

Hypertriglyceridaemia: Aetiology, Complications and Management

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Abstract

The bulk of plasma triglycerides are carried by chylomicrons in the fed and very low-density lipoproteins in the fasted state. These triglyceride-rich lipoproteins are metabolised to remnant lipoproteins by lipoprotein lipase (LPL). Hypertriglyceridaemia results if triglyceride-rich lipoproteins accumulate either due to defective clearance, overproduction or a combination of both mechanisms. Genetic and environmental factors interact in the genesis of hypertriglyceridaemia but occasionally a single factor may be dominant. At a molecular level the most common cause of severe primary hypertriglyceridaemia is loss of function mutations in both alleles of LPL. The most common environmental contributors include diabetes, diet, alcohol and medications (including oestrogen, steroids, retinoids and protease inhibitors). Severe hypertriglyceridaemia can trigger acute pancreatitis while mild to moderate hypertriglyceridaemia is an independent cardiovascular risk factor. Treatment strategies are determined by the severity and aetiology of hypertriglyceridaemia as well as the patient's cardiovascular risk profile. General strategies include lifestyle modifications with restriction of dietary fat intake, cessation of alcohol intake and increased exercise. Contributing metabolic disorders should be controlled and aggravating medications withdrawn or reduced where possible. Moderate hypertriglyceridaemia may be treated with high doses of omega-3 fatty acids (4 g/day), fibrates, niacin or statins. Fibrates are the agents of choice in severe hypertriglyceridaemia.

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Introduction

Clinicians mostly do not treat all members of the 'lipid family' with the equal respect they deserve. Triglycerides often find themselves in the role of the neglected and ignored stepsister while all attention is lavished on the 'evil' sister, cholesterol. Triglyceride metabolism is, however, ignored at the clinician's peril, as severe hypertriglyceridaemia can trigger potentially fatal acute pancreatitis. Less marked elevations of plasma triglycerides (TG) may also be deleterious by independently raising the risk for cardiovascular disease. Partially metabolised triglyceride-rich lipoproteins (TGRL) (remnants) are among the most atherogenic lipoproteins. In addition, hypertriglyceridaemia often associates with other cardiovascular risk factors such as obesity, Type II diabetes, inflammation and a pro-thrombotic state.^{1,2} This article reviews hypertriglyceridaemia and focuses on severe hypertriglyceridaemia (TG > 10–15 mmol/L) and recent advances in the genetics of hypertriglyceridaemia.

Being members of the 'lipid family', both cholesterol and TGs are insoluble in plasma and are packaged in lipoproteins for plasma export. Although lipoproteins may vary markedly in size and composition (e.g. from triglyceride-rich to cholesterol-rich), no lipoprotein exclusively transports a single lipid type. Triglyceride and cholesterol metabolism are thus intertwined and should not be considered separately, but viewed from the perspective of lipoprotein metabolism.

Triglyceride-rich lipoprotein metabolism

Plasma TGs derive from two main sources: exogenous (uptake from dietary fat) and endogenous (hepatic synthesis). Following digestion and absorption, dietary fat is packaged into chylomicrons, which enter the circulation via the lymphatic system. Excess chylomicrons (hyperchylomiconnaemia) cause turbid or even milky (lipaemia) plasma. Following a meal, up to 90% of plasma TGs are found in chylomicrons. The liver exports TGs (from endogenous synthesis or derived from uptake of chylomicrons) mainly as very low-density lipoproteins (VLDLs). In healthy individuals there should be no circulating chylomicrons following a 12-hour fast, and the bulk of TGs is found in VLDLs. VLDL particles may be subdivided into large, triglyceride-rich VLDL1 and smaller, less triglyceride-enriched VLDL2. Although triglyceride is the major lipid constituent of chylomicrons and VLDL, both these lipoproteins do contain cholesterol, and accumulation of TGRL may elevate the total cholesterol very substantially.

Chylomicrons are normally rapidly cleared from the circulation following partial hydrolysis of their triglyceride content by lipoprotein lipase (LPL), an enzyme found mainly in the capillaries of adipose and muscle tissue. The resulting chylomicron remnants are cleared from the circulation by hepatic uptake via apolipoproteinE (apoE) mediated binding. The triglyceride content of VLDL is also partially hydrolysed by LPL. The resultant VLDL-remnants can either be hepatically cleared via apoE or undergo further modification to form low-density lipoproteins (LDL).

LPL activity is regulated at multiple levels. At the genetic level, peroxisome proliferator-activated receptor γ (PPAR γ) upregulates adipose tissue LPL, while liver LPL is upregulated by PPAR α and liver X receptor (LXR). Exercising increases skeletal muscle LPL expression. The enzymatic activity of LPL is increased by apolipoproteinCII (apoCII) (essential cofactor) and apolipoproteinAV (apoAV), while apolipoproteinCIII (apoCIII) inhibits LPL.³ Recent research has led to the identification of multiple other proteins involved in the lipolytic process. These include two members of the angiopoetin-like protein family (ANGPLT), namely ANGPLT3 and ANGPLT4. ANGPLT3 inhibits LPL catalytic activity in the presence of substrate while ANGPLT4 inhibits LPL activity by promoting the conversion of active LPL dimers into inactive monomers.⁴ Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPI-HBP1) is a high-affinity anchor for LPL.⁴

Increased plasma TGRL can therefore mechanistically result from increased production (increased hepatic synthesis, high-fat diets) or reduced clearance (mainly decreased LPL activity or occasionally dysfunctional apoE). In many patients hypertriglyceridaemia is multifactorial with both mechanisms contributing to accumulation of TGRL. Plasma TGs can fluctuate widely and rapidly. Dietary indiscretions (fatty meals) or metabolic stressors (e.g. uncontrolled diabetes mellitus) can rapidly raise plasma TGs, converting moderate hypertriglyceridaemia into severe hypertriglyceridaemia (see Box 1 for an example).

Box 1: Triglyceride response to a fatty meal

Assumptions:

- Complete digestion and absorption of dietary fat
- Clearance is zero (e.g. LPL deficiency)
- Ignore VLDL production
- Fasting triglycerides are 4 mmol/L
- Plasma volume of 3 L
- 1 mol triglycerides \approx 885 g

Take-away meal: Triglyceride content

- | | |
|--|------|
| • Double hamburger with cheese | 42 g |
| • French fries (large) | 30 g |
| • Chocolate triple thick shake (supersize) | 28 g |

Total meal is 100 g of triglyceride \rightarrow 113 mmol

Change in triglycerides: 113 mmol of triglyceride / 3 L plasma volume: 37.66 mmol/L

Triglycerides can rise from 4 mmol/L to over 40 mmol/L

Cholesterol consumed: 255 mg (\approx 0.7 mmol)

Classification

There is no uniform classification system for hypertriglyceridaemia. A frequently used classification is: primary hypertriglyceridaemia (molecular aberration of lipoprotein metabolism, no other metabolic abnormalities) or secondary hypertriglyceridaemia due to metabolic precipitants. This classification is somewhat simplistic, as many patients with secondary hypertriglyceridaemia are likely to have 'susceptibility genes', as equivalent metabolic stressors provoke very variable individual triglyceride responses (see below). In most patients, including those with primary hypertriglyceridaemia, the molecular cause remains unknown.⁵

Hypertriglyceridaemia can also simply be classified according to the degree of triglyceride elevation: TG < 1.7 mmol/L is regarded as normal (2.3 mmol/L in some classifications), TG < 5.0 mmol/L is mild hypertriglyceridaemia, TG 5–10 mmol/L is moderately severe hypertriglyceridaemia and TG > 10 mmol/L is very severe hypertriglyceridaemia.

The Fredrickson classification of hyperlipidaemia⁶ is also widely used, but often poorly understood – leading to much confusion. Fredrickson simply grouped similar agarose electrophoresis patterns and labelled them with Roman numerals. The intention was not to create an aetiological classification but to group electrophoretic patterns. Further details regarding the Fredrickson classification can be found in Table I. As our knowledge of lipoprotein metabolism and its disorders grew, some electrophoretic patterns were found to be characteristic of molecularly defined disorders (e.g. Type I pattern \rightarrow LPL deficiency), while other patterns have no specific molecular correlates (e.g. Type IIa). Yet other molecularly defined disorders have variable patterns such as dysbetalipoproteinaemia (apoE mutations) – the Type III pattern is characteristic but the electrophoresis may also variably be classified as a Type IIb, Type IV or even Type V pattern. The conflation of electrophoretic patterns and metabolic and genetic diagnoses are responsible for much of the confusion surrounding the Fredrickson classification.

Genetics of hypertriglyceridaemia

Monogenic disorders

Homozygous mutations in LPL cause severe primary hypertriglyceridaemia from birth. The clinical phenotype is characterised by eruptive xanthomata, hepatosplenomegaly and lipaemic plasma. Pancreatitis may occur in infancy. The agarose electrophoresis is characterised by an accumulation of chylomicrons (Fredrickson Type I pattern), and LPL deficiency is thus often also known as Type I hyperlipidaemia. LPL deficiency is a rare condition, but in South Africa there are founder mutations in the Indian and Afrikaner populations. Cases have, however, been reported from all population groups.⁷ As this is a recessive disorder, there is usually no family history of hypertriglyceridaemia. LPL deficiency is a potentially fatal disorder and all children with hypertriglyceridaemia should be referred for urgent specialist evaluation. Establishing the correct diagnosis is essential in planning management. The University of Cape Town's Lipid Laboratory can estimate lipolytic activity and screen for the common founder mutations in LPL. Currently, the only available management is dietary, with severe restriction of dietary TGs. The implementation of a very low-fat diet, while still providing adequate calories and essential fatty acids for growth and nutrition, requires advice from a dietitian specialised in lipid disorders and is especially challenging in infants. Lipid-lowering drugs are ineffective but are still frequently prescribed inappropriately, especially when an exact diagnosis has not been made. Gene therapy may be a therapeutic option in the future. Early Phase I human trials using adeno-associated virus as a vector to express an LPL allele with enhanced catalytic activity in muscles have been completed in humans with encouraging short-term results.^{8,9}

Although heterozygous mutations in LPL reduce measured lipolytic activity, most carriers have normal lipid phenotypes. In situations of metabolic stress or in the presence of mutations or polymorphisms in other genes involved in lipid metabolism, hypertriglyceridaemia, usually of mild to moderate severity, may manifest. The Fredrickson pattern is variable, with Type IV and Type V patterns being the most common. In a

Table I: Agarose gel electrophoretic patterns according to Fredrickson's classification

| Pattern | Predominant stain/band | Lipoprotein predominantly increased | Comments |
|-----------|-----------------------------|-------------------------------------|---|
| Type I | Origin | Chylomicrons | LPL + apo CII deficiency |
| Type II A | Beta-band | LDL | TG > 2.3 mmol/L distinguishes IIA from IIB |
| Type II B | Beta-band and pre-beta-band | LDL and some VLDL | |
| Type III | Broad-beta band | Remnant particles | Broad beta describes uniform staining from beta to pre-beta |
| Type IV | Pre-beta band | VLDL | |
| Type V | Origin + pre-beta band | Chylomicrons + VLDL | |

Legend: Lipoproteins migrate as follows from origin: origin (chylomicrons), beta-band (LDL), pre-beta band (VLDL) and alpha-band (HDL). The Fredrickson's classification does not comment on HDL staining.

recent report, the entire LPL, apoCII and apoAV genes were sequenced in 110 non-diabetic patients with TG >10 mmol/L (Fredrickson Type V pattern) on at least two occasions. Known disease-causing mutations in LPL were identified in seven patients, indicating that heterozygous LPL mutations may be an important contributory factor in some patients with adult-onset severe hypertriglyceridaemia.⁵

ApoCII activates LPL, and homozygous apoCII deficiency is phenotypically indistinguishable from LPL deficiency.¹⁰⁻¹³ Fresh frozen plasma contains apoCII and may be infused at times of severe hypertriglyceridaemia or when pancreatitis has developed. To the best of my knowledge, there are no known cases of apoCII deficiency in South Africa.

Dysbetalipoproteinaemia (also known as Fredrickson Type III hyperlipidaemia or remnant removal disease) is characterised by the accumulation of remnants of TGRL. The most common molecular cause is homozygosity for the receptor-binding defective ϵ 2 isoform of apoE.¹⁴ Phenotypic expression of the disease usually requires the presence of additional metabolic stressors such as diabetes, obesity or hypothyroidism. Patients typically present with severe mixed hyperlipidaemia (molar ratio of total cholesterol to plasma TGs approximates 2 : 1.) and high levels of apoE.¹⁵ Severe hypertriglyceridaemia, however, is not infrequent and high levels of apoE2 have been shown to impair lipolytic activity mainly by displacing or masking apoCII.¹⁶ Polymorphisms in apoAV may also explain why hypertriglyceridaemia is more severe in some dysbetalipoproteinaemic patients.¹⁷

More recently, mutations in several novel genes have been identified as causes of severe hypertriglyceridaemia. Some of these genes are listed below.

- ApoAV is encoded on chromosome 11, and homozygosity for rare truncating mutations in ApoAV (Q139X) may cause hyperchylomicronaemia.^{18,19} In the majority of patients, hypertriglyceridaemia was first documented in adulthood. The molecular mechanism of hypertriglyceridaemia in apoAV deficiency is not well understood, but may include failure to inhibit hepatic VLDL-triglyceride production as well as impaired lipolysis due to LPL not having adequate access to the lipoprotein core in the absence of functional apoAV.²⁰ The genotype is not fully penetrant and not all mutation carriers have hypertriglyceridaemia.
- Lipase maturation factor (LMF 1) is involved in the endoplasmic maturation of LPL and hepatic lipase peptides. Homozygous nonsense mutations in LMF 1 have been identified in a few patients with severe hypertriglyceridaemia.^{21,22}
- GPI-HBP1 is an endothelial cell surface protein found in the capillaries of organs where lipolysis occurs. GPI-HBP1 likely provides a platform for lipolysis to occur by anchoring LPL, TGRL and apoAV-phospholipid disks.²³ Homozygous mutations in this

protein have been identified in several patients with severe hypertriglyceridaemia in whom other known genetic causes of hypertriglyceridaemia had previously been excluded.^{24,25}

The term familial hypertriglyceridaemia (FHTG) is often used to describe inheritance of a lipid phenotype characterised by an isolated increase in VLDL (Fredrickson Type IV pattern) – often with concomitantly low high-density lipoprotein cholesterol (HDL). Most patients with FHTG have moderate elevations in TGs in the 3 to 10 mmol/L range. The disorder is familial but the molecular basis is unknown and is likely polygenic in many patients (see below).²⁶ FHTG is often found in association with other cardiovascular risk factors such as obesity, insulin resistance, hypertension and hyperuricaemia and overlaps with the metabolic syndrome. In future, the clinically described entity of FHTG is likely to be progressively replaced by a multiplicity of molecularly diverse disorders with similar lipid phenotypes.

Familial combined hyperlipidaemia (FCH) is inherited in an autosomal dominant fashion with variable penetrance.²⁷ The population frequency is reported to be 2 to 5%, making it the most common genetic dyslipidaemia. The lipid phenotype may vary widely within families, ranging from phenotypes dominated by increases in VLDL to those in which increased LDL is the major abnormality. HDL is often low and apoB levels are usually high. Atherosclerotic risk is high. Severe hypertriglyceridaemia is uncommon in FCH and TGs are usually less than 5 mmol/L. The diagnosis is clinical and requires knowledge of the family history and lipid values in family members.²⁸ The genetics of FCH have not been fully elucidated and it is likely that FCH is a genetically heterogeneous disorder. FCH has been linked to the APOAI/CI/III/IV/AV gene cluster,²⁹ but the strongest candidate gene currently is Upstream Stimulatory Factor 1 (USF1), which encodes a transcription factor that modulates the expression of many genes involved in lipid and glucose homeostasis.^{30,31} Mutations in USF 1 may result in defective insulin-mediated induction of USF 1 and subsequently reduced expression of target genes.³²

Polygenic hypertriglyceridaemia

In the majority of patients, the genetic basis of hypertriglyceridaemia remains unknown. Genome-wide association studies (GWAS) are improving our understanding of the genetic architecture of complex diseases. Single nucleotide polymorphisms (SNPs) at many loci have been linked to triglyceride metabolism in healthy controls, although the absolute effect on triglyceride levels is generally very small.³³ In a recent study of hypertriglyceridaemic patients, previously identified SNPs were found to cluster according to Fredrickson phenotype. SNPs in ApoAV, Transducin-beta-like-2 (TBL2 – function unknown) and homologue of Drosophila Tribbles 1 (TR1B1 – function unknown) significantly associated with Fredrickson IIB, III, IV and V phenotypes. SNPs in other

genes, including ANGPTL3 and apoE, associated with selected phenotypes only.¹⁷ Taken together, these genotypes explained about 20% of variation in triglyceride concentration. Direct sequencing of some of these genes linked to hypertriglyceridaemia by GWAS but of as yet unknown function may identify rare loss of function mutations and provide a monogenic explanation for some patients with severe hypertriglyceridaemia. Clearly, our understanding of triglyceride metabolism is not yet complete. A plausible genetic model for hypertriglyceridaemia is that rare loss of function mutations with large effect sizes (e.g. LPL mutations) are found in a small group of patients, usually with extreme phenotypes. In most other patients, hypertriglyceridaemia may result from accumulating multiple common alleles that each individually only have a minor effect on triglyceride metabolism. Such a genetic background would not necessarily lead to hypertriglyceridaemia in itself, but would markedly increase the likelihood of hypertriglyceridaemia developing with environmental or metabolic stressors.

Secondary causes of hypertriglyceridaemia

Metabolic stressors or exposure to certain drugs may lead to hypertriglyceridaemia in some but not all patients. Those that develop hypertriglyceridaemia are likely genetically predisposed (see above), although we do not fully understand the interactions between the

genome and the environment as yet. In clinical practice, diabetes is the most common metabolic stressor. In susceptible individuals certain drugs can also trigger hypertriglyceridaemia. Further information on secondary causes of hypertriglyceridaemia can be found in Tables II and III.

Clinical manifestations

Physical signs

Eruptive xanthomata (Figure 1) are cutaneous manifestations of severe hypertriglyceridaemia regardless of aetiology. They are small yellow papules often on an erythematous base. They tend to occur in crops



Figure 1: Eruptive xanthomata

Legend: Eruptive xanthomata occur in hyperchylomicronaemia and are usually asymptomatic. They indicate severe hypertriglyceridaemia and a high risk of acute pancreatitis. Eruptive xanthomata tend to occur in crops on the elbows, knees, thighs, buttocks and trunk.

Table II: Secondary causes of hypertriglyceridaemia

| Condition | Comments |
|----------------------|--|
| Obesity | Mild hypertriglyceridaemia frequent in metabolic syndrome Increased waist circumference highly predictive of mild hypertriglyceridaemia |
| Diet | See Box 1 for the effect of dietary fat in patients with lipolytic defects |
| Diabetes mellitus | Most common secondary cause in our experience Controlling diabetes mellitus often lowers TGs substantially |
| Alcohol | Alcohol can increase VLDL synthesis Pancreatitis risk from alcohol and TGs |
| Renal disease | Mild hypertriglyceridaemia frequently seen in uremia |
| Pregnancy | Increased VLDL production may expose lipolytic effect Pancreatitis has high fatality rate in pregnancy |
| Paraproteins | May inhibit lipolytic proteins |
| Autoimmune disorders | Systemic lupus erythematosus (SLE) may generate auto-antibodies to LPL |
| Other disorders | Glycogen storage disorders may have mild hypertriglyceridaemia |

Table III: Drugs associated with hypertriglyceridaemia

| Drug | Comments |
|--------------------------|--|
| Oestrogen | Oral oestrogen elevate TGs more than transdermal preparations May cause marked hypertriglyceridaemia in susceptible individuals |
| Corticosteroids | Variable lipid phenotypes, may cause predominant hypercholesterolaemia |
| Isotretinoin | Severe hypertriglyceridaemia possible Check baseline TGs before therapy and once on treatment |
| Antiretrovirals | Protease inhibitors, especially ritonavir, most often implicated Hypertriglyceridaemia often severe |
| Cholestyramine | May aggravate hypertriglyceridaemia Avoid prescription when TGs are increased |
| Immunosuppressant drugs | Sirolimus frequently implicated |
| Beta blockers, thiazides | Increase in TGs usually minor |
| Atypical antipsychotics | Weight gain, insulin resistance and diabetes commonly accompany rise in TGs |



Figure 2: Lipaemic plasma

Legend: Plasma that has stood overnight at 4 °C appears milky and turbid. Chylomicrons have floated to the top and have formed a creamy layer.



Figure 3: Tuberoeruptive xanthomata

Legend: Tuberoeruptive xanthomata may occur with long-standing hyperchylomicronaemia but are most commonly seen in severe mixed hyperlipidaemia such as dysbetalipoproteinaemia.

and are most commonly found on the extensor surfaces of elbows and knees, the buttocks, thighs and trunk. Eruptive xanthomata resolve over several weeks to months once the TGs have been controlled. The retina may appear pink with 'milky' vessels in severely hypertriglyceridaemic patients – this is known as lipaemia retinalis. Plasma that has been left standing overnight at 4 °C (Figure 2) appears turbid (VLDL excess) with a creamy layer on top (chylomicron excess). In long-standing, severe hypertriglyceridaemia or in patients with dysbetalipoproteinaemia, eruptive xanthomata may coalesce to form tuberoeruptive xanthomata (Figure 3).

Pancreatitis

Severe hypertriglyceridaemia is a well-established trigger for acute pancreatitis.^{34,35} Accurate measurement of serum amylase is challenging in the presence of lipaemia, and pancreatitis may be falsely ruled out when the amylase is not elevated.³⁶ Pancreatitis rarely occurs when TGs are under 10 to 15 mmol/L. In many patients, TGs are only measured several days after the onset of pancreatitis and a prolonged period of nil per mouth. In such situations, hypertriglyceridaemia may have improved markedly and may then be erroneously excluded as a possible cause of pancreatitis. As illustrated in Box 1, TGs may vary markedly and rapidly and a patient with only moderately elevated TGs may develop pancreatitis following a short period of dietary indiscretion. However, there are also patients with persistently marked hypertriglyceridaemia who never develop pancreatitis. Pancreatitis is therefore an unpredictable complication of hypertriglyceridaemia that strikes unexpectedly. The pathophysiology of hypertriglyceridaemic pancreatitis remains imperfectly understood. Intravascular triglyceride hydrolysis by pancreatic lipase with subsequent release of free fatty acids is the most commonly postulated pathophysiological mechanism.³⁵

The treatment of hypertriglyceridaemic pancreatitis does not differ fundamentally from that of pancreatitis of any other cause. Metabolic disturbances should be sought and controlled. Should total parenteral nutrition be necessary, it is important to avoid excess fat supply (e.g. Intralipid or Lipovenous). Subsequently, severe restriction of dietary fat intake is necessary. Apheresis will rapidly, but transiently, lower plasma TGs.^{34,37} There is no evidence that patients treated with apheresis recover more rapidly or have fewer pancreatitis-associated complications, and this expensive treatment modality cannot be routinely recommended.³⁸

Atherosclerosis

Moderate hypertriglyceridaemia is an independent risk factor for atherosclerosis, and TGs have been incorporated in the PROCAM cardiovascular risk-prediction algorithm.^{39,40} Subsequent studies have confirmed these findings⁴¹ and also suggest that non-fasting TGs are a better predictor of risk than fasting TGs.^{42,43} Non-fasting TGs probably predict risk better than fasting TGs, as they, at least in part, reflect the duration of postprandial lipaemia and the rapidity with which atherogenic remnant lipoproteins are cleared. It is, however, almost impossible to precisely determine the contribution that moderate hypertriglyceridaemia makes to cardiovascular risk independently due to the multiple metabolic abnormalities (diabetes, obesity, hypertension), secondary lipid changes (low HDLC, small dense LDLC) and pro-inflammatory and pro-thrombotic changes seen in association with hypertriglyceridaemia.

Treatment of hypertriglyceridaemia

Treatment to reduce cardiovascular risk

The evidence base for specifically targeting mild to moderate hypertriglyceridaemia beyond control of other risk factors, including LDLC, in patients at high cardiovascular risk is limited. Most clinical outcome studies have focused on LDLC reduction as the primary target and have used statins that have modest triglyceride-lowering properties. The strongest evidence of benefit for a non-LDLC-centred strategy comes from studies in which fibrates were given to patients with well-defined lipid phenotypes: moderate hypertriglyceridaemia with low HDLC.^{44,45} The ACCORD study is currently investigating the use of a statin versus a statin + fibrate strategy in high-risk Type II diabetes mellitus. There are no well-established triglyceride target values and treatment selection currently requires careful analysis of the lipid phenotype as well as a lifestyle review and clinical judgement. A fuller discussion of these issues can be found in Yuan et al⁴⁶ and Brunzell.⁴⁷

Treatment of severe hypertriglyceridaemia

The primary goal is to lower TGs rapidly to reduce the risk of acute pancreatitis. Cardiovascular risk reduction is of secondary concern, but becomes increasingly relevant once the pancreatitis risk has been dealt with.

Non-drug treatment

Secondary factors that may be contributing to hypertriglyceridaemia need to be actively sought out and treated (Tables II and III). In clinical practice, the most common problem is either undiagnosed or uncontrolled diabetes. Admission to hospital is often helpful to rapidly control hyperglycaemia. If drugs are contributing significantly to hypertriglyceridaemia, treatment should be switched or discontinued if the patient's clinical condition allows this and there are effective alternative treatment options. In the longer term, weight loss and exercise contribute to improved metabolic control.

Marked restriction of dietary fat intake is essential when managing severe hypertriglyceridaemia (see Box 1). At Groote Schuur Hospital we prescribe an extremely low-fat diet (less than 10 g of fat a day [g/d]) for about three days when patients with severe hypertriglyceridaemia are initially referred. This diet is colloquially known as the 'Rescue diet' and rapidly lowers TGs (Box 2). It is not nutritionally adequate in the long term and the long-term dietary goal is to restrict total fat intake to around 20–30 g/d. This is not always easy to achieve and requires dedication from the patient (reading labels, assessing portion sizes, calculating expenditure on 'fat budget') and the assistance of a dietitian with specific experience in the management of severe hypertriglyceridaemia. Dietary fat restriction needs constant re-enforcement and spiking triglyceride values on follow-up are often related to dietary indiscretions. Alcohol should ideally be avoided completely or intake should be reduced drastically.

Omega-3 fatty acids (fish oils) lower TGs by reducing the synthesis and secretion of VLDL⁴⁸ and by increasing expression of LPL in adipose tissue.⁴⁹ Pharmacological doses of around 4 g/d of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are required for maximal effect. Fish oils are most effective in moderately severe hypertriglyceridaemia and may lower TGs by up to 40% in some patients.^{50,51} Fish oils are ineffective in LPL deficiency and related disorders and may worsen hypertriglyceridaemia if prescribed inappropriately. Preparations of

Box 2: 'Rescue diet' for severe hypertriglyceridaemia

| Daily menu | | | |
|---|-----------|-------------------------------|-----|
| <i>Breakfast</i> (1.7 g) | | | |
| 125 ml orange juice | 0.3 | 1 banana | 0.4 |
| 3/4 cup Rice Crispies | 0.0 | 250 ml skim milk | 0.5 |
| 1 slice white bread | 0.5 | 15 ml honey | 0.0 |
| <i>Lunch</i> (1.6 or 2.4 g) | | | |
| 2 med potatoes (2 bread) | 0.2 (1.0) | 60 g fat-free cottage cheese | 0.9 |
| Salad (lettuce, cucumber, tomato ...) | 0.5 | | |
| <i>Supper</i> (2.4 or 3.6 g) | | | |
| 375 ml white rice (pasta) | 0.6 (1.6) | 125 ml tomato/onion mix | 0.4 |
| 125 ml lentils | 0.4 | Vegetables (carrot, broccoli) | 0.4 |
| Fruit (3 slices of pineapple) | 0.6 | | |
| <i>Snacks</i> (1.3 g) | | | |
| Apple, morning | 0.6 | Pear, afternoon | 0.7 |
| Other supplements | | | |
| No diabetes | | Diabetes | |
| <i>Beverages</i> | | | |
| Carbonated drinks including colas | | Dietetic cold drinks | |
| Lucozade | | Low calorie Lecol, Oros | |
| Fruit juice, including orange, apricot, apple, grape | | | |
| <i>Sweets</i> | | | |
| Boiled sweets | | Artificially sweetened | |
| Jelly babies, wine gums, marshmallows | | | |
| Peppermints, vitamin C sweets | | | |
| <i>Spreads</i> | | | |
| Sugar syrup, honey, molasses | | Dietetic jams | |
| Jam, marmalade | | | |
| <i>Desserts</i> | | | |
| Jelly, canned fruit, custard made with skim milk (0.4 g fat/250 ml) | | Artificially sweetened jelly | |
| Meringues without cream | | Low-calorie canned fruit | |
| Dried fruit | | | |

Fats are often poorly declared on food labels, and recipes may variably include fats and are best not trusted.

Medium-chain TGs, although not necessarily destined to chylomicrons, could still undergo chain elongation and enter chylomicrons and thus aggravate hypertriglyceridaemia. Intravenous lipid supplementation (Intralipid, Lipovenous) is contra-indicated. Diet developed at the Lipid Clinic with the assistance of Cecily Fuller (RD).

sufficient strength and purity are not always readily available in South Africa.

Drug treatment

Monotherapy is preferred initially, but many patients do ultimately require combination lipid-lowering therapy to achieve optimal control. Combination therapy should be prescribed with due consideration of contra-indications and with careful monitoring. The second drug is selected based on the predominant remaining lipid abnormality once a steady state has been reached on monotherapy.

Fibric acid derivatives include bezafibrate, fenofibrate and gemfibrozil. These drugs influence lipid metabolism at multiple points by binding to PPAR- α in the liver and modulating transcription of many genes involved in lipoprotein metabolism. Fibrates are central to the management of severe hypertriglyceridaemia and are the drugs of first choice. Fibrates

lower TGs, increase HDLC and may either lower or in some cases raise LDLC. The latter situation often arises in hypertriglyceridaemic subjects when the more efficient lipolytic processing brought about by fibrates results in increased LDL production. Fibrates are excreted renally and doses need to be adjusted to renal function. Fibrate therapy is often accompanied by a modest (\pm 10%) rise in creatinine but this is not due to a lowered glomerular filtration rate and reverses on discontinuation.^{52,53}

Niacin may lower TGs by up to 45% but is most frequently prescribed in mild to moderate hypertriglyceridaemia. There are multiple other beneficial effects on the lipid profile (LDLC reduction, HDLC increase, Lp(a) reduction) and niacin prescription is generally targeted at cardiovascular risk reduction rather than the management of severe hypertriglyceridaemia. Flushing and pruritus limit the acceptability to patients but newer preparations with reduced flushing due to slow-release formulation and the addition of a prostaglandin D2 receptor 1 blocker should be available in South Africa soon.⁵⁴

Statins do lower TGs but are not effective in severe hypertriglyceridaemia. In the experience of the Groote Schuur Hospital's lipid clinic, statins continue to be frequently prescribed for severe hypertriglyceridaemia with predictably disappointing results. Statins may be used as monotherapy in mild to moderate hypertriglyceridaemia or in combination with fibrates if LDLC remains high after TGs have been controlled.

Ezetimibe does not lower TGs significantly but can be combined with fibrates if additional LDLC lowering is required and statins are contra-indicated or not tolerated. Cholestyramine can raise TGs and should be avoided in hypertriglyceridaemia.

Conclusion

Marked hypertriglyceridaemia is a risk factor for pancreatitis, while moderate hypertriglyceridaemia is a cardiovascular risk factor. Several new proteins that play important roles in lipolysis have been discovered recently and GWAS have identified linkages to many genes of as yet unknown function. We may yet have a lot to learn about lipolysis and TGRL metabolism in general.

The case for treating severe hypertriglyceridaemia is unequivocal, while treatment strategies and triglyceride goals are less well defined in moderate hypertriglyceridaemia, where the focus is on cardiovascular risk reduction.

Although LDL rightly remains the focus of our attention for cardiovascular risk reduction and the belle of the ball, TGRL are attracting increasing scientific attention and study. Unfortunately, this is not a true fairytale transformation, as the emerging Cinderella certainly has a mean and vindictive streak, causing mayhem in the pancreas or partnering with her stepsister to ravage the arteries.

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