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Diabetic dyslipidemia

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Abstract

By the year 2025, there will be more than 300 million type 2 diabetes sufferers worldwide. This epidemic will be followed by a wave of cardiovascular disease. Diabetes is in fact a serious vascular disease with poor prognosis, and not only a disease characterized by elevated blood glucose. If adequate attention were paid to this, it would be much easier to relieve the burden of cardiovascular disease in type 2 diabetes patients. One important cardiovascular risk factor in type 2 diabetic people is dyslipidemia. This is characterized by low HDL-cholesterol, high serum VLDL-triglycerides, and a preponderance of small, dense LDL. Even slight elevations of LDL-cholesterol in type 2 diabetic patients are associated with a substantial increase in cardiovascular risk. The composition of lipid particles in diabetic dyslipidemia is more atherogenic than in dyslipidemia in general. This means in turn that normal lipid concentrations are more atherogenic in diabetic than in non-diabetic patients. Retrospective analyses show that, in terms of protection from cardiovascular endpoints, the benefit of lipid lowering in type 2 diabetic patients is at least as great as in the non-diabetic population. Lowering of LDL-cholesterol is a very attractive target for the reduction of coronary heart disease in type 2 diabetic people. © 2002 Published by Elsevier Science Ireland Ltd.

Keywords: Type 2 diabetes; Cardiovascular risk; Diabetic dyslipidemia; Atherogenicity; Lipid lowering

1. Introduction

The poor cardiovascular prognosis of diabetes is reflected by the findings of a Finnish study [1]. Type 2 diabetic patients without previous myocardial infarction have the same risk of dying from cardiovascular disease within 8 years as non-diabetic patients with prior myocardial infarction.

These Finnish data were confirmed by a recent study in six different populations in different parts of the world [2]. This study also showed that diabetic patients without previous cardiovascular disease and non-diabetic patients with cardiovascular disease have a similar risk of suffering cardiovascular death or a new myocardial infarction (Fig. 1). The direct implication of this finding is that it is essential to prevent initial myocardial infarction in diabetes sufferers, in order to relieve the burden of coronary heart disease.

2. High prevalence of dyslipidemia

The most significant cardiovascular risk factor in type 2 diabetic patients is dyslipidemia. The key components of diabetic dyslipidemia are elevation of serum VLDL-triglycerides and lowering of HDL-cholesterol. LDL-cholesterol, however, is usually not increased, or only slightly.

In the UKPDS study [3], the initial triglyceride, HDL-cholesterol and LDL-cholesterol levels were not so much different in diabetic and non-diabetic people. A finding such as this may give physicians the wrong impression, namely, that this is not a serious problem and that there is no need to intervene.

The situation is, however, completely different. According to the results of our BOTNIA study in more than 2500 subjects, almost 50% of type 2 diabetic people have serum triglyceride levels above 1.7 mmol/l and about 25% above 2.3 mmol/l [15] (Fig. 2). This study also showed that 84% of diabetic men and 88.7% of diabetic women have LDL-cholesterol levels above 2.6 mmol/l. This means that diabetic dyslipidemia is a very prevalent phenomenon in everyday practice.

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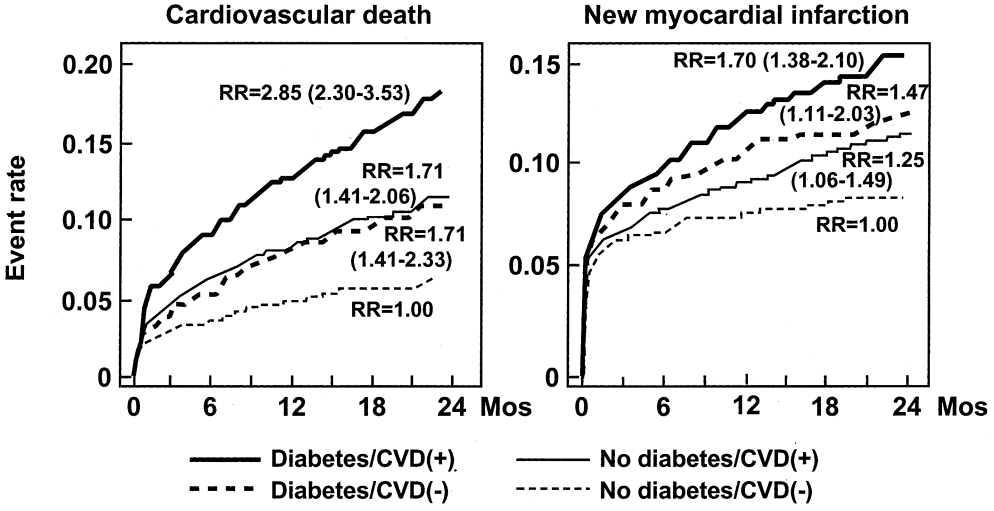

Fig. 1. Cumulative event curves for patients with and without diabetes in relation to previous CVD [2].

3. Diabetes-specific increase in CVD risk

The influence of multiple risk factors on cardiovascular mortality was investigated in the MRFIT study [4]. A total cholesterol > 5.2 mmol/l, smoking, and a systolic blood pressure above 120 mmHg were regarded as risk factors in this study. Even in diabetic people without any of these risk factors, the cardiovascular death rate was higher than in a non-diabetic cohort without other risk factors. Together with the number of risk factors, the cardiovascular death rate increased in both the diabetic and non-diabetic patients, but the increase was much greater in the diabetic group.

What are the diabetes specific risk factors? In the UKPDS study in 3055 type 2 diabetic patients followed up for 7.9 years, 11% of patients suffered a myocardial infarction or developed angina. None of these patients had any signs of cardiovascular disease at baseline.

The investigators identified the following modifiable risk factors in this population: raised LDL-cholesterol, low HDL-cholesterol, raised blood pressure, hyperglycemia and smoking. They also calculated the anticipated risk reduction attributable to modification of these risk factors [5].

According to the findings, the lowering of LDL-cholesterol is a very attractive target for the reduction of coronary heart disease in type 2 diabetes.

In another population-based study, the Strong Heart Study, the relationship between cardiovascular disease and risk factors was investigated in 4549 American Indians, 2034 with diabetes, aged between 45 and 74 years [6]. All participants had no cardiovascular disease at baseline and were followed up for an average of 4.8 years. The hazard ratio for fatal and non-fatal cardiovascular disease increased stepwise from the lowest to the highest quartile for LDL-cholesterol. Even between the lowest quartile (1.8 mmol/l) and the second (2.53 mmol/l), there was a 37% higher risk (Fig. 3). In contrast, the cardiovascular risk decreased stepwise from the lowest to the highest quartile for HDL-cholesterol (Fig. 3). The authors concluded that a 0.26 mmol/l increase in LDL-cholesterol was associated with a 12% increase in cardiovascular risk, and also, that a 0.26 mmol/l decrease in HDL-cholesterol was associated with a 22% increase in risk.

4. Small, dense LDL

Diabetic dyslipidemia is a complex cluster of abnormalities. In addition to high LDL-cholesterol and low HDL-cholesterol, the serum triglycerides are elevated, there is excessive postprandial lipemia, a preponderance of small, dense LDL (LDL-phenotype pattern B), and, together with a lowering of HDL-cholesterol, a preponderance of small, dense HDL.

Small, dense LDL is a strong risk factor for cardiovascular disease and is considered to be highly atherogenic. It is also associated with the high

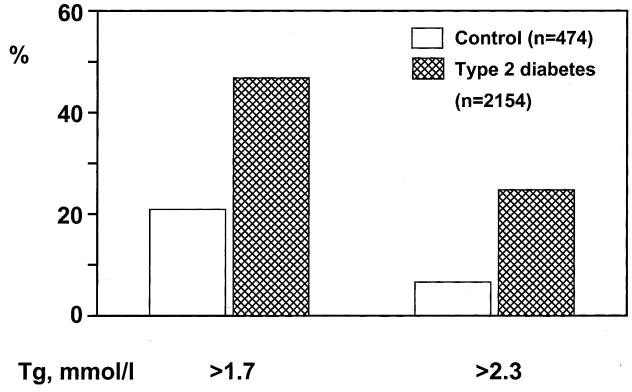

Fig. 2. Prevalence of high triglycerides in type 2 diabetes [15].

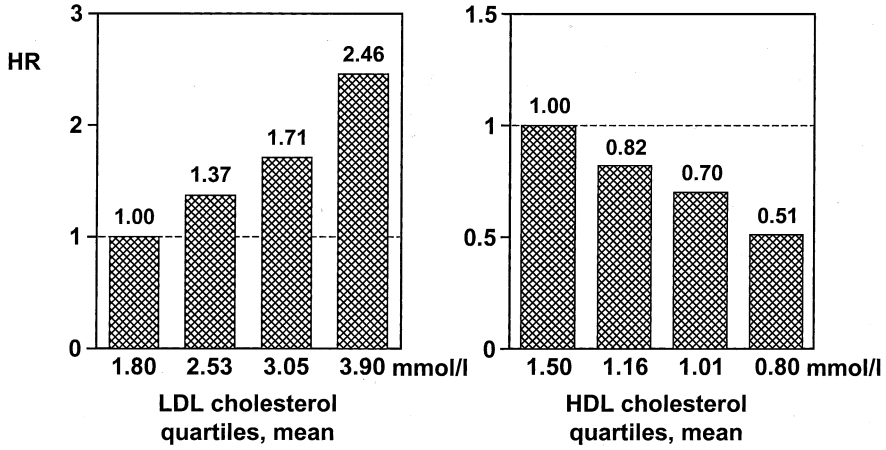

Fig. 3. Hazard ratios for fatal or non-fatal CVD by quartiles of LDL and HDL cholesterol [6].

triglycerides/low HDL-cholesterol cluster. The higher the triglyceride levels are, the more prevalent LDL-phenotype pattern B becomes. This is not a linear, but a curvilinear relationship [7] (Fig. 4). The majority of diabetic people have serum triglyceride levels in a range reflecting LDL-phenotype B.

One of the several studies demonstrating the preponderance of small, dense LDL in type 2 diabetes is the Strong Heart Study. It shows that there is a stepwise decrease in LDL-size according to diabetic status from normal to impaired glucose tolerance, and then to diabetes. This association is more striking in women than in men [8] (Fig. 5). It may be one reason why women lose sex-specific cardioprotection when they are diabetic. Small, dense LDL is mainly generated by the following mechanism: due to the elevation of triglyceride-rich lipoproteins, both VLDL and chylomicron particles remain in circulation for longer periods; this allows for an increased transfer of cholesterol esters, resulting in triglyceride-rich LDL. These are the substrate for the enzyme, hepatic lipase, which is usually elevated in type 2 diabetic individuals. The end product of this process is the formation of small, dense LDL [9] (Fig. 6).

Small, dense LDL is a marker for atherosclerosis. It is easily oxidized and binds more readily to arterial wall proteoglycans. It has also been shown to be an independent determinant of intima-media thickness (IMT) and an independent predictor of coronary artery disease in healthy men [10,11]. Small dense LDL also seems to be associated with endothelial dysfunction, particularly in diabetic patients, as two studies show [12,13]. The size of small, dense LDL correlates with flow-mediated dilatation in type 2 diabetic patients, independent of other lipid variables, such as body mass index, HbA_{1c}, intima-media thickness, blood pressure, and the plasma total peroxyl radical trapping capacity (TRAP). Small, dense LDL, therefore, seems to be associated with very early signs of vascular injury called endothelial dysfunction.

5. HDL changes

In diabetic dyslipidemia, not only the concentration of HDL-cholesterol is reduced, but also its composition and distribution is changed. The electrophoretic spectrum shows a shift towards smaller HDL-particles and HDL2 is reduced [14]. Changes in HDL in type 2

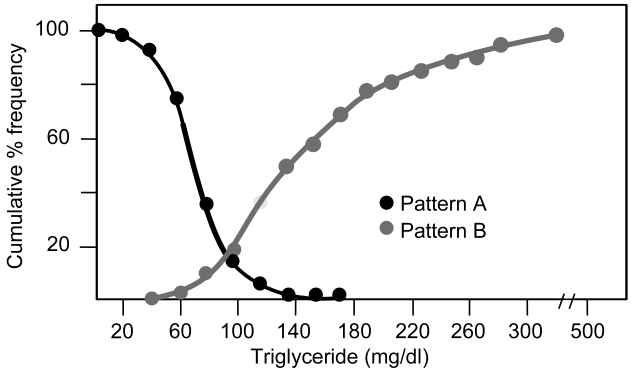

Fig. 4. Cumulative distribution of adjusted TG levels by LDL phenotype.

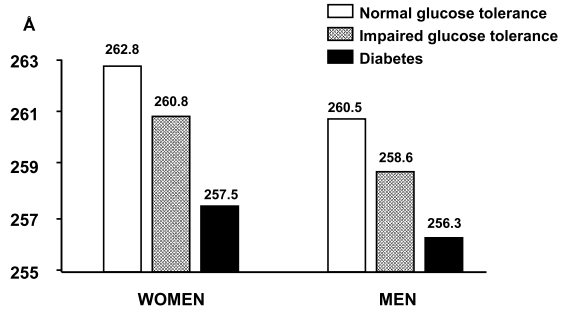

Fig. 5. LDL size by diabetic status and gender.

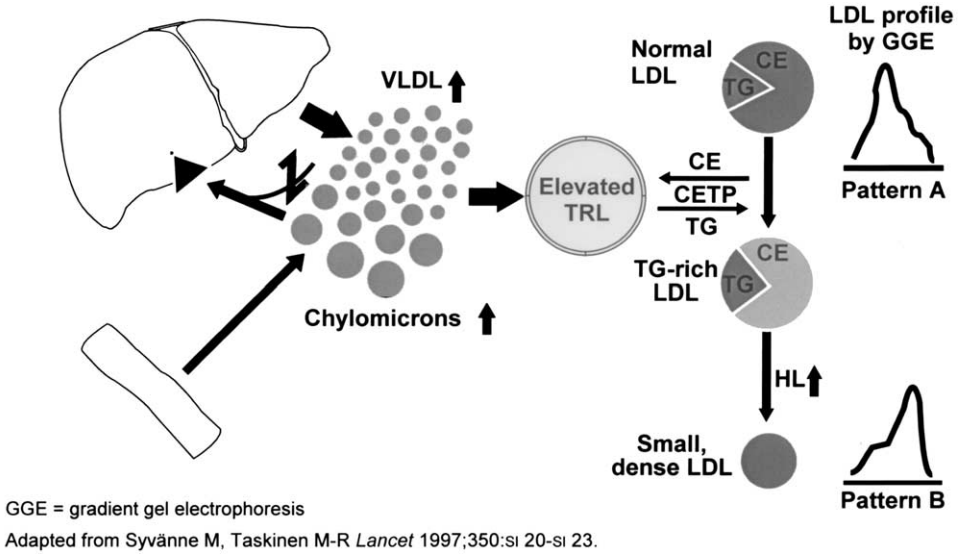

Fig. 6. Proposed mechanisms for generation of small, dense LDL.

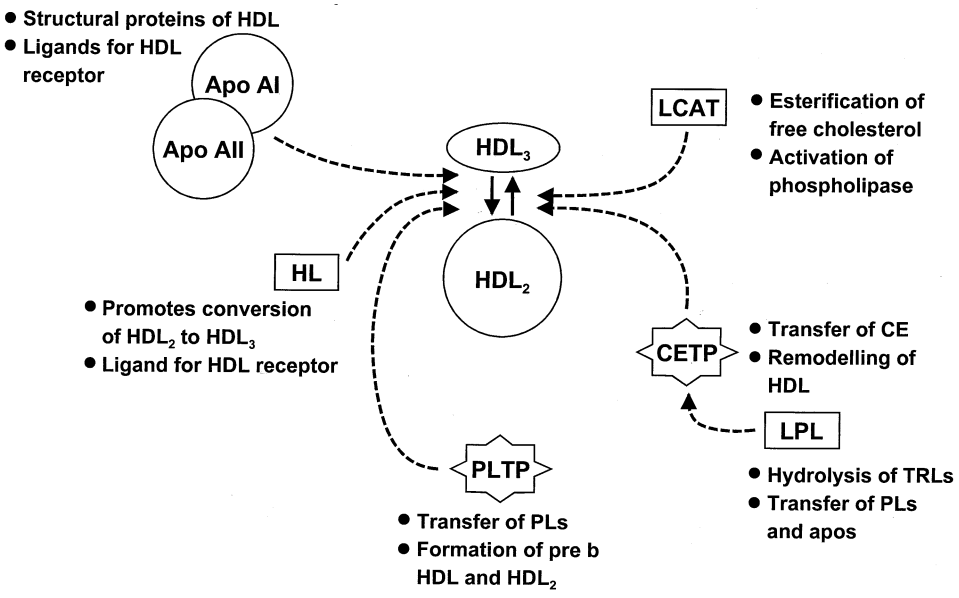

Fig. 7. Enzymes, transfer proteins and apolipoproteins regulating metabolism of HDL.

diabetes are mediated via two pathways: plasma triglyceride elevation, and a reduced ratio between lipoprotein lipase and hepatic lipase. Both lead to a modulation of HDL composition with an enhanced catabolic rate of HDL in circulation. This process results in lower HDL levels.

This appears to be a relatively simple picture, but in reality is much more complicated, because there are other factors involved such as apolipoprotein M and AII (apoA-I, apoA-II), phospholipid transfer protein (PLTP), hepatic lipase (HL), cholesterol ester transfer protein (CETP), lipoprotein lipase (LPL) and lecithin cholesterol acyltransferase (LCAT) (Fig. 7). Several of these factors are modulated by insulin resistance.

6. Conclusion

Altogether, three main lipoprotein particles cause atheroma: small, dense LDL; small, dense HDL; and cholesterol-ester rich remnants resulting from elevation of triglyceride-rich lipoproteins. All these components are elevated in diabetic patients.

In addition, normal lipid concentrations are more atherogenic in diabetic patients than non-diabetic patients due to changes in the composition of lipid particles. This forms the basis for the recommendations that in diabetic patients LDL-cholesterol should be decreased to below 2.6 mmol/l and triglyceride concentrations to below 2.3 mmol/l, and that HDL-cholesterol should be increased above 1.2 mmol/l.

Study	Drug	No.	CHD Risk Reduction (overall)	CHD Risk Reduction (diabetes)
Primary Prevention				
AFCAPS/TexCAPS	Lovastatin	239	–37%	–43%
Secondary Prevention				
CARE	Pravastatin	586	–23%	–25% (P=0.05)
4S	Simvastatin	202	–32%	–55% (P=0.002)
LIPID	Pravastatin	782	–25%	–19%
4S-Extended	Simvastatin	483	–32%	–42% (P=0.001)

Adapted from Downs JR et al *JAMA* 1998;279(20):1615-1622; Pyörälä K et al *Diabetes Care* 1997;20(4):614-620; Goldberg RB et al *Circulation* 1998;98:2513-2519; The Long-Term Intervention with Pravastatin Disease (LIPID) Study Group *N Engl J Med* 1998;339(19):1349-1357; Haffner SM et al *Arch Intern Med* 1999;159:2661-2667.

Fig. 8. CHD Prevention Trials with Statins in Diabetic Subjects: Subgroup Analysis (cont'd).

So far, no large-scale study has specifically investigated whether lipid lowering is beneficial in terms of cardiovascular endpoints in type 2 diabetic patients. There is much evidence that this is the case in diabetic people from retrospective subgroup analyses in a number of landmark studies (Fig. 8). If anything, the message from these studies is that the benefit of lipid lowering in type 2 diabetic patients is at least as great as in the non-diabetic population. At the moment, there are several ongoing studies in more than 15 000 subjects which will prospectively assess this question in type 2 diabetic patients and provide information on tailoring therapy in diabetic patients to achieve the best results.

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