TREATMENT OF DIABETIC DYSLIPIDAEMIA

MARGO A. DENKE and SCOTT M. GRUNDY
Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX 75235-9052, U.S.A.

Lipid evaluation in a diabetic patient begins with averaging several measurements of blood sugar, total cholesterol, triacylglycerol and high-density lipoprotein (HDL) cholesterol after a 12 h fast. Patients with non-insulin-dependent diabetes may have any one of several lipid disorders [1], but typically diabetic dyslipidaemias share the characteristics of high very-low-density lipoprotein (VLDL) cholesterol levels and low HDL cholesterol levels [2]. Lipid disorders can be classified as in Table 1. Aggressive, appropriate treatment of these disorders may be crucial because of this population's increased risk of cardiovascular disease. Diabetics may not respond to the usual diet and drug regimens useful in non-diabetics [3] (Table 2). This paper briefly outlines a treatment approach to these disorders, including diet and drug therapy.

Abbreviations used: HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HMG-CoA, hydroxymethylglutaryl-CoA.

Initial treatment: diabetic control

Non-insulin-dependent diabetes is a disorder of insulin metabolism. As reviewed by other contributors to this Colloquium, insulin affects both glucose and triacylglycerol metabolism. Since triacylglycerols are an integral part of lipoproteins, lipoprotein metabolism is altered. Increased production rates and decreased fractional clearance rates, as well as changes in lipoprotein composition, may be found.

For this reason, the first step in the treatment of diabetic dyslipidaemia is to improve the underlying derangement in insulin metabolism. This may be broken down into three components: (1) weight loss, (2) adherence to a diabetic diet and (3) adjustment of insulin or oral hypoglycaemic agents to improve fasting blood sugar.

(1) Weight loss. Clinically, weight loss, or a hypocaloric diet without achieving ideal body weight, will improve diabetic control, presumably by reducing the resistance to the peripheral action of insulin [4, 5].

(2) Adherence to a diabetic diet. The exchange diet recommended by the American Diabetes Association allows the patient to plan the distribution of total calories and sources of calories (fat, protein, carbohydrate) over the day. A more even distribution of calories (be they fat or carbo-

Table 1. Classification of dyslipidaemias in diabetics

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Triacylglycerol</th>
<th>HDL</th>
<th>Class</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>200–240</td>
<td>&lt; 250</td>
<td>Normal or low</td>
<td>Mild hypercholesterolaemia</td>
<td>May respond to weight loss, low-saturated-fat diet; bile acid sequestrants in selected patients or HMG-CoA reductase inhibitors.</td>
</tr>
<tr>
<td>&gt; 240</td>
<td>&lt; 250</td>
<td>Normal or low</td>
<td>IIa</td>
<td>May respond to weight loss, low-saturated-fat diet; bile acid sequestrants in selected patients or HMG-CoA reductase inhibitors.</td>
</tr>
<tr>
<td>&gt; 240</td>
<td>&gt; 250</td>
<td>Normal or low</td>
<td>III</td>
<td>Apolipoprotein E abnormality confirmed with phenotyping; responds to weight loss and low-fat diet; fibric acid derivatives or HMG-CoA reductase inhibitors.</td>
</tr>
<tr>
<td>&gt; 240</td>
<td>&gt; 250</td>
<td>Normal or low</td>
<td>Mixed hyperlipidaemia</td>
<td>May not resolve with improved diabetic control; HMG-CoA reductase inhibitors are the drug of choice.</td>
</tr>
<tr>
<td>&lt; 240</td>
<td>250–500</td>
<td>Normal or low</td>
<td>IV</td>
<td>May respond to weight loss or improved diabetic control; high-fat diet may improve; fibric acid derivatives in selected patients or HMG-CoA reductase inhibitors.</td>
</tr>
<tr>
<td>&gt; 240</td>
<td>&gt; 500</td>
<td>Low</td>
<td>V</td>
<td>Typically the result of poor diabetic control; low-fat diet indicated; fibric acid derivatives are the drug of choice.</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>&lt; 250</td>
<td>&lt; 40</td>
<td>Low HDL</td>
<td>May respond to high-fat diet; HDL levels have not increased to levels seen in non-diabetics with drug therapy.</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Nephrotic syndrome</td>
<td>HMG-CoA reductase inhibitors are the only known effective treatment besides improved diabetic control.</td>
</tr>
</tbody>
</table>

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to be well tolerated in diabetics and may lead to improved food choices, since stearic acid comprises more than one-third of the saturates in beef and pork. High-fat diets that are low in saturated fatty acids appear to be well tolerated in diabetics and may lead to improved glucose control, decreased fasting triacylglycerol and increased HDL cholesterol levels [12]. The significance of an increase in non-esterified fatty acids seen in this type of diet has yet to be balanced against these positive effects in the research setting.

3. Adjustment of hypoglycaemic agents to improve diabetic control. In our experience, the diabetic dyslipidaemia may improve even when the fasting blood sugar is brought from 140 mg/100 ml to less than 120 mg/100 ml. There is no clinical evidence that the use of one type or another of glucose-lowering drugs (oral agents versus insulin) is better for lipid lowering if these two treatment programmes provide equivalent control of fasting blood sugar levels. This further supports the link between dyslipidaemia and blood sugar, and before contemplating drug therapy (which will not improve the insulin abnormalities) all efforts should be aimed at the primary cause of the dyslipidaemia itself.

Drug therapy

Dyslipidaemias may change in character after improved diabetic control (e.g. type V changing to type IV). Using the classifications in Table 1, and the known effects of common lipid-lowering drugs detailed in Table 2, treatment of specific dyslipidaemias are discussed below.

Mild hypercholesterolaemia with normal triacylglycerol levels. Weight control and control of fasting blood sugar are important components of the appropriate treatment. Weight control is important even in patients who do not have a triacylglycerol disturbance, as it is known that overfeeding in normal subjects leads to a 20 mg/100 ml increase in total cholesterol for the first 20 kg of excess body weight [16]. If weight loss is unsuccessful, the use of typical agents recommended for non-diabetics (nicotinic acid, bile acid sequestrants) may be associated with adverse side effects. Niacin may worsen plasma glucose and uric acid levels. Bile acid sequestrants increase VLDL cholesterol levels, and in diabetics this could potentially lead to a worsening of the dyslipidaemia. We recommend the drug of first choice as bile acid sequestrants, with careful follow-up of fasting triacylglycerols.

### Table 2. Effect of common lipid-lowering drugs in diabetic dyslipidaemia

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Lipoprotein effects</th>
<th>Considerations for use in diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>Lower LDL and total cholesterol levels; increases VLDL levels and may increase triacylglycerols.</td>
<td>Exacerbates the typical increase in VLDL seen in diabetics; causes constipation, a potential problem in diabetics with autonomic neuropathy.</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Lowers VLDL, LDL, total cholesterol and triacylglycerol levels; increases HDL cholesterol levels.</td>
<td>Exacerbates glucose intolerance; increases uric acid levels.</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Lowers VLDL and triacylglycerol levels; may increase LDL and total cholesterol levels; increases HDL levels.</td>
<td>Increases lithogenicity of bile.</td>
</tr>
<tr>
<td>Probufol</td>
<td>Lowers LDL and HDL cholesterol levels.</td>
<td>May provide a theoretical advantage as an antioxidant for LDL; lowering of HDL cholesterol may be seen.</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Lowers total cholesterol, VLDL and LDL levels; mild decrease in triacylglycerols seen; increases HDL cholesterol levels.</td>
<td>Long-term potential toxicity in humans unknown.</td>
</tr>
</tbody>
</table>
levels as well. Glycerol levels in 3-6 weeks. If the triacylglycerol concentration is greater than 250 mg/100 ml, we consider the patient the preferred treatment, as these agents decrease VLDL concentration.

Type III: high cholesterol levels with normal triacylglycerol concentrations. Beyond weight loss, a low-saturated-fat and low-cholesterol diet, and improved diabetic control, cautious use of bile acid sequestrants may improve this disorder in selected patients. HMG-CoA reductase inhibitors may be the preferred treatment, as these agents decrease VLDL levels as well as LDL levels. Our experience is that the potential toxicity of this class of drugs in humans is still unknown.

Mixed hyperlipidemia (including type IIb). After weight reduction and improved diabetic control, HMG-CoA reductase inhibitors are the drug of choice for mixed hyperlipidemia. In rare cases where the LDL cholesterol is not increased, fibric acid derivatives with or without low-dose bile acid sequestrants (dose not to exceed 15 g/day) may be effective.

Type III hyperlipidemia. The presence of this disorder can be confirmed by apolipoprotein E phenotyping. This disorder is partially due to a defect in the apolipoprotein E. Particles which rely on receptor recognition clearing apo- lipoprotein E (such as VLDL remnants and chylomicron remnants) have reduced fractional clearance rates if they are rich in the E2 isofrom. Normally, only 10% of patients homozygous for the E2 isofrom express the dyslipidemia; however, diabetics with this E2/2 phenotype may more commonly express this disease, as over half of the patients with type III are obese and have abnormal glucose tolerance tests [17]. The optimum dietary therapy is a low-fat diet, which will reduce formation of chylomicrons and chylomicron remnants. Drug therapy includes either fibric acid derivatives or HMG-CoA reductase inhibitors.

Type IV hyperlipidemia. This disorder may respond immediately to weight loss and improved diabetic control. In our experience, redistribution of calories to give a more con- 

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Type V hyperlipidemia. This disorder is most commonly seen in poorly controlled diabetics. Therapy should be aimed at improving diabetic control and, if triacylglycerol concentrations are greater than 1000 mg/100 ml, decreasing the risk for pancreatitis. A low-fat diet, by decreasing the formation of chylomicrons, is helpful particularly during the acute phase of the disorder. Fibric acid derivatives are the drug of choice.

Low HDL cholesterol levels. This may be the most common dyslipidemia in well-controlled diabetics. Unfortunately, none of the drugs known to increase HDL levels have been effective in diabetics. Niacin may worsen glucose control; fibric acid derivatives and HMG-CoA reductase inhibitors have failed to increase HDL cholesterol levels in diabetes to normal [18, 19]. We are left with conservative measures such as weight loss and a high-fat (with low saturated fatty acids) diet. Nephrotic syndrome. The nephrotic syndrome may be accompanied by any of the above dyslipidaemias. The only effective drug treatment for this disorder involves the use of HMG-CoA reductase inhibitors.

Conclusion

The treatment of diabetic dyslipidaemia is different to that of similar dyslipidaemias in the non-diabetic population. Before beginning drug therapy, emphasis should be placed on weight loss, improved diabetic control, the use of an exchange diet to spread out the timing of calories, and, in some disorders of triacylglycerols and HDL, a carefully selected high-fat diet that is low in saturated fatty acids. The choice of drugs is limited in diabetics. Niacin, because of its tendency to worsen glucose control, cannot be widely used. Bile acid sequestrants can be used only in carefully selected patients who do not develop hypertriglyceridaemia from this treatment. Fibric acid derivatives are effective in lowering triacylglycerol, but in patients with a combined defect may lead to further increases in LDL cholesterol levels. HMG-CoA reductase inhibitors, while effective in many of these disorders, must be used with caution until the long-term toxicity of these agents is known.


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