Diabetes, Triglycerides and Atherosclerosis

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Abstract

Raised triglycerides reflect elevated levels of the triglyceride-rich lipoproteins. Triglycerides are a risk factor for cardiovascular disease. Both the apolipoprotein (apo) B48-containing chylomicrons and the apo B100 hepatically derived very low density lipoprotein (VLDL), triglyceride rich particles which, if elevated, confer cardiovascular risk. Fibrates are effective in lowering serum triglycerides and have a very low side effect profile. Trials that have used fibrates to raise high density lipoprotein (HDL) have been unsuccessful as have trials that target patients with normal triglycerides but there is strong evidence that lowering raised triglycerides is beneficial in both primary and secondary cardiovascular prevention. The recent renewed interest in triglycerides as a therapeutic target has resulted in the development of new drugs which show promise.

Keywords: *Diabetes; Triglycerides; Cholesterol; Low Density Lipoprotein (LDL); High Density Lipoprotein (HDL); Chylomicrons; Statins; Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors*

Introduction

Atherosclerotic cardiovascular disease continues to be a major disease burden. Indeed, in spite of new treatments to reduce this burden, the problem has escalated with the increase in obesity, diabetes and non-alcoholic fatty liver disease. Elevated low density lipoprotein (LDL) cholesterol, a major risk factor for atherosclerosis, has been conquered to a large extent by statins, ezetimibe and the new PCSK9 antagonists but there is still considerable residual risk particularly in patients who already have had an event [1-3]. The concept of atherogenic dyslipidaemia, emphasises the point that lipoproteins other than LDL play an important part in the genesis of atherosclerosis [4].

Low HDL-C has long been recognised as an important risk factor for cardiovascular disease Genetic studies however do not support a protective role of HDL-C in humans [5] and clinical outcome trials to raise HDL-C have not been successful [6]. Thus, focus has again returned to the apo B containing lipoproteins other than LDL. The chylomicron is recognised by its apo B48 protein, a truncated form of apo B100. It is derived from the intestine and carries triglyceride and cholesterol from the intestine into the circulation. The particles are large and contain mostly triglyceride, but in the post prandial state they are numerous and because they are quickly cleared in minutes have considerable cholesterol transport function, whereas LDL particles take days to clear. Thus, the cholesterol carrying ability of chylomicrons is similar to LDL. The larger particles may not be taken up through the endothelial surface but they are quickly delipidated by lipoprotein lipase and can then be taken up by the macrophage in an unregulated way without modification [7-10].

The chylomicron particles end up in the liver where they deposit apo E for transfer to HDL and triglyceride which is exported in VLDL particles with cholesterol which is either derived from the chylomicron or de novo synthesised for export. The VLDL particle, although

larger than the LDL particle, can also deliver cholesterol to the atherosclerotic plaque and like chylomicrons does not need to be modified before being taken up by macrophages through the B/E receptor [11]. As delipidation continues the particle loses apo E and becomes IDL and then LDL. Thus, it is not surprising that the triglyceride rich particles are atherogenic and that the measurement of triglycerides reflects the level of these particles in the blood.

There is a very strong inverse relationship between triglyceride and HDL due to the necessity of nascent HDL to acquire apo E from the VLDL particle. It is to be expected that studies have found it difficult to distinguish the benefit of raising HDL rather than lowering triglycerides. In diabetes most patients have raised triglycerides raised LDL-C and low HDL-C. In the ACCORD study [12] patients with triglycerides > 2.3 mmol/l and HDL < 0.88 mmol/l had an increase in cardiovascular event rates. It is not clear whether the event rate is due to the low HDL or the raised triglycerides.

A question raised in a recent excellent review [3] "Is it triglyceride or triglyceride rich lipoproteins that are atherogenic?" Triglycerides, if deposited in excess in the liver and muscle through excess intake, result in insulin resistance and hyperglycaemia. This further drives deposition of fat in the liver, stimulating an increase in apo B production and excess VLDL production, thus increasing the atherogenic particles. Lipoprotein lipase is insulin sensitive so delipidation of the particles is delayed [13]. It is worth mentioning that loss of function variants in gene encoding of Lipoprotein lipase result in higher triglycerides and an increase in cardiovascular disease [14].

Patients with diabetes are at high risk of cardiovascular disease and mortality [15]. Mediation analysis offers a tool to assess the magnitude of risk of different pathways (Mediators) leading to the outcome [16] SMART (Second Manifestations of arterial disease) is a prospective cohort in Utrecht of subjects with vascular disease or important risk factors for atherosclerosis [16]. Using mediation analysis Sharif., *et al.* report that only 35% of the excess cardiovascular risk caused by type 2 diabetes is mediated by classical cardiovascular risk factors. The largest mediated effect was through insulin resistance followed by elevated triglycerides and microalbuminuria. Only 42% of the excess mortality risk was mediated by the classical risk factors.

We have argued that although triglyceride rich chylomicrons and VLDL particles carry relatively little cholesterol per particle, the rapid turnover of these particles, in minutes or hours as compared to LDL which has a 4-day turnover, makes these particles potentially just as atherogenic as LDL particles [18,19]. Balling., *et al*. [20] examined 9000 individuals from the Copenhagen general population study using nuclear magnetic resonance spectroscopy to examine the composition of the various lipoproteins in the non-fasting state. They found that one third of total cholesterol was carried in the remnant particles (VLDL and intermediate density lipoprotein (IDL)). The authors make the point that these particles are taken up by macrophages in the intima directly to form foam cells (unlike LDL which first has to be modified).

The fibrates have a long history as useful drugs to lower triglycerides and to a lesser extent cholesterol. In 1962 Thorpe and Waring [20] described a compound ethyl-a-alpha-4 chlorophenoxy isobutyrate which was called clofibrate. This was the most effective compound with minimal toxicity of the compounds they were screening to decrease total lipid and cholesterol concentrations in rat plasma and liver. This compound had already been described [27] quoted in [28]. Clofibrate was approved in the USA in 1967 for the treatment of hyperlipidaemias. In 1968 Duncan., *et al.* [29] showed that clofibrate reduced hard waxy exudates in the retina but no improvement in retinal vascular lesions. In 1969 Harrold., *et al.* [30] described a double blind controlled trial of clofibrate in the treatment of diabetic retinopathy; Fifty six patients completed one year treatment. There was a significant reduction in hard exudates in the treatment group. In 1974 procetofen was synthesised and was introduced in clinical practice in the same year in France. The drug significantly decreased plasma lipid concentrations in hyperlipidaemic patients and was later called fenofibrate [28,31].

Fenofibrate is the fibrate which has best survived the test of time although other fibrates like Bezafibrate are still being used in animal studies [21] and in treatment of primary biliary cholangitis [22]. The safety of fenofibrate in animal studies was first reported in 1980

[23]. The uricosuric effect was reported in 1980 by Desager., *et al*. [24] and Cranzier., *et al.* [25] described the effectiveness of fenofibrate on lipoproteins in 32 subjects with primary familial hyperlipidaemia (FH).

In 1992 Dreyer and Krey [32] cloned 3 novel members of the xenopus nuclear hormone receptor super family. They showed that the 3 receptors activate the promotor of the acyl coenzyme A oxidase gene which encodes the key enzyme for peroxisomal fatty acid beta-oxidation. Thus, peroxisome proliferator activators (PPARs) may exert their hypolipidaemic effects through these receptors. Fibrates were shown to activate PPAR alpha and therefore are called PPAR alpha activators [33]. It should be noted that at that time fibrates like clofibrate were known to be hepatocarcinogens in rodents as well as causing proliferation of peroxisomes. However in 1983 Blumcke., *et al.* [34] found that this was not the case in hyperlipidaemic patients and the safety of fenofibrate was further confirmed in a review of US and world wide experience [35].

The Helsinki Heart Study [36] examined the efficacy of gemfibrozil in asymptomatic men with non-high density lipoprotein (HDL) cholesterol greater than or equal to 5.2 mmol/l. Many of the subjects had normal triglyceride levels (Mean triglyceride 1.94 mmol/l). There was a 34% reduction in incidence of coronary heart disease. Apart from an increase in upper gastrointestinal symptoms there were no differences in adverse events between the placebo and treatment groups.

The SENDCAP trial [37] examined bezafibrate or placebo on cardiovascular outcomes in Type 2 diabetes. This was a placebo-controlled trial over a minimum of 3 years in Type 2 diabetic patients without a history of clinical cardiovascular disease. There were only 164 patients included in the trial but there was a significant reduction in 'definite' CHD events.

The VA -HIT trial [38] was a trial in secondary prevention of cardiovascular disease events. This was a trial of gemfibrozil designed to examine the effect of raising HDL rather than lowering triglycerides. The subjects were chosen to have coronary disease and low HDL cholesterol rather than high triglycerides. The mean triglyceride level of the patients was only 1.8mmol/l. After a median follow up of 5.1 years, there was a 24% reduction in the combined outcomes of death from coronary heart disease non-fatal myocardial infarction and stroke. Dyspepsia was the only side effect that was higher in the gemfibrozil treated patients. The ACCORD study [39] investigated whether combination of a statin and a fibrate compared to statin mono therapy would reduce the risk of cardiovascular disease in patients with type 2 diabetes who were at high risk for cardiovascular disease. Median triglyceride was only 1.8mmol/l at the start of the study. There was no benefit in adding a fibrate in this study. However in 2017 Elam., *et al.* [40] published a 9.7 year follow up of 4644 surviving participants who had Type 2 diabetes and either prevalent CVD or CVD risk factors and HDL < 0.56 mmol/l (< 0.62 mmol/l for women and African American individuals) Only 4.3% of the patients continued fenofibrate after the end of the trial so the study was looking to find a 'Legacy' effect. The study found that participants with dyslipidaemia, i.e. low HDL and high triglycerides, had a 27% reduction in cardiovascular events.

The diabetes atherosclerosis intervention study (DAIS) [41] investigated the effect of fenofibrate on patients with type 2 diabetes and at least one visible coronary lesion. The results showed that the patients on fenofibrate had reduced angiographic progression. The trial was not powered to examine clinical end points but there were fewer in the fenofibrate group.

One of the largest examinations of triglycerides and risk of coronary heart disease was published in 2007 [42]. Ten thousand incident cases among 262000 participants in 29 Western prospective studies. They found a moderate and highly significant association.

The long term trajectories of lipid and glucose levels were studied by Ivert., *et al.* in subjects who developed a major cardiovascular event before the age of 50 [43]. As much as 20 years before an event cholesterol, triglycerides and glucose were higher in cases as compared to controls.

Creatinine: Many studies have reported increase in serum creatinine in some patients treated with a fibrate. The reversibility of the increased creatinine in the ACCORD study was examined by Mychaleckyj., *et al* [44]. They found that the increase in creatinine was re-

versed after cessation of fenofibrate. Similar results were found for cystatin C which suggests that the increase is not due to an increase in production of muscle creatinine. Interestingly the 25% of patients who had no increase in creatinine had preservation of renal function after 5 years on fenofibrate.

The FIELD Study [45] was a double blind placebo controlled trial of fenofibrate. Nine thousand seven hundred and ninety five patients with type 2 diabetes took part, for an average of 5 years. There was no dose adjustment for any degree of renal impairment. Subjects with an eGFR less than 30 were excluded as were some with eGFR 30 - 59 ml/min/1. The mean triglyceride level of the patients was only 1.95 in the fenofibrate group at the start of the trial. Eight hundred and ninety of the 4895 patients on fenofibrate who entered the study were started on other lipid lowering therapy during the study, mostly statins (94%). Of these patients 38% stopped the fibrate. There was a 24% relative reduction in non-fatal coronary heart events. The rate of progression to albuminuria was significantly reduced by fenofibrate. Retinopathy progression as measured by need for laser treatment was significantly less in the fenofibrate group. Adverse events were few. The same number of patients on the fenofibrate arm discontinued treatment as on the placebo arm. Twenty three patients on placebo and 40 on the fibrate had an episode of pancreatitis. There was also was a slight increase in risk of pulmonary embolism and deep vein thrombosis, the latter being nonsignificant. Creatinine was slightly higher in the fenofibrate group but fell to pre-study levels on cessation of fenofibrate at the end of the trial when retested after 8 weeks. The changes in creatinine are not related to changes in a fall in GFR [46].

Ceramide is a strong marker of atherosclerosis. Plasma samples of 102 patients in the FIELD study were analysed, before and after treatment with fenofibrate, in order to find other markers that might that might help to identify patients who would benefit from fenofibrate therapy [47]. They found that there was a significant reduction of 18% in ceramide. Seventy five % of patients had reduced ceramide which may suggest that ceramide could be used as a marker of benefit, since the reduction was independent of the usual lipid parameters.

The effects of fenofibrate on renal function in patients with type 2 diabetes mellitus was reported from the FIELD study in 2011 [48**.** During the run-in phase of FIELD the creatinine rose by 10.0 umol/l but quickly reversed on placebo assignment. At the end of the study fenofibrate had reduced urine albumen concentrations by 24%. Creatinine rose more slowly on the fenofibrate treatment and greater preservation of estimated GFR was observed over the 5 years.

The benefit and safety of long term fenofibrate therapy in people with type 2 diabetes and renal impairment was reported in 2012 [49]. This was a further analysis of the FIELD study by dividing the subjects into baseline eGFR 30 - 59, 60 - 89 and < 90 ml/min 1.73m^2. Overall fenofibrate reduced cardiovascular events compared to placebo (Hazard ratio 0.89 (95% CI 0.800.99) P = 0.035). There was no significant difference in benefit across the three eGFR groups. There were no drug safety concerns.

Amputation events were reported in the Field study in 2009 [50]. The risk for both first amputation and microvascular (below ankle) amputation was significantly lower in the fenofibrate treated patients.

A pharmacoepidemiology safety study of fibrate and statin concomitant therapy was reported in 2010 [51]. This was a retrospective cohort study comparing rates of hospitalisation for specific diagnoses in a cohort of new users of statin, fibrate or statin and fibrate therapy from 2004 - 2007. The Authors used claims data from a large United States health insurer. Renal impairment was defined by a creatinine level (either a doubling or twice the Laboratory normal when there was no base line level available). There was no increase in renal failure requiring renal replacement. The incidence rate for rhabdomyolysis was slightly more for statin/fibrate combination than statin alone (3.75 vis 3.30 per 100000 patient-years). Hepatic injury was not different but Pancreatitis was more common in the combination group (157.94 viz 45.76 per 1000000 patient years) but there were only 42 cases in the combination group). The authors conclude that the risk for rhabdomyolysis and pancreatitis was low but increased in the fibrate group. The increase in renal impairment as measured by an increase in serum creatinine was consistent with all the other trials that show that the rise in creatinine is reversible There was no evidence of risk of end stage renal failure.

The role of fenofibrate in stabilising diabetic retinopathy and diabetic nephropathy appears to be independent of its lipid lowering effect. Apoptotic cytokines appear to mediate inflammatory damage. Angiopoietin-like 3 exerts significant pathogenic effects on vascular endothelial cells which are critically involved in the pathogenesis of diabetic retinopathy. Fenofibrate has been shown to inhibit angiopoietin-like 3 and other inflammatory cytokines [45,52]. In another study Liu., *et al.* have shown in mice that fenofibrate ameliorates diabetic retinopathy by reducing reactive oxygen species production through inhibition of enhanced reactive oxygen species (ROS) production [53]. Nuclear factor erythroid-2- related factor 2 (Nrf2) a master regulator of anti-oxidative defense was upregulated by fenofibrate, Fenofibrate has been shown to reduce serum cytokines such as IL-1B and TNF-a in patients with diabetic retinopathy [54].

The role of triglycerides as a risk factor in atherosclerotic events has been addressed in the CHART study in Japan [55]. The authors addressed the residual risk of recurrent myocardial infarction even after LDL was well controlled by statins. One thousand eight hundred and forty three consecutive patients with previous history of MI treated with statins were examined after a median of 8.6 years of follow up. They found that higher levels of non-HDL cholesterol, but not triglycerides or LDL alone, were associated with higher incidence of recurrent MI. Higher triglycerides levels were associated with higher incidence of recurrent MI in patients with LDL<100mg/dl but not in those with LDL above this threshold.

Fujihara., *et al*. Fujihara Y Circ J 2019 83 1302-1308 examined the predictive value of remnant lipoprotein (RLP-C) levels for cardiovascular events in patients with stable coronary artery disease and LDL cholesterol. <70 mg/dl. They found that RLP-C was a significant predictor of primary end point of cardiac death, nonfatal myocardial failure, peripheral artery disease, aortic event, and ischaemic stroke. This after adjustment for known risk factors including triglycerides and apo B.

Another boost for targeting triglycerides to combat atherosclerosis has come from the REDUCE-IT trial [57]. A trial with 8000 statin treated patients with elevated triglycerides(135-500mg/dl) and LDL cholesterol at target (40 - 100 mg/dl) and a history of atherosclerosis or diabetes and at least one other risk factor. The patients were followed for a median of 4.9 years. Icosapent ethyl a highly stable eicosapentaenoic ethyl ester formulation was used to lower triglycerides. This was a placebo-controlled trial. The drug was associated with a significant reduction in both primary and secondary events.

Chronic kidney disease is another condition in which there is a large residual risk of atherosclerotic cardiovascular disease despite treatment with statins. A prospective cohort study by Bajaj [58] examined lipoproteins and risk and found that higher VLDL-C and Apo B levels but not LDL-C were significantly associated with events as well as lower HDL-C and Apo-A1.

Saeed., *et al.* [59] reexamined the ARIC study 9334 subjects were followed for up to 16 years for incident cardiovascular events. They examined the relationship between events and remnant like particle cholesterol and triglycerides and LDL triglyceride levels. They found that both levels were associated with CVD risk but after adjustment for traditional risk factors LDL triglyceride levels were predictive of Cardiovascular and stroke risk. This is not surprising as the oxidisability of LDL and therefore its atherogenicity depends on the fatty acid composition [60,61].

Duncan., *et al.* [62] examined trajectories of blood lipid concentrations over the Adult life course and risk of cardiovascular disease and all-cause mortality using the Framingham Offspring Participants Study. They showed that using trajectories unfavorable lipid trajectories were associated with higher cardiovascular morbidity and mortality risk. Interestingly, only trajectories of triglycerides that were elevated were significant.

The association of LDL triglycerides with hepatic lipase activity and coronary heart disease was examined by Silbernagel., *et al* [63]. This was an epidemiologic and Mendelian randomisation study. The conclusion was that there was a continuous positive association between LDL triglycerides and cardiovascular mortality, Genome wide association studies suggested that low hepatic lipase activity may be the cause of this link.

New treatments in development

Fibrates are PPAR a agonists that lower triglycerides. They affect fatty acid transport and fatty acid oxidation [65]. They increase lipoprotein lipase and decrease apoC 111. A selective PPAR-a modulator Pemafibrate (SPPARM) which does not raise creatinine as much as fenofibrate and decreases liver enzymes has been described [66,67]. In a 24 week trial comparing pemafibrate to fenofibrate there was a modest 6% increase in efficacy in triglyceride lowering compared to fenofibrate (46% viz 40%). LDL cholesterol was not lowered by the drug whereas fenofibrate lowered by 0.8%. There were significantly less adverse events [68]). In Type 2 diabetes the drug over a 52 week period was well tolerated with its effect continuing [69].

Angiopoietin-like protein 3 (ANGPTL 3) inhibits lipoprotein lipase Activity and increases triglycerides, An antisense oligonucleotide targeting Angptl 3 messenger RNA has been shown to reduce triglycerides by up to 63%9 [70]. Ahmad., *et al.* [71] describe a monoclonal antibody Evinacumab which reduced triglycerides in 2 Phase 1 studies in patients with serum triglycerides 150 - 450 mg/dl. Few side effects were observed. Triglycerides fell by 75 - 85% in the highest doses used subcutaneously or intravenously. The reduced levels were similar to those found in patients with loss of function mutations of ANGPTL-3. These mutations are cardioprotective [72].

Apo A-V secreted from the liver circulates on the triglyceride rich lipoproteins. It reduces plasma triglycerides by stimulating LPL mediated plasma triglyceride clearance and another portion is involved intracellularly in association with lipid droplets [73]. In Apo A V deficiency steroid regulatory element binding protein (SREBP-1c) is activated on high carbohydrate feeding to form large VLDL [74]. The possibility of gene therapy to increase apo A-V has been suggested as a therapeutic option [75].

Apo C-3 inhibits the delipidation of triglyceride rich particles and raised levels are associated with raised triglycerides and increased cardiovascular risk. It has recently been shown that the secretion rate of ApoC3 is increased in diabetic patients and can be reduced by improvement in diabetic control. This improvement was associated with lowering of triglycerides [76]. Silencing of Apo C3 has been shown to suppress NF-kB pathway thereby exercising a protective effect on cell injury induced by oxidative stress and reducing inflammatory response in a mouse model of pre-eclampsia [77]. An exciting finding in relation to atherosclerosis?

Volanesorsen is an investigational drug which reduces serum triglycerides by inhibiting Apo C3. It is an antisense inhibitor of ApoC3 synthesis. In patients with familial chylomicronemia syndrome, a condition of lipoprotein lipase absence or deficiency, there was a significant reduction in triglycerides and reduction in symptomatology such as steatorrhoea and pancreatic pain [78].

In 15 patients with Type 2 diabetes volanesorsen has been shown to reduce ApoC3 and triglycerides and increase HDL. Glucose disposal and insulin sensitivity improved in this 15 week trial [79].

Conclusion

Abnormalities in triglyceride metabolism are associated with atherosclerotic risk. Triglycerides are transported in both the apoB48 chylomicron particles and in the apo B100 VLDL, IDL and LDL particles. The triglyceride rich larger particles carry much less cholesterol per particle than the LDL particle but the half life much quicker, therefore the ability to carry cholesterol to the arterial wall similar and only the LDL particle needs to be modified before taken up by the Macrophage. The strong association between LDL and atherosclerosis and the major benefit of lowering LDL cholesterol with statins to prevent atherosclerotic events, has obscured to some extent the importance of elevated triglyceride rich particles when triglycerides are abnormally high as often found in uncontrolled diabetes. Early fibrate studies focused on raising HDL and so patients with low triglycerides were treated. It is not surprising that treatment of low triglycerides with a drug that lowers triglyceride might not be effective. The newer trials and re analysis of the older trials show that lowering triglycerides with either ecospentanoeic acid or fibrates do prevent cardiovascular events particularly in patients who have low LDL.

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