and total death according to baseline nonfasting triglyceride level categories of 88.5 - 176.1 mg/dL, 177.0 - 264.6 mg/dL, 265.5 - 353.0 mg/dL,354.0 - 441.6 mg/dL, and e • 442.5 mg/dL) vs triglyceride levels of less than < 88.5 mg/dL.
- With increasing levels of nonfasting triglycerides, levels of remnant lipoprotein cholesterol increased.
- During mean follow-up of 26 years, 1793 participants (691 women, 1102 men) developed MI, 3479 (1567 women, 1912 men) developed ischemic heart disease, and 7818 (3731 women, 4087 men) died.
- In this general population, elevated nonfasting triglyceride levels were linked with increased risk for MI, ischemic heart disease, and death in men and women. This was supported by age-adjusted HRs and mulifactorially adjusted HRs for each respective category (*P* for trend < .001).

Triglyceride-rich lipoprotein remnant levels : Time to adopt these orphan risk factors?

The TGRL lipolysis rates and plasma levels of its resulting remnants appear to be important factors in atherosclerosis risk, and thus are potentially important targets in atheroprevention. These parameters are not yet, however, clinically useful tools for diagnosis and prevention of atherosclerosis.[15-17]

Non-HDL cholesterol as a measure of atherosclerotic risk

Non-HDL-C (total cholesterol minus HDL-C) has been found to be a strong predictor of future cardiovascular risk among patients whether or not they exhibit symptoms of vascular disease, and has been recommended as a secondary treatment target (after LDL-C) in patients with elevated TG .[18]

Elevated Triglyceride Levels in diabetes

Albrink, in 1958, pointed out that: *Hypertriglyceridemia*

Table 6 : Triglycerides in Indian urban subjects[20]

First Author	Year	Age Gr.	Place	Sample size	Triglyceride mg/dl
Gandhi BM	1982	20-70	Delhi	200	120.4 ± 29
Varish S	1990	30-70	Delhi	186	128.1 ± 30
Reddy KS	1992	25-64	Delhi	1581	110.2 ± 43
Gopinath N	1994	25-64	Delhi	1345	131.0 ± 54
Gupta R	1997	20-80	Jaipur	199	126 ± 55
Gupta R	2002	20-80	Jaipur	1123	144 ± 70

is the hyperlipidemia par excellence of the diabetic". Elevated triglycerides in diabetes result from both overproduction and reduced catabolism of triglyceride-rich VLDL. It has been shown recently that insulin sensitivity in healthy non-obese hypertriglycerdemic subjects is lower than the normolipemic subjects. Hypertriglyceridemic subjects had to secrete more insulin to compensate for the decreased insulin sensitivity.[19]

Indian Hypertriglyceridemia

The status of TG alone as a risk factor remains controversial. Combination of raised triglycerides and low HDL is an atherogenic phenotype and it is the characteristic lipid profile in majority of Indians having CAD. Epidemiological studies have shown that mean triglyceride levels in Indians are significantly greater than other developed countries. There is a significant increase in serum triglyceride levels over the years in Indians.[20] At present importance of triglycerides in causation of coronary heart disease is lagging behind and there is need of more prospective epidemiological studies. High TG level [> 130 mg/dL]) is found in nearly half of Indo-Asian men. High TG levels are associated with heightened risk of CAD when accompanied by a modest elevation of non-HDL cholesterol.[21] An often ignored contributing factor for high TG in Indo-Asians is a diet very high in carbohydrates, especially as a single large evening meal. High TG levels make small, dense LDL particles which are three times more atherogenic than large buoyant LDL particles.[22] (Table-6)

Management Pearls

In general, monotherapy with a pharmacologic agent should be attempted first, together with dietary adjustments. Combination treatment may be required for refractory severe hypertriglyceridemia (Tables - 7 to 9).

Fibrates

In patients with cardiovascular disease and moderately elevated triglyceride levels and low HDL-C levels, fibrates have been shown to decrease the risk of cardiovascular events (secondary prevention). Fibrate therapy also has been shown to decrease angiographic progression of coronary heart disease in patients with type 2 diabetes.[23] Because data show decreased cardiovascular mortality rates with triglyceride reduction (more than that achieved with LDL-C reduction alone), there is increasing interest in fibrate use in patients with hypertriglyceridemia and in combination fibrate/statin therapy in patients with mixed dyslipidemia. However, despite several large studies, no fibrate has been shown to decrease all-cause mortality rates, and some trials have shown an increase in all-cause mortality rates.[24]

Fibric acid derivatives such as gemfibrozil, bezafibrate and fenofibrate are a mainstay of hypertriglyceridemia treatment.[25-26] The recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that plasma triglyceride, LDL and HDL-C levels in diabetic patients responded favorably to treatment with fenofibrate, but the reduction in the prespecified end point of cardiovascular disease (16%) was nonsignificant Secondary and tertiary outcomes (e.g., nonfatal myocardial infarction, coronary revascularization, and progression of albuminuria and retinopathy) were significantly reduced.[26] Recently it was shown that Triglyceride-lowering therapy with fenofibrate reduced fasting and postprandial free fatty acid oxidation and inflammatory responses, and these antiatherosclerotic effects were most highly correlated with reductions in large VLDL particles.[27]

Statins

Statins, are not the first choice to treat patients with hypertriglyceridemia because few patients with baseline triglyceride levels > 500 mg/dL are likely

Table 7 : Initial Management of Hypertriglyceridemia

Intervention	Description	Comments
Counsel patients about therapeutic lifestyle changes	Body weight control, regular physical activity, tobacco- use cessation, avoidance of high-carbohydrate foods, diet low in saturated fat and sugar	Patients with triglyceride levels above 1,000 mg per dL should immediately start a very low-fat diet
Screen for metabolic syndrome	Constellation of increased abdominal circumference and low HDL-C levels, high triglyceride and blood sugar levels, and elevated blood pressure	Diagnosis and management remain controversial
Search for secondary causes	Nephrotic syndrome, diabetes, chronic renal failure, hypothyroidism, various medications	Optimizing glycemic control may improve hypertriglyceridemia
Search for acquired causes	Overweight and obesity, excessive alcohol intake, high carbohydrate intake, tobacco use	–
Determine cardiac risk profile	Determine cardiac risk factors, and stratify the patient's 10-year risk of coronary heart disease using Framingham risk calculators	–

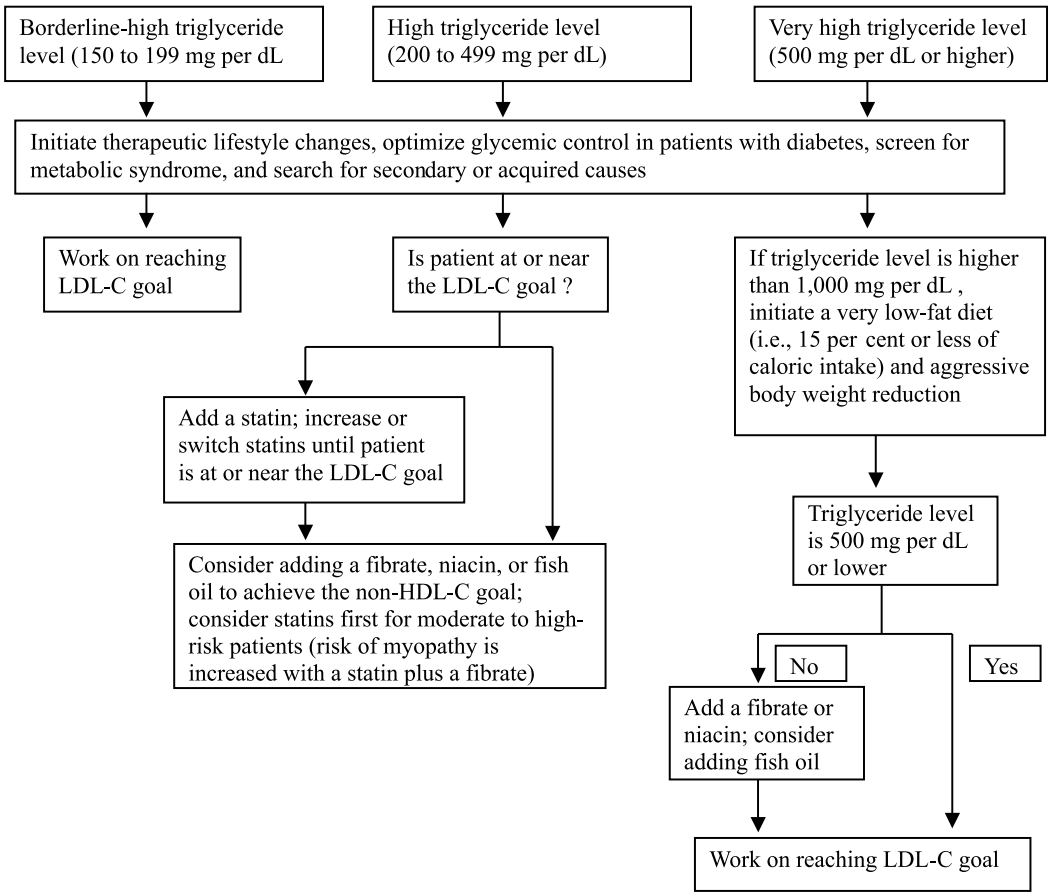
HDL-C = high-density lipoprotein cholesterol.

Table 8 : Selected Therapies for Managing Hypertriglyceridemia

Therapy	Triglyceride Reduction (%)	LDL-C increase/ reduction (%)	HDL-C increase (%)	Possible side effects
Statins Atorvastatin, 10 to 80 mg daily Fluvastatin, 20 to 80 mg daily at bedtime Lovastatin, 10 to 80 mg daily at bedtime Pravastatin, 10 to 80 mg daily Rosuvastatin, 5 to 20 mg daily Simvastatin, 5 to 80 mg daily at bedtime	20 to 40	18 to 55 reduction	5 to 15	Myopathy, rhabdomyolysis, elevated liver - enzyme levels
Fibrates Fenofibrate, 48 to 145 mg daily Gemfibrozil, 600 mg twice daily	40 to 60	5 to 30 increase	15 to 25	Rhabdomyolysis, especially with a gemfibrozil/statin combination
Niacin OTC immediate-release niacin, 0.5 to 2 g two or three times daily OTC sustained-release niacin, 250 to 750 mg Once or twice daily Prescription niacin, 500 mg to 2 g daily at bedtime	30 to 50 reduction	5 to 25	20 to 30	Flushing; worsening glycemic control; elevated liver enzyme levels, especially with OTC sustained-release niacin
Fish oil, 2 to 4 g total EPA/DHA daily OTC omega-3 fatty acid capsules Prescription omega-3 acid ethyl esters, 1 to 2 g twice daily	30 to 50	5 to 10 increase	5 to 10	Fishy aftertaste, gastrointestinal upset

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; OTC = over the counter; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Table 9 : Management of Hypertriglyceridemia



NOTE*: In patients who have achieved the LDL-C goal, the secondary target of treatment should be achieving the non–HDL-C goal (i.e., 30 mg per dL higher than the LDL-C goal.)*

Algorithm for the management of hypertriglyceridemia. (LDL-C= low-density lipoprotein cholesterol; HDL-C= high-density lipoprotein cholesterol.)

to be managed effectively with statins alone. The reduction in triglycerides with statins is from 10% to 30% and, as a general rule, statins with more potent LDL cholesterol-lowering capability have greater effects on non-HDL cholesterol and triglycerides as well. The triglyceride-lowering effect of statins is greater at higher doses and with higher baseline levels of triglycerides. A common clinical error is to initiate treatment with high-dose statins in patients with very high triglycerides (>500 mg/dL).

Niacin

The daily consumption of up to 3 g of niacin (nicotinic acid) can lower plasma triglyceride levels by up to 45%, raise plasma HDL-C by up to 25%, and reduce plasma LDL-C by up to 20%.[28] First-line drug therapy in the treatment of hypertriglyceridemia includes fibrates, niacin and omega-3 fatty acids. Even when LDL cholesterol is controlled, significant residual cardiovascular risk remains in patients with elevated triglycerides. Combination lipid-lowering therapies are often required to manage disorders of hypertriglyceridemia, as well as mixed lipid disorders consisting of elevated LDL cholesterol and triglycerides. Getting more aggressive with combination lipid-lowering therapies that target all the atherogenic lipoproteins may go a long way toward reducing the burden of cardiovascular disease.

Omega-3 fatty acids

Generally, omega-3 fatty acids are indicated as an adjunct to diet in patients with elevated triglycerides, in type IV and type V hypertriglyceridemia, and with statins or other lipid-lowering drugs in patients with mixed hyperlipidemia. At sufficient dosages, the triglyceride reduction with omega-3 fatty acids is 30% to 50%, LDL cholesterol is unchanged or increases slightly and HDL cholesterol is increased slightly. One of the major errors made in clinical practice is using insufficient dosages of omega-3 fatty acids to treat patients with hypertriglyceridemia.[29]

Emerging treatments

Rimonabant, LPL gene therapy,[30] Squalene Synthase Inhibitor: Lapaquistat (TAK-475)[31-32] and Microsomal Triglyceride Transfer Protein (MTP) Inhibition[33] - are some of the new things which are being evaluated for management of hypertriglyceridemia.

Points to Ponder

- Triglycerides are an almost ideal form of energy storage. Almost one-fifth of total mass of a lean 70 kg adult man is made up of triglyceride in adipose tissues. If oxidized, this would give enough energy to survive total starvation for 3 months.It is far more important source of energy than glycogen in the long term.
- Non-HDL cholesterol is a better measure to understand atherogenicity of triglyceride remnants, but it is still not in streamline clinical practice. Non–HDL-cholesterol is particularly misleading when excess (nonatherogenic) chylomicrons carry plasma TG over approximately 1,000 mg/dl.
- In Indians there is no cut off values for treatment of high triglycerides based epidemiological studies.
- The status of fasting triglycerides as a risk factor for coronary heart disease has been considered weak and Post-Prandial Triglyceride estimation gives more insight into the metabolic status. But there is no uniformity in recommendation of measurement of Post Prandial Triglycerides.
- By definition, Isolated Hypertriglyceridemia is mainly found in Familial hypertriglyceridemia(type-IV pattern). In most of the other conditions, it is never isolated.
- Like good cholesterol and bad cholesterol, there is good triglyceride and bad triglyceride depending on its association with apoB.
- If hypertriglyceridemia produces low HDL cholesterol, it makes no sense to conclude that HDL cholesterol is important and triglycerides are not.
- Severe hypertriglyceridemia increases the risk of pancreatitis not of coronary heart disease.
- Moderate hypertriglyceridemia with elevated apoB markedly increases the risk of coronary heart disease. Statins are the first-line therapy to reduce the risk of coronary heart disease in these patients.
- Evidence of clinical benefit is clear for statins but not yet unequivocal for fibrates.

Summary

Hypertriglyceridemia has many varieties, and its relationship to atherosclerosis remains controversial. Two rare genetic causes of hypertriglyceridemia (lipoprotein lipase [LPL] deficiency and apolipoprotein [apo] C-II deficiency) lead to triglyceride (TG) elevations that are astonishingly high. Counterintuitively, these genetic mutations do not confer an increased risk of atherosclerotic disease, which has fostered the unfounded belief that high TGs are not a risk for that condition. Hypertriglyceridemia can be categorized by the Fredrickson classification but this convention has fallen into disuse. Several investigators have suggested that increased plasma lipoprotein remnant particles may contribute to atherogenesis. Recently researchers have explored the utility of fasting and nonfasting triglyceride (TG) levels in predicting cardiovascular events. It is important to

treat hypertriglyceridemia to prevent pancreatitis by reducing triglyceride levels to < 500 mg/dL. However, it is controversial how much isolated hypertriglyceridemia correlates directly with coronary artery disease and further studies are needed to clarify whether treatment for this condition leads to meaningful clinical outcomes. Therapeutic lifestyle changes (TLC) are the first line of treatment for hypertriglyceridemia. In cases of isolated hypertriglyceridemia, fibrates are initially considered. When elevated low-density lipoprotein levels accompany hypertriglyceridemia, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are preferred. In patients with low HDL levels and hypertriglyceridemia, extended release niacin can be considered. A combination of the medicines may be necessary in recalcitrant cases.

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