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Georg P, Ludvik B

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# Lipids and Diabetes

P. Georg, B. Ludvik

Atherosclerosis is a major complication of diabetes being responsible for the increased morbidity and mortality in these patients. Diabetic dyslipidaemia comprises elevated triglyceride levels as well as decreased HDL cholesterol levels. LDL cholesterol is quantitatively not significantly different from non-diabetic subjects, however, there is a preponderance of small dense LDL particles with a greater susceptibility to oxidation. Epidemiological studies have shown that patients with type-2 diabetes mellitus with no history of cardiovascular disease, have the same risk for cardiac events as non-diabetic patients with pre-existing coronary disease have. The increased incidence of cardiovascular disease (CVD) in diabetes, the greater case fatality and 1-year mortality in patients with myocardial infarction strongly suggest that preventive lipid lowering therapy is of great importance. Unfortunately, the rationale for prevention of CVD in patients with diabetes is obtained only from pathophysiological evidence, interventional studies in non-diabetic populations and *post-hoc* subgroup analyses in diabetic patients. Therefore, many questions regarding the therapy of diabetic dyslipidaemia still remain open. However, these studies suggest that lowering cholesterol in patients with type-2 diabetes is at least as effective as in a non-diabetic population. Results from prospective lipid lowering trials in patients with diabetes are therefore awaited with great interest. *J Clin Basic Cardiol* 2000; 3: 159–62.

**Key words:** atherosclerosis, cardiovascular mortality, statins, fibrates

Diabetes mellitus affects more than 100 million people worldwide and its incidence and prevalence are still rising. By the end of the 20<sup>th</sup> century it is expected that worldwide more than one billion people will suffer from diabetes [1]. The majority of these patients has type-2 diabetes which imposes a two- to four-times higher risk of cardiovascular disease as the major cause of death in the diabetic population [2–4]. In addition, diabetic patients with myocardial infarction exhibit a greater case fatality [5] and 1-year mortality [6].

## Risk Factors for Atherosclerosis in Diabetes

### Diabetic dyslipidaemia

In type-2 diabetic patients quantitative and qualitative abnormalities in lipoproteins are presumed to be responsible for the increased risk of macrovascular disease. Each lipid and lipoprotein fraction is affected by insulin resistance and hyperglycaemia [7, 8]. The common pattern of dyslipidaemia in type-2 diabetic patients shows elevated triglyceride levels and decreased HDL cholesterol levels. The concentration of LDL cholesterol is usually not significantly different from non-diabetic subjects. Diabetic patients may have elevated levels of non-HDL cholesterol (LDL plus VLDL). However, type-2 diabetic patients typically have a preponderance of small, dense LDL particles, which possibly increases atherogenicity by a greater susceptibility to oxidation even if the absolute concentration of LDL cholesterol is not significantly increased. Hypertriglyceridaemia often is rather modest. The median triglyceride level in type-2 diabetic patients is < 2.3 mmol/l (200 mg/dl), and 85–95 % of patients have triglyceride levels below 4.5 mmol/l (400 mg/dl) [9].

As in non-diabetic individuals, lipid levels may be affected by factors unrelated to hyperglycaemia or insulin resistance, such as renal disease, hypothyroidism, and genetically determined lipoprotein disorders. Abuse of alcohol and estrogen replacement therapy may also contribute to hypertriglyceridaemia.

In well-controlled patients with type-1 diabetes there is only a small difference in plasma lipid levels compared with

non-diabetic subjects. However, noticeable abnormalities in lipoprotein composition are observed in these patients despite good glycaemic control and near normal plasma lipid levels [10, 11].

### Hyperglycaemia

Hyperglycaemia is a cardiovascular risk factor [12–14] possibly because of non-enzymatic glycation of proteins [15] and lipoproteins, which increases their atherogenic potency. There is evidence that advanced glycation end products enhance the vulnerability of arteries [16]. Many studies have shown that hyperinsulinaemia due to insulin resistance represents an increased risk of atherosclerosis [17–20]. Regarding diabetes control, a level of haemoglobin A1c > 6.2 % is presumed to elevate the risk of cardiovascular disease as reported in some studies [21, 22]. The UKPDS could demonstrate an increased cardiovascular risk of 11 % for each increment of 1 % in haemoglobin A1c.

### Blood pressure

Increased blood pressure is a major risk factor for cardiovascular disease particular in diabetic subjects. In the UKPDS, a 15 % increased risk for cardiovascular disease was reported for an elevation in systolic blood pressure of 10 mmHg, which was similar to that reported in the general population [23].

### Other risk factors

In fact, all factors that increase the risk of atherosclerotic vascular disease in non-diabetic subjects also do so in diabetic patients. These factors include smoking, increased levels of homocysteine and several coagulation abnormalities.

## Plasma Lipids and Cardiovascular Disease

### Total and LDL-Cholesterol

The association between plasma total cholesterol and CVD risk is well established. Results from a 12 year follow up of 316,099 men screened for the Multiple Risk Factor Interven-

tion Trial (MRFIT) showed a strong relationship between serum cholesterol levels and CVD mortality. The death rates ranged from 7.7 per 10,000 person years for men with serum cholesterol levels 3.6 to 4.1 mmol/l, to 54.4 per 10,000 person years for men with cholesterol levels above 8.3 mmol/l [24]. The CVD risk is significantly modified by other factors, such as smoking, hypertension and diabetes. The MRFIT study also showed that the absolute risk of death was at least three times higher for diabetic patients than for a non-diabetic population and that this relationship was amplified by serum cholesterol [25]. The UKPDS presented further evidence regarding the association between CVD risk with LDL and HDL-cholesterol levels in non-insulin-dependent diabetes [26]. Each increment of 1 mmol/l of LDL-cholesterol increased the risk of CVD 1.57 times.

### HDL-Cholesterol

An inverse relationship between plasma HDL-cholesterol and CVD risk has been found for both sexes [27]. The Framingham study showed a nearly six fold increased risk of myocardial infarction in women with HDL-cholesterol levels < 1.2 mmol/l compared with women with HDL-cholesterol levels > 1.7 mmol/l. In the UKPDS, an inverse relationship with HDL was also seen, with a 1.15 relative risk of CVD associated with each 0.1 mmol/l decrement in HDL-cholesterol. Among men in the Helsinki Heart Study, an LDL/HDL ratio > 5 was the strongest predictor of cardiac events [28].

### Triglyceride

Elevated triglyceride levels often appear as a risk factor in univariate analyses, but the relation is weakened or disappears in multivariate analyses that control for HDL-cholesterol. This weakening may be due to the close, inverse metabolic relation between HDL and the triglyceride-rich lipoproteins. In the Framingham Heart Study with a 14-year follow up, triglyceride levels were an independent risk factor in women 50–69 years of age [29]. The significance of hypertriglyceridaemia as a risk factor in patients with non-insulin-dependent diabetes mellitus was also supported by the data from the Paris Prospective Study [30]. An increased risk for ischaemic heart disease in middle-aged and elderly men in the middle and highest tertiles of triglyceride level is shown by the Copenhagen Male Study with a follow-up of 8 years [8]. This study included 2906 white men who were initially free of clinical cardiovascular disease. Baseline fasting lipid measurements and other heart disease risk factors were obtained in each patient. Cumulative incidence rates for first heart disease events were seen in 4.6 % for the lowest, 7.7 % for the middle, and 11.5 % for the highest third of triglyceride levels. Adjusted for age, BMI, alcohol, smoking, physical activity, hypertension, non-insulin-dependent diabetes mellitus, social class, LDL-cholesterol and HDL-cholesterol, relative risks for ischaemic heart disease were 1.5 for lowest third level and 2.2 for the middle and the highest third of triglyceride levels, respectively. In this report, fasting hypertriglyceridaemia was a strong predictor of CVD, independently of other risk factors, including HDL-cholesterol. Although the status of triglyceride as an independent risk factor remains controversial, elevated triglyceride is an important component of metabolic syndrome including postprandial hyperlipidaemia, insulin resistance, hyperglycaemia, hyperinsulinaemia, low HDL-cholesterol, small, dense LDL-cholesterol, increased LDL oxidation and obesity [31].

## Lipid Reduction and Cardiovascular Disease in Type-2 Diabetes Mellitus

### Lipid intervention trials in diabetes – *post hoc* analyses

No prospective clinical trials have been performed on the effects of lipid lowering therapy for the prevention of CVD focused on diabetic patients. However, a number of large clinical trials have also included a small NIDDM population. The Helsinki Heart Study, a primary intervention study, examined the effect of treating hyperlipidaemia with gemfibrozil in middle-aged men [32]. Individuals treated with gemfibrozil had fewer cardiac events (3.4 % of diabetic patients) than those in the placebo group (10.5 % of diabetic patients). However, the diabetic study population of 135 patients was too small to make the difference statistically significant [33].

The other two studies, the Cholesterol and Recurrent Events (CARE) trial [34, 35] and the Scandinavian Simvastatin Survival Study (4S) [36] were secondary intervention studies using pravastatin or simvastatin, respectively, both drugs from the hydroxymethylglutaryl-CoA-reductase inhibitor group. The CARE study included 586 patients with pre-existing type-2 diabetes mellitus. Major coronary events occurred in 37 % of diabetic patients receiving placebo and 29 % of patients receiving pravastatin, with a relative risk reduction of 25 %. The 4S study included 202 patients with type-2 diabetes, randomized to simvastatin treatment or placebo, respectively. In the placebo treatment group, major coronary events occurred in 63 % compared with 32% in the simvastatin group. The relative CVD risk reduction in 4S was 55 %.

Despite limitations in patient enrolment and small population numbers, these studies suggest that treatment of hypercholesterolaemia in diabetic patients will reduce the risk of recurrent cardiac events in individuals with pre-existing coronary artery disease at least to the same extent as in a non-diabetic population.

### Ongoing lipid interventional trial in diabetes

There are no published data from studies designed to examine the effects of lipid intervention on coronary artery disease specifically in diabetes. Based on the analyses of the effects of lipid lowering substances in diabetic subpopulations, several studies are currently under way. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study examines the effect of treatment with fenofibrate on total and fatal coronary disease events in type 2 diabetic men and women. Some subjects of the population will have a pre-existing CVD. There are following lipid entry criteria: triglyceride > 1.0 mmol/l and total cholesterol < 6.5 mmol/l or < 5.5 mmol/l for subjects with preexisting coronary heart disease. Another study, the Collaborative Atorvastatin Diabetes Study (CARDS), investigates the effects of a minimum of 4 years treatment with atorvastatin versus placebo in 2120 patients with type-2 diabetes and no cardiovascular disease in their medical history. The lipid entry criteria are: triglyceride < 6.78 mmol/l and LDL-cholesterol < 4.14 mmol/l. The Atorvastatin Study for the Prevention of End-points in NIDDM (ASPEN) will recruit 2250 diabetic patients for treatment with 10 mg of atorvastatin vs. placebo. In the Lipids in Diabetes Study (LDS) 5000 diabetic patients with normal or near normal lipid levels without evidence of cardiovascular disease will be randomized to 0.4 mg of cerivastatin or to 200 mg of micronized fenofibrate or to a combination of both drugs compared with placebo in a "2 × 2" factorial design with a follow up of 4–5 years.

Nearly completed is the Diabetes Atherosclerosis Intervention Study (DAIS) [37]. The primary aim of the study is

to investigate whether long-term treatment (minimum of 3 years) with micronized fenofibrate will alter the regression or the progression of the coronary artery disease determined by angiography in men and women with type-2 diabetes [38]. Allowed lipid entry criteria are mild hypercholesterolaemia, mild hypertriglyceridaemia, or both. Results from the MRC/BHF Heart Protection Study [39] with 40 mg simvastatin daily or placebo are also expected soon. The study has randomized about 6000 patients with diabetes, 4000 of them without evidence of cardiovascular disease at entry. Another large population of 3500 patients with type-2 diabetes and hypertension is included in the large Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [40]. The Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) is currently recruiting [41].

The results from a finished secondary prevention VA HDL cholesterol Interventional Trial of gemfibrozil, which randomized about 600 patients with diabetes, are awaited with interest [42].

### Management of Dyslipidaemia in Adults with Diabetes

First line agents, which should be used in patients with diabetic dyslipidaemia featuring hypercholesterolaemia are statins. They are well tolerated and decrease the LDL cholesterol levels by 25–55 %, depending on the statin used and dosage. The optimal LDL cholesterol levels for adults with diabetes are < 2.6 mmol/l (100 mg/dl), optimal HDL cholesterol levels are > 1.15 mmol/l (45 mg/dl), and desirable triglyceride levels are < 2.30 mmol/l (200 mg/dl). Higher doses of statins may also be moderately effective in reducing the triglyceride level and therefore reduce the need for a combination therapy. The fibric acid derivatives are more effective in decreasing the triglyceride levels and raising the HDL-cholesterol levels, but do not substantially change the LDL-cholesterol levels. The combination of a statin and fibrate might be particularly effective, because of complimentary effects on the lipid profile, but these drugs have not typically been used together due to the risk of myopathy. However, the large statin trials have not shown an increased risk of myopathy as well as did several small randomized trials of statins and fibrates as a combination therapy [43].

Type-1 diabetic patients tend to have normal lipoprotein levels. Their composition of lipoproteins may be abnormal, but the effects of these abnormalities on CVD have not been investigated in clinical trials. There are only few data from observational studies on lipoproteins and CVD in type 1 diabetic patients. In spite of the lack of data, if these patients have LDL cholesterol levels above the goals recommended for type 2 diabetic patients, they should be aggressively treated [44].

### Conclusion

Atherosclerosis is a major complication of diabetes. Studies indicate that patients with type-2 diabetes mellitus who have no history of cardiovascular disease, have the same risk for cardiac events as do non-diabetic patients with pre-existing coronary disease [45]. The increased incidence of CVD in diabetes, the greater case fatality and 1-year mortality in patients with myocardial infarction [5] strongly suggest that preventive lowering of lipid levels, potentially to goals accepted for secondary prevention, is of great importance. Unfortunately, the rationale for prevention of CVD in patients with diabetes is obtained only from the pathophysiological evidence, from interventional studies in non-diabetic

populations and from *post-hoc* subgroup analyses in diabetic patients. Therefore, many questions regarding the management of blood lipid levels in diabetes still remain open. When should the treatment be started? Should the treatment be based on CVD risk, on lipid levels or other factors? How low should be the target level of cholesterol? For those patients with elevated triglyceride levels, should the first line treatment be a fibrate or a statin, or should a combination be used? How safe is the combination therapy? Are the effects of a combination therapy complimentary? Are there any particular side effects of cholesterol lowering in patients with diabetes, especially when more aggressive regimens are used? Data from the ongoing lipid lowering trials in diabetic populations will hopefully soon answer these questions.

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