ABSTRACT

By the year 2030, it is assumed that there will be more than 300 million type 2 diabetes sufferers worldwide. Diabetes is a serious vascular disease with poor prognosis, and not only a disease characterized by elevated blood glucose. One important cardiovascular risk factor in type 2 diabetic people is dyslipidaemia. This comprises low HDL-cholesterol, high serum VLDL-triglycerides, and a preponderance of small, dense LDL. Even slight elevations of LDL-cholesterol in type 2 diabetes are associated with a substantial increase in cardiovascular risk. The composition of lipid particles in diabetic dyslipidaemia is more atherogenic than in dyslipidaemia in general. Atherosclerosis is a major complication of diabetes responsible for the increased morbidity and mortality. Lowering of LDL-cholesterol is a very attractive target of lipid modifying therapy, dyslipidaemia therapies are efficacious for both LDL-cholesterol reduction and raising HDL-cholesterol might offer more improvements in coronary heart disease in type 2 diabetic people. Statins are first-line pharmacotherapy for dyslipidaemia and can also improve HDL-cholesterol levels. Combining a fibrate or niacin with statin therapy raises HDL-cholesterol more than a statin alone but might be associated with reduced tolerability and increased adverse reactions. Several new therapeutic approaches to raising HDL-cholesterol are in development, including an HDL mimetic and inhibitors of cholesteryl ester transfer protein. Dyslipidaemia therapies are efficacious for both LDL-cholesterol reduction and raising HDL-cholesterol might offer further improvements in coronary heart disease (CHD) risk reduction.

Key words: Type 2 Diabetes mellitus, Dyslipidaemia, Coronary heart disease, Management.

INTRODUCTION

There were estimated 143 million people worldwide sufferings from diabetes, almost five times more than the estimates ten years ago. This number may probably double by the year 2030. Therefore, the human population worldwide appears to be in the midst of an epidemic of diabetes. Reports from the World Health Organization (WHO) indicate
that diabetes mellitus is one of the major killers of our time, with people in Southeast Asia and Western Pacific being most at risk [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]. Diabetes with myocardial infarction exhibit a greater case fatality [5] and 1-year mortality [6].

**Risk factors for CHD in diabetes**

**Diabetic dyslipidaemia:**
In type-2 diabetes 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 most significant cardiovascular risk factor in type 2 diabetic patients is dyslipidaemia. The main cause of diabetic dyslipidaemia are elevation of serum VLDL-triglycerides and lowering of HDL-cholesterol. LDL-cholesterol, is generally not increased, or only slightly. In the UK Prospective Diabetes Study (UKPDS) study, the initial triglyceride, HDL-cholesterol and LDL-cholesterol levels were not so much different in diabetes and non-diabetes [9]. Almost 50% of type 2 diabetic people have serum triglyceride levels above 1.7 m mol/l and about 25% above 2.3 m mol/l [10].

As in non-diabetes, lipid levels may be affected by factors unrelated to hyperglycaemia or insulin resistance, like renal disease, hypothyroidism, and genetically determined lipoprotein disorders. Abuse of alcohol and estrogen replacement therapy may also contribute to hypertriglyceridaemia [11,12].

**Hyperglycaemia**
Hyperglycaemia is a cardiovascular risk factor [13–15] mainly caused by non-enzymatic glycation of proteins [16] and lipoproteins, which increases atherogenic potency. There is evidence that advanced glycation end products enhance the vulnerability of arteries [17]. Hyperinsulinaemia is caused due to insulin resistance which increased risk of atherosclerosis [18–21]. Regarding diabetes control, a level of haemoglobin A1c > 6.2% is presumed to elevate the risk of cardiovascular disease as reported in some studies [22, 23].

**Blood pressure**
Increased blood pressure is a major risk factor for cardiovascular disease particular in diabetes. 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 [24].

**Other risk factors**
All factors increase the risk of atherosclerotic vascular disease in non-diabetes also do so in diabetes. These factors include smoking, increased levels of homocystein and several coagulation abnormalities.

**Plasma lipids associated with diabetes**

**Total and LDL-Cholesterol:**
The association between plasma total cholesterol and CVD risk is well established. Results from Multiple Risk Factor Intervention 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 m mol/l, to 54.4
per 10,000 person years for men with cholesterol levels above 8.3 m mol/l [25]. 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 diabetes than for a non-diabetes and that this relationship was amplified by serum cholesterol [26]. The UKPDS presented further evidence regarding the association between CVD risk with LDL and HDL-cholesterol levels in non-insulin dependent diabetes [27].

**HDL-Cholesterol:**
An inverse relationship between plasma HDL-cholesterol and CVD risk has been found [28]. In the UKPDS, an inverse relationship with HDL was also seen, with a 1.15 relative risk of CVD associated with each 0.1 m mol/l decrement in HDL-cholesterol.

In diabetic dyslipidaemia, 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 [29]. Changes in HDL in type 2 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.

**Triglycerides:**
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. The significance of hypertriglyceridaemia as a risk factor of non-insulin-dependent diabetes mellitus was also supported by the data from the Paris Prospective Study [30]. 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]. Although the increased risk of elevated triglyceride concentrations is independent of HDL-C levels, in diabetes impaired fasting glucose often have low HDL-C levels as well. Elevated triglyceride levels reduce the effect of lipoprotein lipase and that reduces production of HDL-C [32].

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Lipoprotein class</th>
<th>Diameter (nm)</th>
<th>Lipid contained</th>
<th>Source of lipid</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chylomicron</td>
<td>100-500</td>
<td>TG&gt;&gt;CHE</td>
<td>Diet</td>
<td>Dietary TG transport</td>
</tr>
<tr>
<td>2</td>
<td>Chylomicron. remedy</td>
<td>30-50</td>
<td>CHE&gt;&gt;TG</td>
<td>Diet</td>
<td>Dietary CH transport</td>
</tr>
<tr>
<td>3</td>
<td>VLDL</td>
<td>40-80</td>
<td>TG&gt;&gt;CHE</td>
<td>Liver</td>
<td>Endogenous TG transport</td>
</tr>
<tr>
<td>4</td>
<td>IDL</td>
<td>30-35</td>
<td>CHE&gt;&gt;TG</td>
<td>VLDL</td>
<td>Transport CHE and TG to liver</td>
</tr>
<tr>
<td>5</td>
<td>LDL</td>
<td>20-25</td>
<td>CHE</td>
<td>IDL</td>
<td>Transport CH to tissue and liver</td>
</tr>
<tr>
<td>6</td>
<td>HDL</td>
<td>5-10</td>
<td>Phospholipids, CHE</td>
<td>Tissues, cell membrane</td>
<td>Removal of CH from tissues</td>
</tr>
</tbody>
</table>

TG-triglyceride, CHE-cholesterol, VLDL- very low density lipoprotein, HDL- high density lipoprotein, LDL- low density lipoprotein, IDL – intermediate density lipoprotein, CH- Chylomicron
In addition, the HDL-C produced is small, dense, and has decreased antiatherogenic activity. The kidney more readily clears this smaller HDL-C particle, leading to a further reduction of the HDL-C level [33,34]. The dyslipidaemia associated with diabetes or impaired fasting glucose involves atherogenic, dense LDL-C, low levels of HDL-C, with reduced antiatherogenic activity, and elevated concentrations of triglycerides, each of which markedly increases the risk of mortality. It is shown in table 1:

Management and treatment options of dyslipidaemia in diabetes:
First line agents, which should be used in diabetic dyslipidaemia featuring hypercholesterolemia are statins. They are well tolerated and decrease the LDL-cholesterol levels by 25–55 %, depending on the statin used and dosage. 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 [35].

The US National Cholesterol Education Programme (NCEP) (2001) in its 3rd report delineated the optimal levels of plasma lipids and various grades of hyperlipidaemias and revised the guidelines for use of hypolipidemic drugs. The decision to give hypolipidaemic drugs depends not only on the LDL-C levels and the type of lipid abnormality, but also on associated coronary artery disease risk factor or its equivalent like diabetes, vascular disease etc.

The mechanism of action and profile of lipid lowering effect of important hypolipidaemic drug is summarized in table 2.

Table 2. Mechanism of action and pattern of lipid lowering effect of important hypolipidaemic drugs:[36-40]

<table>
<thead>
<tr>
<th>DRUG (daily dose)</th>
<th>Mechanism of action</th>
<th>Effect of lipids(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin (10-80 mg)</td>
<td>↓ CH synthesis by inhibition of rate limiting HMG-CoA reductase</td>
<td>LDL↓20-55, HDL↑5-15, TG↓10-35</td>
</tr>
<tr>
<td>Simvastatin (5-40 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (10-80 mg)</td>
<td></td>
<td></td>
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<tr>
<td>Bile acid sequestrants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine (4-16 gm)</td>
<td>↓ bile acid absorption</td>
<td>LDL↓15-30, HDL↑5-15, TG not affected may ↑ in some</td>
</tr>
<tr>
<td>Colestipol (5-30 gm)</td>
<td>↑ hepatic conversion of CH to bile acids</td>
<td></td>
</tr>
<tr>
<td>↑ LDL receptors on hepatocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzafibrate (1200 mg)</td>
<td>↑ Activity of lipoprotein lipase</td>
<td>LDL↓5-20, HDL↑10-20, TG↑20-50</td>
</tr>
<tr>
<td>Fenofibrate (200 mg)</td>
<td>↓ Release of fatty acids from adipose tissue</td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid (2-6 gm)</td>
<td>↓ production of VLDL</td>
<td>LDL↓15-25, HDL↑20-35, TG↓20-50</td>
</tr>
</tbody>
</table>

For lowering LDL-C first choice of drug are statins, for raising HDL-C level first choice of drugs are niacin or fibrates and for lowering triglyceride level fibric acid derivative is the important drugs but statins are also effective at high doses with elevated levels of triglycerides and LDL-C. Combination therapy with a statin is often required. The statin may be combined with either niacin or with a fibrate. Both agents have been shown to be safe when combined with a statin. Also, both combinations have the ability to reduce...
cardiovascular events in patients with diabetes. These combinations, together are helpful in controlling triglyceride levels, a common derangement in diabetic dyslipidaemia.

CONCLUSION

Atherosclerosis is a major complication of diabetes. The increased incidence of CVD in diabetes, the greater case fatality and 1-year mortality in patients with myocardial infarction [41] strongly suggest that preventive lowering of lipid levels, potentially to goals accepted for secondary prevention, is of great importance. 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? How safe is the combination therapy? Are the effects of a combination therapy complimentary? 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.

REFERENCES