Origin and therapy for hypertriglyceridaemia in type 2 diabetes

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Abstract

Hypertriglyceridaemia (HTG) is a risk factor for cardiovascular disease (CVD) in type 2 diabetes and is caused by the interaction of genes and non-genetic factors, specifically poor glycaemic control and obesity. In spite of statin treatment, residual risk of CVD remains high in type 2 diabetes, and this may relate to HTG and atherogenic dyslipidemia. Treatment of HTG emphasises correcting secondary factors and adverse lifestyles, in particular, diet and exercise. Pharmacotherapy is also required in most type 2 diabetic patients. Statins are the first-line therapy to achieve recommended therapeutic targets of plasma low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol. Fibrates, ezetimibe and n-3 fatty acids are adjunctive treatment options for residual and persistent HTG. Evidence for the use of niacin has been challenged by non-significant CVD outcomes in two recent large clinical trials. Further investigation is required to clarify the use of incretin-based therapies for HTG in type 2 diabetes. Extreme HTG, with risk of pancreatitis, may require insulin infusion therapy or apheresis. New therapies targeting HTG in diabetes need to be tested in clinical endpoint trials. The purpose of this review is to examine the current evidence and provide practical guidance on the management of HTG in type 2 diabetes.

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Core tip: Diabetic dyslipidemia relates collectively to hyperglycaemia, insulin resistance, hyperinsulinaemia, abdominal visceral adipose disposition, increased liver fat content, and dysregulated fatty acid metabolism. Insulin resistance in diabetes induces hypertriglyceridaemia by increasing the enterocytic production of chylomicrons and an impaired clearance capacity is also involved. Usual care for diabetic dyslipidemia is statin treatment, but a significant proportion of patients have residual dyslipidemia, related to hypertriglyceridaemia and atherogenic dyslipidemia. Current evidence supports the use of fenofibrate in type 2 diabetics with high triglyceride levels.

INTRODUCTION

Hypertriglyceridaemia (HTG) is an important risk factor for cardiovascular disease (CVD) and is defined as a fasting plasma triglyceride concentration > 95th percentile for age and sex in a population. HTG may be as prevalent as 50% in type 2 diabetes and is often unresponsive to statin treatment. We review recent evidence on the role of HTG in atherosclerotic CVD and provide practical guidance on the management of HTG in type 2 diabetes.
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Triglycerides, which originate from the intestine postprandially or endogenously from the liver, are packaged into lipoprotein particles containing apolipoprotein B-48 (apoB-48; chylomicrons) and apolipoprotein B-100 (apoB-100; very-low density lipoprotein, VLDL), respectively. Abnormalities in triglyceride-rich lipoprotein (TRL) metabolism are cardinal features of type 2 diabetes. Metabolic dysregulation resulting in HTG include enhanced hepatic secretion of TRL due to insulin resistance and delayed clearance of TRL involving lipoprotein lipase (LPL)-mediated lipolysis. Several genes causing loss of function of LPL can result in severe HTG, such as LPL, APOC2, APOA5, GPD1, CPIHB1 and LMF1[4,5]. Very few patients will have a monogenic disorder. Individuals with severe HTG are likely to be homozygous or compound heterozygous for mutations which impair the TRL catabolic pathway. However, HTG in type 2 diabetes due to several genes with mild effects that interact with non-genetic factors is probably more likely. These non-genetic factors include hyperglycaemia, alcohol intake, concomitant medication, sedentary lifestyle, chronic kidney disease and insulin resistance[6].

Insulin resistance activates de novo lipogenesis, resulting in oversecretion of hepatic TRLs. This is also evident in the postprandial state, with enteroctyotic oversecretion of TRLs in the form of chylomicrons. With both secretion pathways on overdrive, competition between the TRLs and their remnants for lipolytic and receptor-mediated clearance further induces HTG. Insulin resistance is also associated with increased rates of apolipoprotein C-III (apoC-III) secretion, which further impairs receptor-mediated uptake of hepatic chylomicron remnants[7]. Glucose has also found to activate apoC-III transcription, which may be the link between hyperglycaemia, HTG and CVD in type 2 diabetes[8].

Both LPL and hepatic lipase (HL) control the clearance of triglycerides. HL plays a particularly important role in the delipidation cascade from VLDL to LDL. Triglyceride-rich VLDL derives small, dense LDL particles which are more susceptible to oxidation[9]. Additionally, increased TRL in postprandial diabetic dyslipidaemia leads to the exchange of TRL-triglyceride for HDL-cholesteryl ester and hence, triglyceride enrichment of HDL via cholesteryl ester transfer protein (CETP). CETP progressively decreases postprandially and limits the efficient removal of cholesterol[10]. Triglycerides in HDL are good substrates for hepatic lipase which leads to the production of small dense HDL particles and enhanced apolipoprotein A-1 (apoA-1) clearance[11].

Given that HTG is related to a plethora of risk factors, the lack of independent association between triglyceride and CVD is expected[12], although two recent Mendelian randomisation studies have shown a causal association between variations in two related genes (LPL and APOA5) and myocardial infarction[13]. This supports that TRL causes CVD, and this probably applies to diabetes.

Hence, diabetic dyslipidaemia relates collectively to hyperglycaemia, insulin resistance, hyperinsulinaemia, abdominal visceral adipose disposition, increased liver fat content, and dysregulated fatty acid metabolism. Diabetic dyslipidaemia may also be exacerbated by chronic kidney disease and by co-prescribed medications, such as thiazide diuretics, non-selective beta-blockers and steroids.

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Measurement and assessment

Triglyceride concentration is commonly measured with a fasting lipid profile. The fasting triglyceride level facilitates the calculation of the LDL cholesterol by the Friedewald equation[14]. Non-fasting triglyceride concentrations are reflective of the postprandial state and can be useful as a simple and practical screening test for HTG. A second non-fasting measurement is recommended if the initial triglyceride is 2.0 mmol/L. Two or more measurements of elevated triglyceride in both postabsorptive and postprandial states are clinically indicative of HTG. Categories of HTG are differentially defined in international guidelines (Table 1).

Non-HDL cholesterol is another appealing method of assessment as it does not attract additional costs. Non-HDL cholesterol (total cholesterol minus HDL-cholesterol) does not rely on a fasting triglyceride concentration and provides a simple amalgamated measure all the atherogenic lipoproteins[15]. ApoB, on the other hand, does not adequately reflect chylomicron remnants and involves additional laboratory expenses. Discordance between non-HDL cholesterol and apoB measures, particularly in patients with type 2 diabetes and HTG, questions its value in assessing risk and defining treatment targets[16]. In the context of statin-treated patients, a meta-analysis has shown that non-HDL cholesterol is superior in its association with risk of future major cardiovascular events compared with LDL cholesterol and apoB[17]. Other TRL markers such as remnant-like particle cholesterol, apoC-III and apoB-48 are expensive and are yet to be clinically established.

The hypertriglyceridaemic waist (HTWC) phenotype has suggested to be useful in assessing glucometabolic risk[18-21], in particular, among patients with a family history of diabetes[22]. The HTWC phenotype is defined by a waist circumference of 90 cm in men and 85 cm in women and triglyceride concentration ≥2.0 mmol/L. Men with the HTWC phenotype have been shown to have a four-fold risk of diabetes compared to those with waist circumference and triglyceride in the normal ranges[23]. There is also a two-fold risk for development of coronary artery disease (CAD) in women[24] and an overall deterioration of cardiometabolic risk[25] in relation to progression of type 2 diabetes[26].
Guidelines and recommendations

Guidelines for managing HTG in diabetes have been published, with lifestyle modifications being first line therapy followed by statins, fibrates, n-3 fatty acids and/or niacin. The national cholesterol education program (NCEP) adult treatment panel (ATP) III guidelines recommend LDL cholesterol as the primary treatment target and non-HDL cholesterol as a secondary target, with the exception of a fasting triglyceride > 5.60 mmol/L, only then, triglyceride becomes the primary target owing to the risk of pancreatitis. A simplification of the NCEP ATP III guideline is presented in Table 2. Regardless of atherosclerotic disease and presence of other cardiovascular risk factors, type 2 diabetes is considered a coronary heart disease risk equivalent by the NCEP ATP III.

The American Diabetes Association (ADA)/American College of Cardiology Foundation consensus statement recommends a non-HDL cholesterol target of 3.40 mmol/L in diabetic patients with no other cardiovascular risk factor and a target of 2.60 mmol/L if there is one or more cardiovascular risk factor such as hypertension, smoking, dyslipidemia and family history of CAD. The LDL cholesterol target is 2.60 and 1.80 mmol/L, respectively or alternatively a 30%-40% reduction from baseline levels. The ADA position statement is the only guideline that provides desirable targets for triglyceride levels for patients with type 2 diabetes: less than 1.70 mmol/L. Both the NCEP ATP and ADA guidelines place emphasis on weight loss and physical activity. A summary of recommended treatment targets is presented in Table 3.

The Scientific Statement from the American Heart Association (AHA) on triglycerides and CVD particularly emphasises the dietary and lifestyle modifications (weight loss, macronutrient distribution and aerobic exercise) for the treatment of elevated triglycerides, presenting a practical algorithm for screening and management. The European Society of Cardiology (ESC) guidelines on diabetes and CVD developed in collaboration with the European Association for the Study of Diabetes (EASD) suggests targeting residual risk in patients with elevated TG (> 2.2 mmol/L), with dietary and lifestyle advice and improved glucose control, post first-line treatment. The Endocrine Society task force agrees with the NCEP ATP III treatment goals and recommends fibrates as first-line therapy for lowering triglycerides in patients at-risk for pancreatitis.

The International Atherosclerosis Society position paper recognises the atherogenicity of VLDL and triglycerides and also favours non-HDL cholesterol as the main target for therapy, optimally at < 3.40 mmol/L. The American College of Cardiology (ACC)/AHA published a new clinical practice guideline for the treatment of elevated blood cholesterol in people at high risk for CVD.
The guidelines do not provide recommendations for specific LDL-cholesterol or non-HDL targets and instead defines four major groups of primary and secondary prevention patients for whom LDL lowering is proven to be most beneficial.[69] Future guidelines to cover the treatment of HTG are proposed. A recent review by Hegele et al.[70] recommended the simplification and redefinition of HTG: < 2.0 mmol/L as normal, 2.0-10.0 mmol/L as mild-to-moderate and > 10.0 mmol/L as severe; with desirable targets of < 1.7 mmol/L for triglycerides, < 2.6 mmol/L for non-HDL cholesterol and < 0.8 g/L for apoB in high-risk patients.

Treatment of HTG depends on its severity, co-existing lipid abnormalities and overall cardiovascular risk. Severe HTG serves as increased risk of pancreatitis and warrants treatment to acutely reduce triglyceride levels. Current therapeutic strategies include diet and lifestyle modification, pharmacotherapy and in rare cases, continuous insulin infusion and apheresis.

### Dietary and lifestyle modifications

Lifestyle interventions are central for controlling hyperglycaemia and HTG in patients with type 2 diabetic patients and impaired fasting glucose. These interventions include weight reduction, altered dietary composition, exercise and regulation of alcohol consumption. In type 2 diabetes, modest (5%-10%) weight loss can lower plasma triglyceride levels by up to 25%.[30,39] and normalise post-prandial triglyceride concentration.[40] Physical activity can aid the maintenance of weight loss achieved through caloric restrictions,[40] although evidence for linking lifestyle modifications and sustained weight is limited.[40]

The recently published look AHEAD trial, an intensive lifestyle intervention in type 2 diabetics, employing weight loss through caloric restriction and increased physical activity did not reduce the rate of cardiovascular events.[45] Whether alterations in dietary composition, such as with the Mediterranean diet, improves clinical outcome in diabetes warrants additional investigation,[46] though the Mediterranean and low-carbohydrate diet can produce a greater reduction in triglyceride levels compared to the restricted-calorie diet in moderately obese individuals.[45,46] Plant sterols have been suggested for lowering TG in individuals with overt HTG.[47] Alcohol abstinence in patients with excessive alcohol intake can markedly lower plasma triglyceride levels[48,49]. Smoking cessation is also imperative.[50]

### Pharmacotherapy

**Statin monotherapy:** Statin therapy is the cornerstone of treatment of dyslipidemia in diabetes. Whilst reaching the LDL cholesterol target in most patients, only modest effects are exerted on triglyceride and HDL cholesterol. Hence, diabetics with HTG often have residual CVD risk[51] in spite of an optimal LDL cholesterol target. Statins may lower plasma triglyceride by increasing lipolysis and the clearance of TRLs, particularly with potent statins such as atorvastatin and rosuvastatin (up to 26% and 28% reduction in plasma triglyceride, respectively).[63-65] Large statin outcome trials have supported its use in reducing coronary events and mortality.[55-58]

All trials to-date have not specifically selected for HTG and in diabetics. However, sub-group analyses have been undertaken showing risk prevention with pravastatin[59], simvastatin[60] and rosvastatin[61] in a subset of patients with high plasma triglyceride, recently reviewed by Maki et al.[62] and supporting statins as first line of therapy. Whilst use of higher doses of statin has been linked to incidence of diabetes[53,65], the benefits of statin therapy for reducing CVD risk and events are outweighed for all diabetic patients with high CVD risk[57,59]. Aminotransferase, creatine kinase, creatinine and glucose should be monitored prior to initiating statins and before initiating a second agent, if required.

**Fibrates and statin-fibrate combination:** Fibrates (gemfibrozil, fenofibrate) act on peroxisome proliferator-activated receptor alpha. Fibrates decreases hepatic VLDL secretion and can confer an up to 30% reduction in plasma triglyceride, TRL remnants and apoB[66]. Five fibrate trials have undertaken secondary analyses in high triglyceride subgroups[67-70]. Of these, two of these trials were in type 2 diabetic patients[71,72] and one had a subset of diabetics[73,74]. Collectively, these trials advocate the use of fibrates in reducing CVD events among patients with

| Table 3  Recommended treatment targets for diabetic dyslipidaemia |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| LDL-cholesterol (mmol/L) | Very high risk | < 1.8 | < 1.8 | < 2.0 | < 1.8 |
| | High risk | < 2.6 | < 2.6 | < 2.0 | < 2.5 |
| Triglycerides (mmol/L) | Very high risk | < 1.7 | < 2.0 | < 1.7 |
| | High risk | > 1.0 | ≥ 1.0 | > 1.0 |
| HDL-cholesterol (mmol/L) | Male | > 1.3 | ≥ 1.0 | > 1.2 |
| | Female | > 1.3 | ≥ 1.0 | > 1.2 |
| Non-HDL cholesterol (mmol/L) | Very high risk | < 2.6 | < 2.6 | < 2.5 | < 2.6 |
| | High risk | < 3.4 | < 2.5 | < 3.3 |
| ApoB (g/L) | Very high risk | < 0.8 | < 0.8 |
| | High risk | < 0.9 | < 1.0 |

NCEP ATP III: Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult treatment panel III); ADA: American diabetes association; NVDA: National vascular disease prevention alliance of australia; LDL: Low density lipoprotein; HDL: High density lipoprotein.
a high triglyceride and low HDL cholesterol levels
Of note, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that fenofibrate decreased progression of diabetic retinopathy, though unrelated to dyslipidemia, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also showed a delay in the onset of eye complications. Meta-analyses suggest that fibrates are useful for treatment of HTG, in diabetic patients. Every 0.10 mmol/L reduction in triglyceride with fibrates confers a 5% reduction in CVD event, although no benefits were found on cardiovascular mortality.

Niacin and statin-niacin combination: Niacin can decrease plasma triglyceride by 30% via the inhibition of hepatic diacylglycerol acyltransferase-2 (DGAT-2), a rate-limiting enzyme of triglyceride synthesis. Despite the earlier studies showing reduced mortality and regression of subclinical atherosclerosis, the current use of niacin has been challenged by two large recent clinical trials which have failed to show significant benefits on CVD events in spite of positive changes in lipid parameters. Both trials have limitations. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) study was underpowered and confounded by the higher statin and/or ezetimibe doses to match LDL cholesterol between groups. The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study is the largest extend-release niacin trial to-date combined with laropiprant, a prostaglandin D2 inhibitor. Despite no significant benefit on primary CVD endpoints, a recent sub-analysis in patients with both high triglyceride (>2.24 mmol/L) and low HDL cholesterol (<0.85 mmol/L) showed a trend towards benefit with niacin, although not reaching statistical significance (HR = 0.74, 95% CI=0.57-0.96). Of note, the lack of potential benefit or harm in the HPS2-THRIVE study may not necessarily be due to niacin, but potentially to laropiprant. The safety of niacin use in type 2 diabetes has previously been questioned owing to impairment in glycemic control and insulin sensitivity. However, two prospective trials have shown that the effect of niacin on glycemic control is minimal in a majority of patients with stable diabetes and with no changes in low-dose (1 g/d) niacin.

Ezetimibe and statin-ezetimibe combination: Ezetimibe inhibits intestinal cholesterol absorption and primarily lowers LDL cholesterol via the Niemann-Pick C1-Like 1 protein. Ezetimibe has minimal effects in lowering plasma fasting triglyceride (8%) and postprandial triglyceride and apoB-48 concentrations were lowered in type 2 diabetic patients. However, intensive lipid lowering with a statin plus ezetimibe may not consistently lower subclinical carotid atherosclerosis in type 2 diabetes, although progression of carotid artery intima-media thickness was inhibited with the combination. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study that is currently entering completion will endeavor to provide definitive evidence for the role of ezetimibe in high risk subjects on optimal statin therapy.

n-3 fatty acid and statin-n-3 fatty acid combination: Supplemental n-3 polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are well known to improve HTG. However, recent clinical outcome trials with have failed to show significant CVD benefits in high risk subjects including diabetics. Both trials were undertaken against a background of optimal therapy, including statins. Also, patients were not selected for elevated plasma triglyceride levels. Pure EPA (1800 mg/d), added to statin therapy, showed promise in the Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) with major coronary events reduced by 19% (P=0.011) in hypercholesterolaemic patients. Two 12-wk EPA (AMR101) intervention trials in patients with very high and persistent baseline triglyceride observed significant reductions in triglyceride levels. The greatest decrease was seen in the highest triglyceride tertile where there was a 31% reduction compared to placebo on 4 g/d of AMR101. The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) is in progress and will endeavor to obtain the CVD outcome data with AMR101 4 g/d in high-risk patients with HTG and at-target LDL cholesterol on statin therapy. There are also recent data suggesting an increased risk of prostate cancer with high dietary intake of n-3 PUFAs. Hence, caution is warranted when recommending long-term intake.

Incretin-based therapy: Incretins, such as glucagon-like peptide-1 (GLP-1), are insulinotropic, gut-derived hormones secreted in response to diet. GLP-1 receptor analogs such as tiraglutide and exenatide, delay gastric emptying and this parallels the reduction in postprandial triglyceride response. This mechanism may ameliorate impaired TRL metabolism in type 2 diabetes. By increasing plasma concentrations of GLP-1, Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, saxagliptin and alogliptin, can improve insulin sensitivity, β-cell function and postprandial glycaemia and lipaemia. These agents could potentially prevent CVD events, independent of changes in ischaemic events, though the rate of heart failure increased significantly. Similarly, a trial in type 2 diabetic patients post-acute coronary syndrome with alogliptin did not improve cardiovascular event rates compared with placebo. Further investigation is required to clarify...
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Insulin infusion, apheresis and gene replacement therapy

In severe cases of diabetic HTG and poorly controlled diabetes, continuous intravenous insulin infusion appears to be beneficial in restoring serum glucose and triglyceride levels. Most of these patients will have an underlying genetic defect in TRL metabolism. A recent study in a group of 15 diabetics with a median triglyceride concentration of 26.23 mmol/L at admission had their triglyceride levels corrected to a median of 5.75 mmol/L at discharge with an average of 48 h of continuous insulin infusion.[19] For prevention of recurrent severe HTG in susceptible patients, counselling on medication adherence and long-term diet and lifestyle medications should be considered.[20]

In extremely severe HTG and drug refractory HTG, plasma apheresis may be required,[21,22] particularly with severe chylomicronaemia complicated by acute pancreatitis. A single session of apheresis can dramatically lower excess triglyceride levels, 65.8% reduction in 2 h.[12,13] This method of triglyceride lowering is only indicated in medical emergencies owing to high costs and limited availability.[22] Further study is required to clarify the role of plasma exchange in the treatment of hyperlipidaemic pancreatitis.

In patients genetically diagnosed with familial LPL deficiency, Glybera® (alipogene tiparvovec; Amsterdam Molecular Therapeutics, Amsterdam, the Netherlands) is the first approved gene-replacement therapy.[12,17] Glybera® has only been studied in 27 patients, in whom the agent was well tolerated and with plasma triglyceride concentration significantly lowered with reduced rates of acute pancreatitis.[20] Long-term follow-up data and cost-effectiveness studies is warranted.[10,17].

CONCLUSION

HTG is common in type 2 diabetes. HTG associates with a spectrum of cardiometabolic risk factors and increases CVD risk in type 2 diabetes. Dietary and lifestyle modification involving weight loss and exercise is fundamental to the management of HTG. Improved glycaemic control with use of metformin, DPP-4 inhibitors and insulin can also improve HTG. The expression of HTG in context of diabetes may depend on co-existing monogenic and/or multigenic disorders of lipid metabolism, such as familial combined hyperlipidaemia, familial hypertriglyceridaemia and type II hyperlipoproteinaemia. Statins are the first-line of lipid-lowering therapy to target LDL cholesterol and triglycerides. Current evidence supports the use of fenofibrate in type 2 diabetes, with high triglyceride and low HDL, but also to prevent and treat diabetic retinopathy. More evidence is required from CVD outcome trials for the other add-on options, some of which are currently underway. Several new therapies with potential applications for treating HTG are DGAT inhibitors, microsomal triglyceride transfer protein inhibitors, and apoC-III antisense oligonucleotides. These will agents will require to be tested for efficacy, safety and cost-effectiveness in future clinical trials.

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