Diabetic Dyslipidemia: Clinical Significance and Management

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INTRODUCTION

"Diabetic dyslipidemia" refers to lipid abnormalities specifically seen in type-2 diabetes mellitus (T2DM) and the most common pattern is increased triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) along with a preponderance of low-density lipoprotein cholesterol (LDL-C) even when the absolute LDL-C values may not be very high. This pattern of dyslipidemia exists in patients who are metabolically obese.\(^1\) Individuals with atherogenic dyslipidemia have 3–6 times higher risk for cardiovascular (CV) events.\(^2\textsuperscript{-4}\)

MECHANISM

Dyslipidemia in T2DM is linked with insulin resistance, along with increased lipolysis and decreased fatty acid uptake in the skeletal muscle. There is increased supply of nonesterified fatty acid in the liver which in turn leads to TG synthesis.\(^5\) Increased very low density lipoprotein (VLDL) levels and decreased breakdown of TG-rich lipoproteins result in increased TG-rich lipoproteins.\(^6\)

The HDL-C in diabetes is TG enriched and there is increased glycosylation of apoproteins in HDL particles that lead to accelerated HDL catabolism and this results in lower HDL-C levels. The TG from VLDL is exchanged for cholesterol ester from LDL particles, and due to increased VLDL levels, there is an increased generation of TG-rich LDL particles in individuals with T2DM. The latter are hydrolyzed to form small-dense LDL particles, that are highly atherogenic.

The pattern of dyslipidemia may differ in different types of diabetes. Increased TG and reduced HDL-C is the most common pattern of dyslipidemia seen in T2DM,\(^7\) while elevated TG level along with increased chylomicrons is the most predominant dyslipidemia in type 1 diabetes mellitus (TIDM). The elevated TG is related to insulin deficiency and usually normalizes with improvement in glucose control either with insulin or oral hypoglycemic agents.

CLINICAL TRIALS OF DIABETIC DYSLIPIDEMIA

A number of Primary and Secondary Prevention trials have been done on dyslipidemia using statins. The Primary Prevention trials include AFCAPS (Air Force Coronary Atherosclerosis Prevention Study),\(^8\) WOSCOPS (West of Scotland Coronary Prevention Study),\(^9\) HPS (Heart Protection Study),\(^10\) CARDS (Collaborative Atorvastatin Diabetes Study).\(^11\)
The Secondary Prevention trials include 4S (Scandinavian Simvastatin Survival Study),\textsuperscript{12} CARE (Cholesterol and Recurrent Events) and LIPID (Long-term Intervention with Pravastatin in Ischemic Disease),\textsuperscript{13} IDEAL trial [Intensive statin versus low-moderate therapy in stable coronary artery disease (CAD) patients with previous myocardial infarction (MI)]\textsuperscript{14} and Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH).\textsuperscript{15}

The above mentioned trials clearly present us with the efficacy of statin therapy in patients with diabetic dyslipidemia and showed that statins provide significant reductions in mortality, major CV events and their need for coronary artery surgical procedures. Also, statins prevent MI, stroke and death. Additionally, statins are also highly effective in delaying and avoiding costly surgical procedures by primary prevention. Asian Indians have twice the risk of CAD and thrice the risk of diabetes when compared to Whites after adjusting for already existing risk factors for these conditions.\textsuperscript{16,17} In Asian Indians, current evidence supports statin therapy for primary prevention at a younger age with lower targets for LDL-C and non-HDL-C, than those recommended for Americans and Europeans.\textsuperscript{18}

**OTHER CAUSES OF DYSLIPIDEMIA IN DIABETIC PATIENTS**

As per the Adult Treatment Panel-III (ATP-III) guidelines, some of the patients may have primary dyslipidemia (e.g., familial hypercholesterolemia), but secondary dyslipidemia is also much common. The common causes of secondary dyslipidemia are T2DM, cholestatic liver disease, nephrotic syndrome, obesity, hypothyroidism and drugs like thiazide diuretics, β-blockers and steroids.

**TREATMENT GOALS**

The American Diabetes Association (ADA) recommendation [based on the National Cholesterol Education Program (NCEP)-ATP guidelines] state that the initial target is to lower LDL-C followed by reduction in triglyceride levels and increased HDL-C.\textsuperscript{19,20}

Treatment goals of desired levels of diabetic dyslipidemia as laid down by Lipid Association of India (LAI)\textsuperscript{21} include the following:

- LDL-C: Patients without cardiovascular disease (CVD)—less than 100 mg/dL
- LDL-C: Patients with overt CVD—less than 70 mg/dL
- Non-HDL-C: Patients without CVD less than or equal to 130 mg/dL
- Non-HDL-C: Patients with CVD less than or equal to 100 mg/dL
- HDL-C: Desired level (men)—more than 40 mg/dL and (women)—more than 50 mg/dL
- Triglyceride: Desired level less than 150 mg/dL.

**MANAGEMENT OF DIABETIC DYSLIPIDEMIA**

**Lifestyle Modifications**

Lifestyle modifications play an important role in controlling obesity, hyperglycemia and hypertriglycerideremia in patients with T2DM. These changes include weight reduction, healthier diets, increased physical activity, reduced alcohol consumption, stopping smoking habit and quitting tobacco use. In T2DM, even moderate weight reduction lowers TG levels by up to 25% and helps in normalization of postprandial TG concentrations.
Pharmacotherapies

**Statin Monotherapy**

Statins remain the cornerstone of treatment for diabetic dyslipidemia and this is supported by numerous trials. While LDL-C targets can be attained in most patients, more potent statins like atorvastatin and rosuvastatin can also modestly reduce plasma TG levels by increasing lipolysis. Statins are beneficial in reducing coronary events - coronary heart disease (CHD), CHD mortality, cerebral stroke and procedures like percutaneous coronary angioplasty (PTCA), coronary artery bypass graft (CABG).\(^{22}\)

For any given level of total cholesterol, Indians tend to have a greater elevation in non-high-density lipoprotein cholesterol by virtue of increased TG and reduced HDL-C.\(^{23,24}\) Non-HDL-C plays a major role in CVD especially in Indians. The LAI\(^{21}\) guideline advocates the use of high and moderate intensity statin therapy for most Indians with or at risk of CAD including those with high TG.\(^{25-28}\) Statin therapy is highly effective in lowering non-HDL-C, LDL-C, apolipoprotein and remnant cholesterol. Table 1 shows the ADA Guidelines for statin therapy in lipid management.\(^{29}\)

**Fibrates and Statin-Fibrate Combination**

Fibrates act on peroxisome proliferator-activated receptor-α (PPAR-α)\(^{30}\) and they are most effective in diabetes patients whose TG are elevated (>195 mg/dL) with reduced HDL-C (<39 mg/dL). In addition, the statin-fibrate combinations also have a favorable effect on lipid abnormalities in T2DM patients and combined hyperlipidemia.\(^{31}\) There are occasional reports of the HDL-C levels going down very low, if combination therapy of statin/fibrate is used.\(^{32}\)

**TABLE 1: Statin therapy for lipid management\(^{29}\)**

<table>
<thead>
<tr>
<th>Individuals with diabetes and ASCVD*</th>
<th>High-intensity statin therapy + lifestyle changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 years with diabetes and ASCVD risk factors</td>
<td>Moderate- or high-intensity statin + lifestyle</td>
</tr>
<tr>
<td>Age 40–75 years with diabetes but without ASCVD risk factors</td>
<td>Moderate-intensity statin + lifestyle</td>
</tr>
<tr>
<td>Age 40–75 years with diabetes and ASCVD risk factors</td>
<td>High-intensity statin + lifestyle</td>
</tr>
<tr>
<td>Age more than 75 years with diabetes but without ASCVD risk factors(^{1})</td>
<td>Moderate- or high-intensity statin + lifestyle</td>
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</tbody>
</table>

The intensity of statin therapy may require adjustment based on an individual’s response

**ASCVD risk factors**

- LDL-C more than or equal to 100 mg/dL (2.6 mmol/L)
- High blood pressure
- Smoking
- Overweight or obesity
- Family history of premature ASCVD

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Note:
- \(^*\)Regardless of age.
- \(^1\)Routinely evaluate risk-benefit profile of statin therapy, with down-titration as needed.
Niacin and Statin-Niacin Combination

Niacin has helpful effects on lipid and lipoprotein metabolism in addition to its extrahypolipidemic effects of which most important are anti-inflammatory and antioxidative actions and increasing serum adiponectin level. However, niacin has been shown to have some undesirable side effects such as gastrointestinal discomfort, pruritus and flushing. Hence, its popularity has waned in recent years.

Ezetimibe and Statin-Ezetimibe Combination

Ezetimibe lowers LDL-C incremental to statins by preventing the cholesterol absorption in the intestines via Niemann-Pick C1-Like 1 protein. Whereas its effects are minimum on fasting TG and HDL-C, but it can improve postprandial plasma TG significantly in diabetic patients. Both (statin and ezetimibe) when combined together can reduce the progression of carotid atherosclerosis. The action of ezetimibe 10 mg and a statin is equivalent to a statin at a higher dose and there is usually no increase in liver and or muscle-related side effects with combination therapy.

N-3 Fatty Acid and Statin-n-3 Fatty Acid Combination

Supplemental n-3 polyunsaturated fatty acids (PUFAs), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid, reduce TG levels. Recent clinical trials, however, did not show any significant CVD benefits, using lower doses of n-3 PUFAs (1 g/day).

Saroglitazar

Saroglitazar is a new drug and has a dual Peroxisome Proliferator-activated Receptors-α/γ agonist action. It has been approved by Drug Controller General of India (DGGCI) for treating diabetic dyslipidemia. It is relatively free of side effects and specifically there is no increase of body weight. Saroglitazar has shown reduction in fasting glucose (11 mg/dL reduction in 2 mg arm and 22 mg/dL reduction in 4 mg arm) and in HbA1c by 0.3%. Also, 2 mg and 4 mg therapy has shown more than 40% reduction in TG.

Safety of Combination Lipid-lowering Therapy

Diabetic patients on statin and fibrate may commonly have musculoskeletal symptoms. In such cases, plasma creatine kinase should be measured and, if it is five times beyond the upper limit, the second drug should be terminated. One of the harmful side effects is hepatotoxicity, when statin is combined with either a fibrate or niacin. Plasma creatinine levels should be tested every 3 months in patients receiving fenofibrate although the mild increase is reversible.

Therapies in the Pipeline

Some of the new therapies are inhibitors of diacylglycerol O-acyltransferase, proprotein convertase subtilisin/kexin type 9 (PCSK-9), cholesteryl ester transfer protein (CETP) and microsomal TG transfer protein among others. Their efficacy and long-term safety in humans need to be established further, although PCSK-9 is showing great promise.

CONCLUSION

In diabetic patients, atherosclerosis is the foremost cause of death and hence dyslipidemia should be treated aggressively. Statins remain the most commonly used medications and indeed lowering of LDL-C is the first step in diabetic dyslipidemia. Apart from statins,
healthier diets, increasing physical activity and weight reduction (if overweight/obese) are of paramount importance. Several other drugs like fibrates, saroglitazar and some of the newer agents also show great promise and may be used whenever appropriate.

REFERENCES


34. Guyton JR, Bays HE. Safety considerations with niacin therapy. Am J Cardiol. 2007;99:22C-31C.


