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DIABETIC DYSLIPIDEMIA – CURRENT MANAGEMENT GUIDELINES

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ABSTRACT

Diabetic dyslipidemia is immensely common in type 2 diabetes (T2DM), affecting about 70% of patients. It is a bundle of lipoprotein abnormalities characterized by increased triglyceride levels, decreased levels of high-density lipoprotein cholesterol, and increased levels of small, dense low-density lipoprotein (LDL). Diabetes and dyslipidemia are two independent risk factors for atherosclerosis with overlapping pathophysiology. Together, they accelerate the process of atherogenesis and exponentially increase cardiovascular risk. For atherosclerotic cardiovascular disease (ASCVD), diabetes is a significant risk factor, and the most important predictor of ASCVD events in T2DM is LDL cholesterol. This review aims to discuss the pathophysiology and management of diabetic dyslipidemia and provide an understanding of the topic, focusing on diabetes mellitus, followed by the metabolic changes caused by DM, understanding dyslipidemia and its lipid levels, and recent management goals.

Recent advances

The linchpin of treating diabetic dyslipidemia, especially in patients with diabetes and cardiovascular disease (CVD), is lowering LDL. Statin therapy is the treatment of choice and the cornerstone for reducing ASCVD by lowering LDL-C. Complementary therapy, particularly

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with ezetimibe, fibrates, bile acid sequestrants, PCSK9 inhibitors, and omega-3 fatty acids, should be considered, as well as selected new agents to lower blood glucose. Ezetimibe is cost-effective, and PCSK9 inhibitors enhance LDL cholesterol lowering and ASCVD event reduction. In hypertriglyceridemia, fish oil, fenofibrate, and diet are the best strategies to reduce the risk of pancreatitis.

Key Words: Diabetes, Dyslipidemia, ASCVD, Statins, Ezetimibe, PCSK9

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in men and women with diabetes (about 50-70% of deaths) [1]. Diabetes is a significant risk factor for ASCVD and the leading cause of mortality. People with diabetes are 2-4 times more likely to die from ASCVD than non-diabetics. The rapidly increasing number of diabetics, which rose from 108 million in 1980 to 442 million in 2014, poses a significant threat worldwide. [2] Numerous studies have shown that patients with diabetes and cardiovascular disease are at very high risk of another event, suggesting that this population needs incredibly aggressive preventive measures. Several lines of evidence indicate that patients with T1DM are also at increased risk for developing cardiovascular disease. In addition, having T1DM at a young age increases the risk of cardiovascular disease more than having T1DM later in life.[1]

Diabetes can cause both microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications (ASCVD), manifesting as coronary artery disease, stroke, and peripheral arterial disease. Dyslipidemia in diabetes is common and is characterized by hypertriglyceridemia (HTG) with decreased levels of high-density lipoprotein (HDL) cholesterol. Low-density lipoprotein (LDL) cholesterol levels are usually not elevated; small, dense LDL particles predominate and tend to be atherogenic.[2]Premature ASCVD due to increased apolipoprotein B-bearing particles and pancreatitis with severe HTG > 1000 mg/dl are the two main consequences of diabetic dyslipidemia. Because lipid abnormalities are more common in diabetes mellitus and are due to insulin resistance or insulin deficiency affecting crucial enzymes and pathways of lipid metabolism, hyperglycemia, dyslipidemia, and coronary artery disease are closely related in type 2 diabetes. The higher prevalence of cardiovascular disease in type 2 diabetes is thought to be due to chronic, uncontrolled hyperglycemia.[3]

LIPID METABOLISM ABNORMALITIES IN DIABETES

Impaired lipoprotein metabolism is associated with impaired lipoprotein in type 1 and 2 diabetes. Four features characterize diabetes dyslipidemia,

1. Hypertriglyceridemia,
2. Low levels of high-density lipoprotein cholesterol (HDL-C),
3. High proportion of small dense low-density lipoprotein cholesterol (LDL-C) and
4. Postprandial lipemia.

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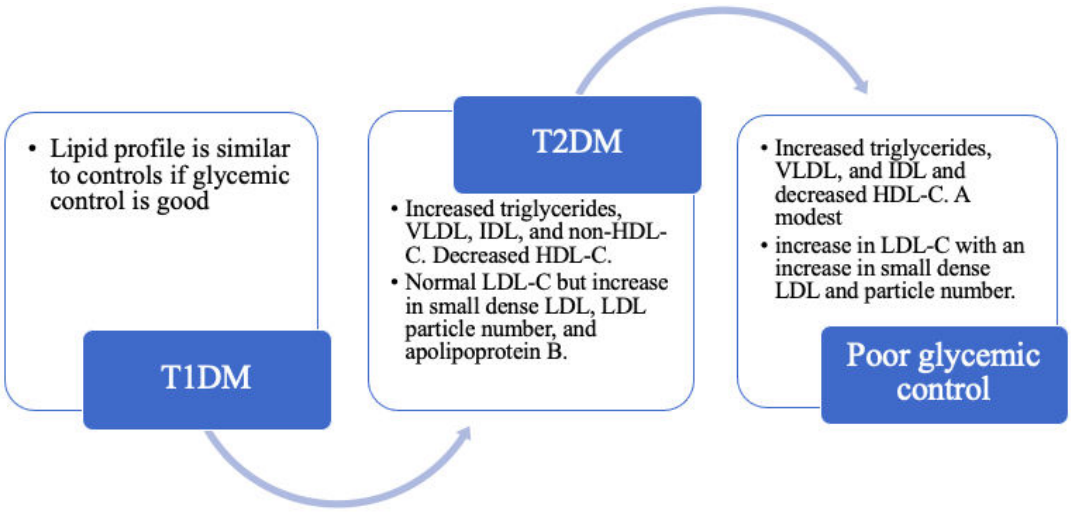
An excessive free fatty acid is due to insulin resistance in the adipocytes and blunted lipoprotein lipase enzyme activity, which results in high hypertriglyceridemia.[1]



DIABETIC DYSLIPIDEMIA

In Diabetic dyslipidemia, there is an elevation of triglycerides, small dense LDL particles, and low HDL cholesterol. The causes of small, dense LDL are controversial. There is a Cholesteryl ester transfer protein (CETP)-mediated transfer of triglyceride from VLDL to LDL followed by lipolysis mediated by hepatic lipase that leads to the formation of smaller LDL. Some data suggest that normal hepatic function will secrete either a specific precursor or directly secrete this smaller LDL into the circulation. There is an increase in the atherogenic lipoprotein particles, including VLDL and chylomicron remnant particles. In type II DM, this process is driven by insulin resistance, which causes an increase in free fatty acids in the serum, leading to increased chylomicron and VLDL production in both fasting and non-fasting states. In uncontrolled type I diabetes, insulin deficiency leads to an increase in a fatty acid release from adipose tissue.[4]

In addition to reducing the risk of pancreatitis due to hypertriglyceridemia, which sometimes accompanies diabetic dyslipidemia, the main reason for treating diabetic dyslipidemia is to reduce the risk of cardiovascular disease. Lifestyle changes, including diet (caloric restriction for weight loss, reduction of carbohydrates, and avoidance of fats and alcohol that exacerbate hypertriglyceridemia) and increased aerobic exercise, are considered the most important first steps in treating diabetic dyslipidemia.[5] Most often, however, lipid-lowering pharmacotherapy is required to normalize diabetic dyslipidemia successfully. A recent meta-analysis of overweight

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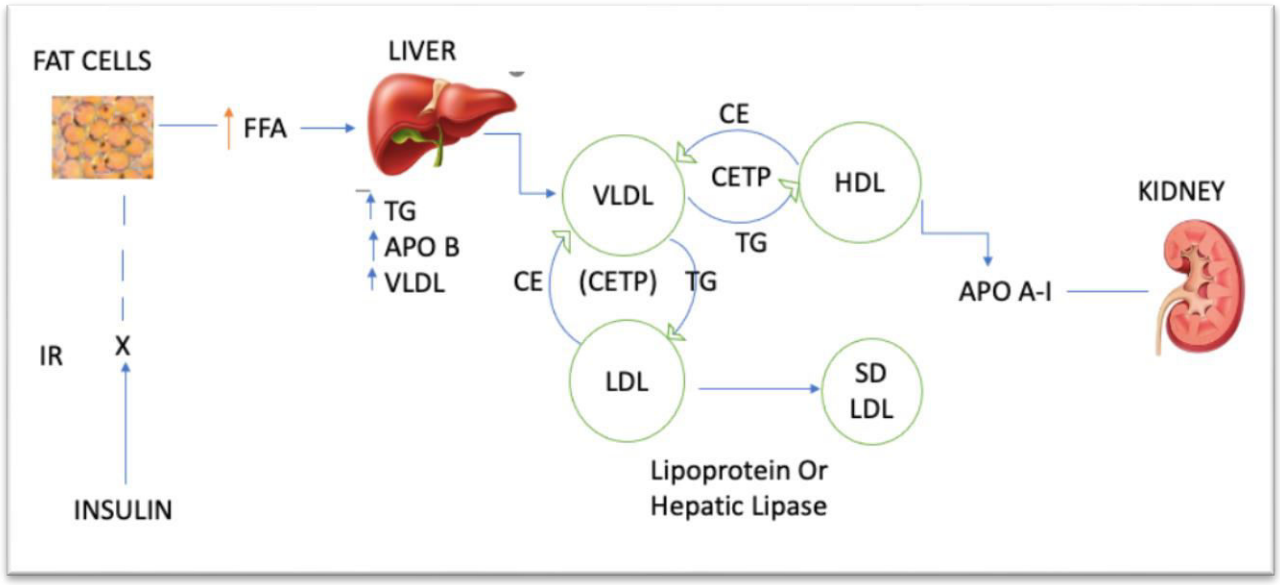
patients with type 2 diabetes mellitus showed that at least 5% weight loss was required to observe any improvements in lipid profile, if only limited.[6]

PATHOGENESIS

72%-85% of patients with dyslipidemia are highly prevalent in type 2 diabetes mellitus (T2DM).[7]



CETP- Cholesteryl Ester Transfer Protein, CE- cholesteryl ester,

Insulin deficiency or resistance has been implicated in the pathogenesis of diabetic dyslipidemia because lipoprotein changes, including an increase in triglycerides (TG), an increase in VLDL particles, small dense LDL particles, and a decrease in HDL level, have been observed in patients with impaired fasting glucose and impaired glucose tolerance and T2DM. Under the action of insulin, the enzyme lipoprotein lipase metabolizeslipids in a healthy individual. In type 2 DM, the relative insulin deficiency and decreased adiponectin cause decreased lipoprotein lipase activity resulting in high levels of low-density lipoprotein (LDL), triglyceride, and low levels of high-density lipoprotein (HDL).In type 2 diabetes, qualitative defects in LDL, including atherogenic, glycated, or oxidized LDL, further increase the risk of atherogenesis. Quantitative changes include increased triglyceride levels and decreased HDL-C levels.[2]

THERAPEUTIC STRATEGIES

Treatments for diabetic dyslipidemia can be divided into nonpharmacological and pharmacological medical nutrition therapy, weight loss, and physical activity are the

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nonpharmacologic treatments. Each diabetic patient must be actively involved in self-management, education, and treatment planning with his or her medical team.
The primary vital points for the improvement of lipid profile and glycemic control and reducing CVD risk:

• Attain healthy weight and aerobic activity level,

• Implement an energy-restricted, well-balanced diet, Mediterranean diet or DASH (Dietary Approaches to Stop Hypertension) diet has been recommended by the American Diabetes Association

• No or minimal alcohol consumption, and

• Smoking (or any other tobacco use) cessation.[8]

Diabetic patients should be vigilant about their dietary habits as diet plays a vital role in managing diabetic dyslipidemia. These patients should increase their intake of plant sterols, viscous fiber (legumes, citrus, oats), and n-3 fatty acids and decrease saturated and trans fatty acids intake. Consumption of a diet rich in walnuts showed improvement in non-HDL cholesterol, and apolipoprotein B. Weight loss is associated with improvement in lipid profile, insulin resistance, and glycemic control in diabetic patients. In addition, weight loss lowers triglyceride levels, increases HDL-C levels, and may also improve blood pressure. Although weight loss has been shown to improve several risk factors, the Look AHEAD study showed no improvement in cardiovascular events (CVE) after long-term weight loss with intensive lifestyle modification, suggesting that pharmacotherapy and lifestyle modification are necessary to reduce ASCVD. Pharmacologic therapy includes statins, cholesterol absorption inhibitors, niacin, fibrates, bile acid sequestrants (BAS), PCSK9 inhibitors, and omega-3 fatty acids.

Drugs that effectively and safely lower LDL- Cholesterol[2]

Metformin	Modestly decreased triglycerides and LDL-C
Sulfonylureas	No effect
DPP4 inhibitors	Decrease postprandial triglycerides
GLP1 analogs	Decrease fasting and postprandial triglycerides
Acarbose	Decrease postprandial triglycerides
Pioglitazone Rosiglitazone	Decrease triglycerides and increase HDL-C. A slight increase in LDL-C but a decrease in small dense LDL
SGLT2 inhibitors	A slight increase in LDL-C and HDL-C
Colesevelam	Decrease LDL-C. May increase triglycerides

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Bromocriptine QD	Decrease triglycerides

	High intensity	Moderate intensity	Low intensity
LDL-C lowering†	≥50%	30%–49%	<30%
STATINS	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 mg (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§	Simvastatin 10 mg

STATIN THERAPY

Statins are used for primary and secondary prevention of cardiovascular diseases and stroke.Reducing cholesterol levels in the liver leads to the upregulation of LDL receptors and, thus, to a reduction in LDL cholesterol in blood plasma. In addition to lowering LDL cholesterol, statins lower the TG level and increase

HDL cholesterol. Statins are divided into high potency, which can lower LDL-C by about 50% or more, intermediate potency, which can lower LDL-C by about 30%-50%, and low potency, which lower LDL-C by < 30%.

High-, Moderate-, and Low-Intensity Statin Therapy[2]

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		Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Cholesterol absorption inhibitors (Ezetimibe)

Ezetimibe lowers cholesterol by inhibiting the absorption of cholesterol in the intestine. Significant LDL-C lowering has been observed in combination with statins or in patients who cannot tolerate the required dose of statins.

The combination of ezetimibe and simvastatin reduced the risk of recurrent ischemic stroke compared with simvastatin in patients with T2DM, underscoring the importance of ezetimibe in diabetic patients with CVD.[2]

Fibrates

Fibrates include bezafibrate, gemfibrozil, ciprofibrate, and fenofibrate and activate nuclear peroxisome proliferator-activated receptor alpha, which causes a decrease in triglyceride levels by stimulating lipoprotein lipase activity. Fibrates can lower fasting plasma triglyceride levels by 30%-50% and reduce postprandial lipemia by decreasing fatty acid synthesis. Fibrates increase HDL levels by upregulating Apo-1 and A-II.

Niacin

Niacin is a very effective drug for increasing HDL-cholesterol levels. Niacin also lowers TG and LDL cholesterol. However, the combination of statin and niacin showed no additional cardiovascular benefit compared with a statin alone.

Proprotein convertase subtilisin/Kexin type 9 inhibitors.

When used as monotherapy or in combination with statins, the proprotein convertase subtilisin/Kexin type 9 inhibitors (PCSK-9 inhibitors) alirocumab and evolocumab significantly lower LDL-C. They are administered as subcutaneous injections every 2-4 weeks.PPCSK9 inhibitors are very effective drugs. PCSK9 binding prevents PCSK9 from binding to LDL receptors and targeting them for intrahepatic lysosomal degradation. It leads to increased expression of LDL receptors causing a reduction in LDL-C levels [10]. PCSK9 inhibitors are very

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expensive, with an annual cost of > $14500[2], which can be a significant economic burden even in developed countries.

Drug class	MOA	CLINICAL EFFICACY	ADVERSE EFFECTS
Statins	Inhibition of HMG coenzyme A Reductase	Highly effective	Myalgia, myositis, rhabdomyolysis, elevation in liver enzymes, new-onset diabetes
Ezetimibe	Decrease intestinal cholesterol absorption by binding to Niemann- Pick C1-like 1 protein.	Moderately effective; Safe addition to statin therapy	Worsening liver function, myopathy, or rhabdomyolysis with concomitant statin use; nasopharyngitis, diarrhea, and upper respiratory tract infections
PCSK9 inhibitor	Inhibition of proprotein convertase subtilisin/Kexin type 9.	cost-efficient in combination with statin therapy.	Injection site reactions: itching, swelling, redness, and pain.
Bile acid sequestering agents	Binds bile acids in the small intestine and prevents reabsorption.	Moderately effective, safe in combination with statin therapy, not desirable if triglycerides are > 300 mg/dL	Constipation, abdominal pain, flatulence, malabsorption of medications.

HMG: hydroxymethylglutaryl; PCSK9: proprotein convertase subtilisin/Kexin type 9.

CONCLUSION

In conjunction with therapeutic lifestyle modification, statin therapy remains the treatment of first choice in most patients. Many other lipid-lowering agents are now available for the treatment of patients who do not achieve LDL-C goals with statins, such as ezetimibe and PCSK9 inhibitors. Diabetic dyslipidemia is a prevalent condition, and patients with diabetic dyslipidemia are at exceptionally high risk for ASCVD. It has been concluded that hyperglycemia, dyslipidemia, and coronary heart disease are closely related to type 2 diabetes, and it has been suggested that there is a higher prevalence of cardiovascular disease in type 2 diabetes. Therefore, these physicians must strive for the best possible lipid control and encourage

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their patients to adhere to pharmacological therapy and make lifestyle changes to reduce their CVD risk.

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