Hypertriglyceridaemia: Aetiology, complications and management

Blom DJ, MBChB(UCT), FCP(SA), MMed(UCT), PhD(UCT)
Division of Lipidology, Department of Medicine, University of Cape Town
Correspondence to: Dirk Blom, e-mail: dirk.blom@uct.ac.za
Keywords: triglycerides; pancreatitis; fibrates; lipoprotein lipase; eruptive xanthomata

Abstract

The bulk of plasma triglycerides is 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. 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 commonest cause of severe primary hypertriglyceridaemia is loss of function mutations in both alleles of lipoprotein lipase (LPL). The commonest environmental contributors include diabetes, diet, alcohol and medications (oestrogen, steroids, retinoids, 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 Contributing metabolic disorders should be controlled and aggravating medications withdrawn or reduced where possible.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 grammes/day), fibrates, niacin or statins. Fibrates are the agents of choice in severe hypertriglyceridaemia.

Ⓟ **Peer reviewed.** **Note: This is an abridged version of an article previously published in JEMDSA 2010;15(1):11–17**

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 amongst the most atherogenic lipoproteins. Additionally hypertriglyceridaemia often associates with other cardiovascular risk factors such as obesity, type II diabetes, inflammation and a pro-thrombotic state.[1;2] This article will review hypertriglyceridaemia emphasising severe hypertriglyceridaemia (TG > 10–15 mmol/L)

As members of the "lipid family" both cholesterol and triglycerides 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 (TGRL) metabolism

Plasma triglycerides 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 (hyperchylomicronaemia) cause turbid or even milky (lipaemia) plasma. Following a meal up to 90% of plasma triglycerides are found in chylomicrons. The liver exports triglycerides (from endogenous synthesis or derived from uptake of chylomicrons) mainly as very low density lipoproteins (VLDL). In healthy individuals there should be no circulating chylomicrons following a 12 hour fast and the bulk of triglycerides is found in VLDL. 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).

Increased plasma TGRL can therefore mechanistically result from increased production (increased hepatic synthesis, high fat diets) or reduced clearance (mainly decreased LPL activity or dysfunctional apoE). In many patients hypertriglyceridaemia is multifactorial with both mechanisms contributing to accumulation of TGRL. Plasma triglycerides can fluctuate widely and rapidly. Dietary indiscretions (fatty meals) or metabolic stressors (e.g. uncontrolled diabetes mellitus) can rapidly raise plasma triglycerides, 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 ≈ 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 → 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 (≈ 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 likely do have "susceptibility genes" as equivalent metabolic stressors provoke very variable individual triglyceride responses. In most patients, including those with primary hypertriglyceridaemia, the molecular cause remains unknown.[3]

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 hyperlipidaemia[4] is also widely used but often poorly understood leading to much confusion. The Fredrickson classification groups electrophoretic patterns and not molecularly defined disorders. Some molecularly defined disorders have characteristic patterns but other disorders may have highly variable patterns.

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 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.[5] 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. Currently the only available management is dietary with severe restriction of dietary triglycerides. Implementing a very low fat diet, while 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.

ApoCII activates LPL and homozygous apoCII deficiency is phenotypically indistinguishable from LPL deficiency.[6–9] 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 commonest molecular cause is homozygosity for the receptor-binding defective ε2 isoform of apoE.[10] Phenotypic expression of the disease usually requires the presence of additional metabolic stressors such as diabetes, obesity or hypothyroidism. Classically, patients present with a severe mixed hyperlipidaemia (molar ratio of total cholesterol to plasma triglycerides approximates 2:1) and high levels of apoE.[11] Severe hypertriglyceridaemia, however, is not infrequent.

Mutations in other genes (ApoAV, Lipase maturation factor 1 and others) have also been linked to monogenic hypertriglyceridaemia but these seem to be exceptionally rare disorders.

The term familial hypertriglyceridaemia (FHTG) is often used to describe inheritance of a lipid phenotype characterised by an isolated increase in VLDL often with concomitantly low high density lipoprotein cholesterol (HDLC). Most patients with FHTG have moderate elevations in triglycerides in the 3–10 mmol/L range. The disorder is familial but the molecular basis is unknown and is likely polygenic in many patients.[12] 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 the future, the clinically described entity of FHTG is likely to be progressively replaced by a collection of molecularly diverse disorders with similar lipid phenotypes.

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.[13] 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 commonest metabolic stressor. In susceptible individuals certain drugs can also trigger hypertriglyceridaemia.

Further information on secondary causes of hypertriglyceridaemia can be found in Tables I and II.

Table I: 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 II: 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
Isotretinion	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

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 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 triglycerides 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 tuboeruptive xanthomata (Figure 3).

Pancreatitis

Severe hypertriglyceridaemia is a well established trigger for acute pancreatitis.[14;15] 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.[16] Pancreatitis rarely occurs when triglycerides are under 10–15 mmol/L. In many patients triglycerides 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, triglycerides may vary markedly and rapidly and a patient with only moderately elevated triglycerides 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 and usually 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.[15]

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 triglycerides.[14;17] There is no evidence that patients treated with apheresis recover more rapidly or have fewer pancreatitis associated complications and this expensive treatment modality can not be routinely recommended.[18]

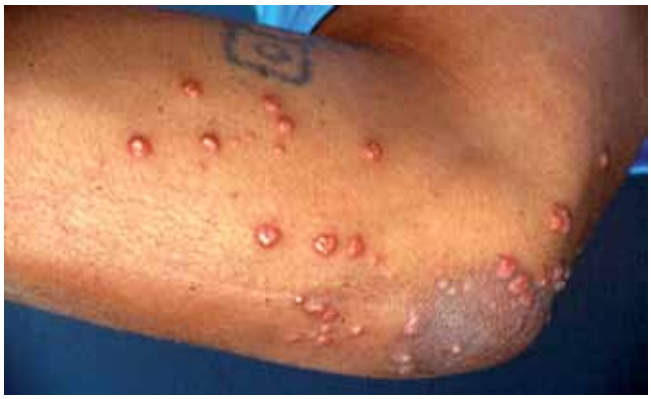

Figure 1: Eruptive xanthomata

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.

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.

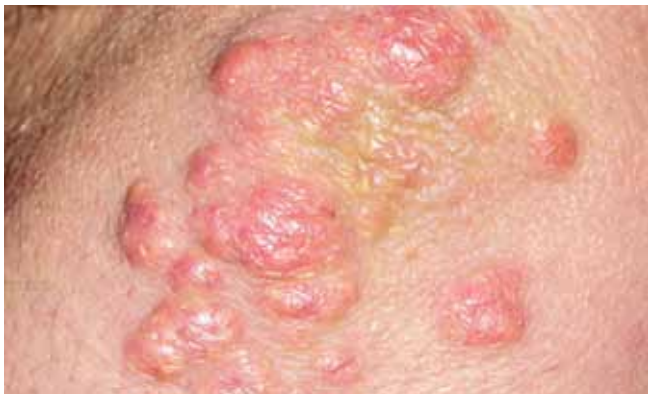

Figure 3: Tuboeruptive xanthomata

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

Atherosclerosis

Moderate hypertriglyceridaemia is an independent risk factor for atherosclerosis and triglycerides have been incorporated in the PROCAM cardiovascular risk prediction algorithm.[19;20] Subsequent studies have confirmed these findings[21] and also suggested that non-fasting triglycerides are a better predictor of risk than fasting triglycerides.[22;23] Non-fasting triglycerides probably predict risk better than fasting triglycerides 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 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 utilised statins which have modest triglyceride-lowering properties. The strongest evidence of benefit for a non-LDLC centered strategy comes from studies in which fibrates were given to patients with well defined lipid phenotypes: moderate hypertriglyceridaemia with low HDLC.[24;25] The ACCORD study is currently investigating the utility of 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, lifestyle review and clinical judgment. A fuller discussion of these issues can be found in the following references.[26;27]

Treatment of severe hypertriglyceridaemia

The primary goal is to lower triglycerides 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 and treated (Tables I and II). In clinical practice the most common problem is either undiagnosed or uncontrolled diabetes. Admission to hospital is often helpful in rapidly controlling hyperglycaemia. If drugs are contributing significantly to hypertriglyceridaemia, treatment should be switched or discontinued if the patient's clinical condition allows 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 grammes of fat/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 triglycerides (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 reduced drastically.

Omega-3 fatty acids (fish oils) lower triglycerides if given in pharmacological doses of around 4 g/d of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA). Fish oils are most effective in moderately severe hypertriglyceridaemia and may lower triglycerides by up to 40% in some patients.[28;29] Fish oils are ineffective in LPL-deficiency and related disorders and may worsen hypertriglyceridaemia if prescribed inappropriately. Preparations of 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. Fibrates are central to the management of severe hypertriglyceridaemia and are the drugs of first choice. Fibrates lower triglycerides, increase HDLC and may either lower or in some cases increase 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

Box 2: 'Rescue diet' for severe hypertriglyceridaemia

Daily menu

Breakfast	(1.7 or 1.9 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
Lunch	(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		
Supper	(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		
Snacks	(1.3 g)		
Apple, morning	0.6	Pear, afternoon	0.7

Other supplements

No diabetes	Diabetes
Beverages	
Carbonated drinks including colas	Dietetic cold drinks
Lucozade	Low calorie Lecol, Oros
Fruit juice, including orange, apricot, apple, grape	
Sweets	
Boiled sweets	Artificially sweetened
Jelly babies, wine gums, marshmallows	
Peppermints, vitamin C sweets	
Spreads	
Sugar syrup, honey, molasses	Dietetic jams
Jam, marmalade	
Desserts	
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	

Legend: Fats are often poorly declared on food labels, and recipes may variably include fats and are best not trusted. Medium chain triglycerides though 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)

(± 10%) rise in creatinine but this is not due to a lowered glomerular filtration rate and reverses on discontinuation.[30;31]

Niacin may lower triglycerides 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 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.[32]

Statins do lower triglycerides but are not effective in severe hypertriglyceridaemia. In the GSH lipid clinic experience 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 triglycerides have been controlled.

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

References

1. Hodis HN. Triglyceride-rich lipoprotein remnant particles and risk of atherosclerosis. Circulation 1999;99(22):2852–4.
2. Hodis HN, Mack WJ, Krauss RM, Alaupovic P. Pathophysiology of triglyceride-rich lipoproteins in atherothrombosis: clinical aspects. Clin Cardiol 1999;22(6 Suppl):II15–II20.
3. Wang J, Cao H, Ban MR, et al. Resequencing genomic DNA of patients with severe hypertriglyceridemia (MIM 144650). Arterioscler Thromb Vasc Biol 2007;27(11):2450–5.
4. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins--an integrated approach to mechanisms and disorders. N Engl J Med 1967;276(1):34–42.
5. Pouwels ED, Blom DJ, Firth JC, Henderson HE, Marais AD. Severe hypertriglyceridaemia as a result of familial chylomicronaemia: the Cape Town experience. S Afr Med J

2008;98(2):105–8.

6. Fojo SS, Baggio G, Gabelli C, et al. Apolipoprotein C-II deficiency: identification of a structural variant ApoC-II Padova. Biochem Biophys Res Commun 1988;154(1):73–79.
7. Fojo SS, Lohse P, Parrott C, et al. A nonsense mutation in the apolipoprotein C-IIPadova gene in a patient with apolipoprotein C-II deficiency. J Clin Invest 1989;84(4):1215–9.
8. Fojo SS, de Gennes JL, Beisiegel U, et al. Molecular genetics of apoC-II and lipoprotein lipase deficiency. Adv Exp Med Biol 1991;285:329–33.
9. Beil FU, Fojo SS, Brewer HB, Jr, Greten H, Beisiegel U. Apolipoprotein C-II deficiency syndrome due to apo C-IIHamburg: clinical and biochemical features and HphI restriction enzyme polymorphism. Eur J Clin Invest 1992;22(2):88–95.
10. Mahley RW, Huang Y, Rall SC, Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J Lipid Res 1999;40(11):1933–49.
11. Blom DJ, Byrnes P, Jones S, Marais AD. Dysbetalipoproteinaemia--clinical and pathophysiological features. S Afr Med J 2002;92(11):892–7.
12. Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. Am J Hum Genet 2001;69(6):1161–77.
13. Hegele RA, Pollex RL. Hypertriglyceridemia: phenomics and genomics. Mol Cell Biochem 2009;326(1–2):35–43.
14. Kyriakidis AV, Raitsiou B, Sakagianni A, et al. Management of acute severe hyperlipidemic pancreatitis. Digestion 2006;73(4):259–64.
15. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. Curr Opin Lipidol 2009;20(6):497–504.
16. Sharma P, Lim S, James D, Orchard RT, Horne M, Seymour CA. Pancreatitis may occur with a normal amylase concentration in hypertriglyceridaemia. BMJ 1996;313(7067):1265.
17. Nakagawa M, Kimura S, Fujimoto K, et al. A case report of an adult with severe hyperlipidemia during acute lymphocytic leukemia induction therapy successfully treated with plasmapheresis. Ther Apher Dial 2008;12(6):509–13.
18. Chen JH, Yeh JH, Lai HW, Liao CS. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. World J Gastroenterol 2004;10(15):2272–4.
19. Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol 1996;77(14):1179–84.
20. Assmann G, Schulte H. Role of triglycerides in coronary artery disease: lessons from the Prospective Cardiovascular Munster Study. Am J Cardiol 1992;70(19):10H–13H.
21. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3(2):213–9.
22. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 2007;298(3):309–16.
23. Ridker PM. Fasting versus nonfasting triglycerides and the prediction of cardiovascular risk: do we need to revisit the oral triglyceride tolerance test? Clin Chem 2008;54(1):11–13.
24. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341(6):410–8.
25. Manninen V, Elo MO, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988;260(5):641–51.
26. Yuan G, Al Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ 2007;176(8):1113–20.
27. Brunzell JD. Clinical practice. Hypertriglyceridemia. N Engl J Med 2007;357(10):1009–17.
28. Calder PC, Yaqoob P. Understanding omega-3 polyunsaturated fatty acids. Postgrad Med 2009;121(6):148–57.
29. Sadovsky R, Kris-Etherton P. Prescription omega-3-acid ethyl esters for the treatment of very high triglycerides. Postgrad Med 2009;121(4):145–53.
30. Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron 2002;92(3):536–41.
31. Broeders N, Knoop C, Antoine M, Tielemans C, Abramowicz D. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? Nephrol Dial Transplant 2000;15(12):1993–9.
32. Sood A, Arora R. Mechanisms of flushing due to niacin and abolition of these effects. J Clin Hypertens (Greenwich) 2009;11(11):685–9.