Review Article

Atherogenic Dyslipidemia and its Management in Diabetes

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Abstract: Atherogenic dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. In patients treated with a statin to LDL-cholesterol goals, the addition of ezetimibe, fenofibrate, niacin, or n-3 fatty acid ethyl esters may be required to correct the persistent atherogenic dyslipidemia.

Keywords: Atherogenic dyslipidemia, Type 2 diabetes, Lipids, Lipoproteins, pharmacotherapy.

INTRODUCTION

In 1990, Austin and colleagues first explained Atherogenic Dyslipidemia (AD) as a clinical condition [1] characterized by elevated levels of serum triglyceride (TG) levels and small-dense low-density lipoprotein (sdLDL) particles with low levels of high-density lipoprotein cholesterol (HDL-C), highlighting its atherogenic lipoprotein phenotype[2]. With a focus on type 2 diabetes patients, we review in this article recent clinical trials employing therapeutic agents for the treatment of atherogenic dyslipidemia.

Atherogenic Dyslipidemia

Atherogenic dyslipidemia is one of the metabolic abnormalities that define the metabolic syndrome, the cluster of cardiovascular risk factors frequently associated with intra-abdominal (or visceral) obesity. Diabetic dyslipidemia involves a cluster of lipid and lipoprotein abnormalities. Elevated plasma concentrations of triglycerides and reduced high density lipoprotein cholesterol (HDL-Cholesterol), in both the fasting and postprandial states, are the core lipoprotein abnormalities[3]. Insulin resistance believed to contribute to this atherogenic dyslipidemia by increasing the hepatic secretion of VLDL and other apolipoprotein (apoB)-containing lipoprotein particles, as a result of increased free fatty acid flux to the liver[4,5]. This may also be the result of a diminished suppressive effect of insulin on apoB secretion, either at the level of the regulation of apoB degradation, or inhibition of microsomal TG transfer protein activity[6]. Through the action of cholesterol ester transfer protein, TGs are transferred from VLDL to HDL, creating TG rich HDL particles, which are hydrolyzed by hepatic lipase and rapidly cleared from plasma[7]. A similar cholesterol ester protein-mediated transfer of TGs from VLDL to LDL contributes to the formation of small dense LDL particles[8].

Guidelines for the management of Atherogenic dyslipidemia

Several guidelines provide evidence-based recommendations for addressing diabetic dyslipidemia [9, 10-13]. Two recent reports more specifically on elevated triglycerides and low HDL cholesterol [14].

Table 1: summarizes the recommended treatment targets for diabetic dyslipidemia.

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>NCEP ATPIII</th>
<th>ADA</th>
<th>NVDPA</th>
<th>European guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>Very high risk</td>
<td>&lt; 1.8</td>
<td>&lt; 1.8</td>
<td>&lt; 1.8</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>&lt; 2.6</td>
<td>&lt; 2.6</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td></td>
<td>&lt; 1.7</td>
<td>&lt; 2.0</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>Male</td>
<td>&gt; 1.0</td>
<td>≥ 1.0</td>
<td>&gt; 1.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&gt; 1.3</td>
<td>≥ 1.0</td>
<td>&gt; 1.2</td>
</tr>
<tr>
<td>Non HDL-cholesterol (mmol/l)</td>
<td>Very high risk</td>
<td>&lt; 2.6</td>
<td>&lt; 2.6</td>
<td>&lt; 2.5</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>&lt; 3.4</td>
<td>&lt; 2.5</td>
<td>&lt; 3.3</td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>Very high risk</td>
<td>&lt; 0.8</td>
<td>&lt; 0.8</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>&lt; 0.9</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
</tr>
</tbody>
</table>
to moderate chronic kidney disease, including diabetes[19]. The lipid-regulating effects of fibrates, mediated via the peroxisome proliferator-activated alpha (PPAR-α) receptor, predominantly promote fatty acid catabolism and reverse cholesterol transport, resulting in triglyceride lowering and increased HDL-Cholesterol and LDL particle size[20]. Fibrates also increase HDL-Cholesterol by up to 50% and 20%, and enhance the formation of large, less dense LDL-particles Clinical trials also confirm the benefits of fibrates in type 2 diabetes[21-24].

**Ezetimibe:** It is a selective cholesterol absorption inhibitor, is an effective lipid-lowering agent when used as monotherapy and is useful in patients who are unable to tolerate statin therapy. Ezetimibe can also be used in combination with statin therapy for greater lipid lowering efficacy. Ezetimibe plus atorvastatin, for example, can provide LDL-C lowering equivalent to that achieved with high dose atorvastatin, but with better tolerability in some patients, and may be a useful adjunctive therapy in patients with type 2 diabetes who have demonstrated an inadequate response to statin treatment.

**Nicotinic Acid (niacin):** At therapeutic doses, niacin exerts a global improvement in lipid and lipoprotein metabolism, and remains the most efficacious therapy available for increasing HDL cholesterol. Niacin has been shown to decrease plasma triglycerides and LDL-cholesterol by up to 35% and 15% respectively, and increase HDL-cholesterol by up to 30% in a dose dependent manner. It was suggested in the Coronary Drug Project (CDP) that niacin monotherapy may decrease cardiovascular events and mortality with post-trial follow up demonstrating that the benefits were independent of hyperglycemia, metabolic syndrome, and diabetes. This is important as it has been suggested that niacin impairs glucose/insulin homeostasis. Niacin significantly improves diabetic dyslipidemia, and may deteriorous effects on glycemic control can be offset by adjusting anti-diabetic therapy.

**N-3 fatty acid ethyl esters:** Supplementation with n-3 fatty acid ethyl esters (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), dose dependently lowers plasma triglycerides, particularly in patients with hypertriglyceridemia[25]. Doses of 3-4g daily of EPA and DHA are required. Therefore, commercially available concentrates of n-3 fatty acid ethyl esters, such as omearc, are required for lowering plasma triglycerides. These are FDA approved, as an adjunct to diet, to mitigate the risk of pancreatitis in patients with plasma triglycerides>5.5mmol/l.

**CONCLUSION**

Atherogenic dyslipidemia is a part of complex cluster of abnormalities called the metabolic syndrome which has a direct correlation with CVD events.
Dyslipidemia is a common risk factor and a strong predictor of CVD in type 2 diabetes. Therapeutic interventions, including lifestyle changes and lipid regulating agents, correct diabetic dyslipidemia via several mechanisms. Recent evidence suggests that residual diabetic dyslipidemia and cardiovascular risk in statin-treated patients with type 2 diabetes may be targeted with fenofibrate.

REFERENCES
18. Guyton JR, Bays HE; Safety considerations with niacin therapy. Am J Cardiol, 2007; 99(6A):22C-31C.