Lipid disorders in type 2 diabetes
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INTRODUCTION

Diabetes affects currently about 5% of world’s populations, and its prevalence is rapidly increasing particularly in elderly subjects. Because over 80% of all diabetic subjects have type 2 diabetes, the increase in the number of diabetic individuals implies an epidemic of type 2 diabetes. Although microvascular disease is also common in patients with type 2 diabetes, cardiovascular disease (CVD), particularly coronary heart disease (CHD), is a major complication of this disease, and over 50% of all patients die of CHD.

Type 2 diabetes is usually preceded by a long period of asymptomatic hyperglycemia which may last for years. Both insulin resistance and type 2 diabetes are characterized by dyslipidemia, which increases the risk for CVD. Although several mechanisms are likely to contribute to accelerated atherosclerosis and increased risk of CVD observed in patients with type 2 diabetes mellitus, dyslipidemia is perhaps the most important single risk factor among all risk factors.

DIABETIC DYSLIPIDEMIA

Type 2 diabetes is associated with several changes in lipids and lipoproteins as presented in table 1. The most typical feature of diabetic dyslipidemia is the abundance of triglyceride-rich lipoproteins. Patients with type 2 diabetes usually have normal levels of total and LDL (low-density lipoprotein) cholesterol, but compositional changes in LDL particles occur frequently (small, dense LDL, high triglyceride content and oxidative modification of LDL particles).

Triglyceride levels are inversely correlated with HDL (high-density lipoprotein) cholesterol levels. Therefore, it is difficult to investigate the independent role of triglyceride-rich lipoproteins with respect to atherosclerosis and CVD events. HDL in patients with type 2 diabetes is characterized by decreased particle number, and several qualitative changes in particle composition.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that the most important risk factor for fatal and non-fatal MI (myocardial infarction) was high LDL cholesterol. We also demonstrated in 1059 Finnish patients with type 2 diabetes that
TABLE 1. Diabetic dyslipidemia

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<thead>
<tr>
<th>Triglyceride-rich lipoproteins</th>
<th>Increased particle numbers</th>
<th>Increased postprandial concentrations</th>
<th>Triglyceride-enriched and cholesterol-enriched particles</th>
<th>LDL</th>
<th>Decreased particle numbers</th>
<th>Several changes in particle composition</th>
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HDL: high-density lipoprotein; LDL: low-density lipoprotein.

MECHANISMS FOR THE DEVELOPMENT OF DIABETIC DYSLIPIDEMIA

Triglyceride-rich lipoproteins

Very-low-density lipoproteins (VLDL) and metabolites of VLDL, and chylomicron remnants are the triglyceride-rich lipoproteins in patients with type 2 diabetes. The fundamental defect in diabetic dyslipidemia is hepatic overproduction of large VLDL particles, particularly VLDL\(_1\). This process is tightly linked to insulin resistance, although it is unclear, what is the causal role of insulin resistance in this process. Overproduction of VLDL particles initiates a series of other changes in lipoproteins and lead to higher levels of remnant particles, small dense LDL, and secondarily to low HDL cholesterol levels. In a recent study fasting insulin, plasma glucose, intra-abdominal fat, liver fat and insulin resistance were predictors of VLDL\(_1\)-apoB and VLDL\(_1\)-triglyceride production.\(^5\)

LOW-DENSITY LIPOPROTEINS

LDL cholesterol level is not elevated in patients with type 2 diabetes. However, for any LDL cholesterol level, type 2 diabetic individuals generally have increased number of LDL particles indicating that they have more small, dense lipid-poor LDL particles.\(^4\) Because each LDL particle contains one apolipoprotein B molecule, patients with type 2 diabetes also have increased levels of apolipoprotein B. An increased number of LDL particles might contribute to atherogenesis and cardiovascular disease risk.\(^5\) Small, dense LDL particles are atherogenic. These particles rapidly enter the arterial wall and can be toxic to endothelial cells, cause greater production of procoagulant factors, and can be oxidised more readily than the large buoyant particles. The formation of small dense LDL is closely associated with insulin resistance and hypertriglyceridemia.\(^7\) Therefore, it is not surprising that the VLDL\(_1\)-triglyceride level is the major predictor of LDL size in individuals with or without type 2 diabetes.

HIGH-DENSITY LIPOPROTEINS

Reduced levels of HDL cholesterol and apolipoprotein A1, the major apolipoprotein in HDL cholesterol, are typical to patients with type 2 diabetes.\(^3\) In addition, there are abnormalities in the size and composition of the HDL particles.\(^7\) The function of HDL and apolipoprotein A1 is to remove excess cholesterol from atherosclerotic plaques. Therefore, their reduced concentrations promote the accumulation of cholesterol in the vessel wall, and lead to atherosclerosis. Furthermore, HDL has anti-inflammatory and antioxidant properties. Compositional abnormalities in HDL in patients with type 2 diabetes may lead to impaired antiatherogenic properties.

MANAGEMENT OF DYSLIPIDEMIA

The cornerstone of the management of CVD in diabetes is the use of LDL cholesterol-lowering drugs, statins, even though patients with type 2 diabetes do not have increased concentrations of LDL cholesterol. Several trials have been published on the effects of statin treatment to reduce CVD events. The main report of the Cholesterol Treatment Trialists’ Collaboration showed that statin therapy safely reduced the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 20% per 1 mmol/L reduction in LDL cholesterol, largely irrespective of initial lipid profile or other baseline characteristics.

In a subsequent report the Cholesterol Treatment Trialists’ Collaborators analyzed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of a further 71 370 without diabetes in 14 randomised trials of statin therapy. During a mean follow-up of 4-3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes, which was similar to the 13% reduction in those without diabetes. This finding reflected a significant reduction in vascular mortality (0·87, 0·76-1·00; \(p = 0·008\)) and no effect on non-vascular mortality (0·97, 0·82-1·16; \(p = 0·7\)) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72-0·86; \(p < 0·0001\)), which was similar to the effect observed in those without diabetes (0·79, 0·76-0·82; \(p < 0·0001\)). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69-
0.87; \ p < 0.0001), coronary revascularisation (0.75, 0.64-0.88; \ p < 0.0001), and stroke (0.79, 0.67-0.93; \ p = 0.0002). The authors concluded that statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.

Fibrates have been used since the 1970s in the treatment of dyslipidemia. These drugs especially lower plasma triglycerides and increase HDL cholesterol and lower moderately LDL cholesterol. Therefore, it was anticipated that these drugs may significantly reduce CVD event rate. However, the results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were not as favorable as expected\(^\text{11}\). The FIELD study was designed to assess the effect of fenofibrate on cardiovascular disease events in patients with type 2 diabetes\(^\text{12}\). The study was a multinational, randomised controlled trial with 9795 participants aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry. Patients (2131 with previous cardiovascular disease and 7664 without) with a total-cholesterol concentration of 3.0-6.5 mmol/L and a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or plasma triglyceride of 1.0-5.0 mmol/L were randomly assigned to micronised fenofibrate 200 mg daily (n = 4895) or matching placebo (n = 4900). The primary outcome was coronary events (coronary heart disease death or non-fatal myocardial infarction). The outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularisation).

Analysis was by intention to treat. Averaged over the 5 years' study duration, 5.9% (n = 288) of patients on placebo and 5.2% (n = 256) of those on fenofibrate had a coronary event (relative reduction of 11%; hazard ratio [HR] 0.89, 95% CI 0.75-1.05; \ p = 0.16). This finding corresponds to a significant 24% reduction in non-fatal myocardial infarction (0.76, 0.62-0.94; \ p = 0.010) and a non-significant increase in coronary heart disease mortality (1.19, 0.91-1.57; \ p = 0.22). Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% (0.89, 0.80-0.99; \ p = 0.035). This finding included a 21% reduction in coronary revascularisation (0.79, 0.68-0.93; \ p = 0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (p = 0.18). Fenofibrate was associated with less albuminuria progression (p = 0.002), and less retinopathy needing laser treatment (5.2% vs 3.6%, \ p = 0.0003). There was a slight increase in pancreatitis (0.5% vs 0.8%, \ p = 0.031) and pulmonary embolism (0.7% vs 1.1%, \ p = 0.022), but no other significant adverse effects.

Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit.

**Conflict of interest**

The author declares he has no conflict of interest.

**REFERENCES**