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Lipids and Diabetes

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) remains a formidable public health issue and is associated with decreased survival predominantly due to cardiovascular disease (CVD). Evidence suggests T2DM and CVD are integrally related with regard to pathophysiologic processes and clinical outcomes. Diabetes is associated with a 2 to 4-fold increase in the risk of CVD compared with non-diabetic subjects. Approximately 80% of patients with T2DM will develop and possibly die of macrovascular disease. Coronary Artery Disease (CAD) and stroke are the top causes of death and disability in diabetes. Many diabetics possess other CVD risk factors, such as obesity, hypertension, and dyslipidemia. Whereas blood glucose control is fundamental to prevention of microvascular complications, controlling atherogenic cholesterol particle concentrations is fundamental to prevention of atherosclerotic CVD (ASCVD). To reduce the significant risk of ASCVD in T2DM patients, early intensive management of dyslipidemia is warranted.

It has been reported that that the prevalence of dyslipidemia in Indian diabetic population is very high (90%). Studies in Indian subjects have also demonstrated that coronary artery disease in Indian diabetics develops earlier than general population, is more advanced at the time of diagnosis, more diffuse and progresses faster. Furthermore, results after interventions are inferior and hence carry a higher risk of mortality and morbidity.

Table 1: Diabetic dyslipidemia

Elevated total TG
Reduced HDL-C
LDL-C may be normal or slightly elevated
↑ Small, dense LDL-C
↑ HDL_3 and ↓ HDL_1 and HDL_2
Postprandial Hyperlipemia

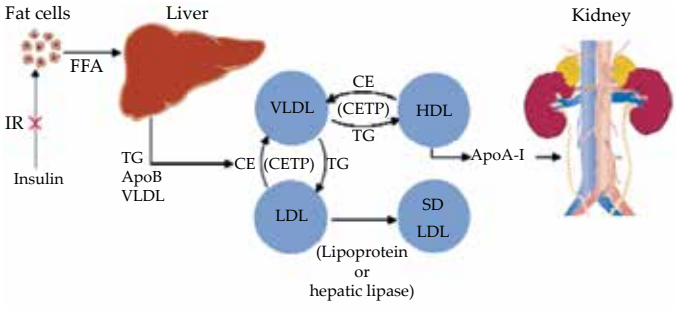

Fig. 1: Pathogenesis of diabetic dyslipidemia

LIPID ABNORMALITIES IN DIABETES

In uncontrolled T1DM the predominant abnormality is hypertriglyceridemia, secondary to absolute insulin deficiency. As expected, the level normalizes with adequate insulin therapy.

The lipid profile in people with T2DM is characterized by elevated triglycerides (TG) and low levels of HDL-cholesterol (HDL-C). LDL-cholesterol (LDL-C) levels in diabetic patients are not usually significantly increased compared with those in non diabetic patients. However, there are important differences in the types of LDL particles seen. Diabetics tend to have LDL particles that are small and dense compared with those in non diabetic individuals. This pattern, characterized by high TG, low HDL-C and small, dense LDL particles, referred to as diabetic dyslipidemia (Table 1), is a typical atherogenic lipid profile.

Pathogenesis of diabetic dyslipidemia

As a consequence of Insulin Resistance (IR) in T2DM the inhibitory effect of insulin on hormone-sensitive lipase is removed leading to increased lipolysis in the fat cells in adipose tissue, which leads to increased delivery of free fatty acids (FFAs) to the liver. Increased delivery of FFA to liver increases VLDL formation (insulin resistance also increase Apo-B formation in the Liver) due to which plasma VLDL and hence TG level is increased. VLDL exchanges its TGs with HDL via cholesterol ester transfer protein (VLDL gives away TG and accepts cholesterol ester from HDL). By the same mechanism it exchanges its TG for cholesterol esters from LDL as well. The TGs now acquired by HDL and LDL are digested by lipoprotein lipase and/or hepatic lipase. LDL thus gets converted to

Table 2: Lipid targets for patients with T2DM

	High risk patients: DM but no other major risks and/or age < 40	**Very high risk patients: DM + ≥ 1 ASCVD risk factor (family history, HTN, low HDL-C, smoking) or established ASCVD**
LDL-C	< 100	< 70
Non HDL-C	< 130	< 100
HDL-C	> 40 (men), > 50 (women)	> 40 (men), > 50 (women)
TG	< 150	< 150

Table 4: Drug therapy

Drug class: Agents and daily doses			
MoA	**Lipid/lipoprotein effects**	**Side effects**	**Contraindications**
HMG-CoA reductase inhibitors (Statins): Atorvastatin (10-80 mg), Rosuvastatin (5-40 mg), Lovastatin (20-80 mg), Pravastatin (20-40 mg), Simvastatin (20-80 mg), Fluvastatin (20-80 mg), Cerivastatin (0.4-0.8 mg)			
Competitive inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis.	LDL ↓ 20-55% HDL ↑ 5-15% TG ↓10-30%	Myopathy, Increased liver Enzymes	Absolute: Active or chronic liver disease Relative: Concomitant use of certain drugs*
Fibric acid derivatives: Fenofibrate (200 mg), Gemfibrozil (600 mg BID), Clofibrate (1000 mg BID)			
Activate PPAR-α in liver, muscle and adipose tissue: activates lipoprotein lipase, ↓ release of fatty acids from adipose tissue	LDL ↓ 5-20% (may be increased in patients with high TG) HDL ↑ 10-20% TG ↓ 20-50%	Dyspepsia, Gallstones, Myopathy,	Severe renal disease, Severe hepatic Disease
Bile acid sequestrants: Cholestyramine (4-16 g), Colestipol (5-20 g), Colesevelam (2.6-3.8 g)			
↓ bile acid absorption, ↑ hepatic conversion of CH to bile acids, ↓ LDL receptors on hepatocytes	LDL ↓ 15-30% HDL ↑ 3-5% TG no change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: dysbetalipoproteinemia, TG >400 mg/dL Relative: TG >200 mg/dL
Nicotinic acid: Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (1-2 g), sustained release nicotinic acid (1-2 g)			
↓ production of VLDL, ↓ lipolysis in adipocytes	LDL ↓ 5-25% HDL ↑ 15-35% TG ↓ 20-50%	Flushing, Hyperglycaemia, Hyperuricemia (or gout), Upper GI distress, Hepatotoxicity	Absolute: Chronic liver disease, Severe gout Relative: Diabetes, Hyperuricemia, Peptic ulcer disease
Ezetimibe (10 mg)			
Inhibits absorption of dietary cholesterol at intestinal brush border	↓ LDL 15-20%	Headache, diarrhoea	None
Saroglitazar (4 mg)			
Dual PPAR-α/γ agonist	↓ TG 45%	Dyspepsia, gastritis	None

* Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

the more atherogenic small-dense LDL and HDL loses its Apo-A-1 which gets excreted through kidneys thereby lowering HDL levels (Figure 1). The atherogenic potential of diabetic dyslipidemia is conferred by the small, dense LDL particles as they readily enter subendothelial space and become oxidized.

How Indians are different

Indian dyslipidemia is different from its western counterparts in terms of lipid parameters. A study of Asian Indians living in the United States found that 54% of men had an HDL level below 40 mg/dL, and 68% of women had levels below 50 mg/dL. In the United States, 43% of Asian Indian males and 24% of Asian Indian females have TG levels that exceed 150 mg/dL. Lipoprotein(a) is still considered an emerging risk factor in the US population at large, but appears to be a major risk factor in Asian Indians. A high level of Lp(a) is the most prevalent dyslipidemia in patients with premature CHD. Although Lp(a) levels above 30 mg/dL are generally considered the threshold at which high risk of premature CHD increases rapidly, levels below 20 mg/dL are considered optimal, particularly in Asian Indians. Studies of Asian Indians in North America found that 25-50% of sampled population had Lp(a) levels above 30 mg/dL.

SCREENING FOR DYSPIPIDEMIA

The 2015 the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines recommend screening of all

Table 5: Recommendations for statin treatment in diabetics

2013 ACC/AHA statin benefit groups	2014 NLA recommendations
Any clinical ASCVD	Moderate intensity statin if age > 75 or if not a candidate for statin therapy High intensity statin if ≤ 75 y
LDL-C ≥ 190 mg/dl	High intensity statin
Diabetes, age 40-75 y, no clinical ASCVD, LDL-C 70-189 mg/dl	Moderate intensity statin High intensity statin if ASCVD risk ≥ 7.5%
Estimated 10-y ASCVD risk of 7.5%, age 40-75 y, no clinical ASCVD, LDL-C 70-189 mg/dl	Moderate-to-high intensity statin

Table 6: High-intensity and moderate-intensity statin therapy*

Moderate-intensity statin therapy	High-intensity statin therapy
Lowers LDL cholesterol by 30 - <50%	Lowers LDL cholesterol by ≥ 50%
• Atorvastatin 10–20 mg • Rosuvastatin 5–10 mg • Simvastatin 20–40 mg • Pravastatin 40–80 mg • Lovastatin 40 mg • Fluvastatin XL 80 mg • Pitavastatin 2–4 mg	• Atorvastatin 40–80 mg • Rosuvastatin 20–40 mg

adult diabetics with yearly fasting lipid profile: total cholesterol, TG, HDL-C, and LDL-C. If not at goal, lipid profiling should be repeated more frequently after initiation of treatment.

TARGET LIPID LEVELS IN DIABETES

The 2016 AACE/ACE consensus statement recognises that T2DM carries a high lifetime risk for developing ASCVD, stratifies risk for primary prevention as "high" or "very high" and recommends LDL-C targets of <100 mg/dL or <70 mg/dL and non-HDL-C targets of <130 mg/dL or <100 mg/dL, respectively. Currently, HDL-C is not a target for therapy according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment guidelines and the 2016 AACE/ACE consensus statement. However, the ADA considers levels of HDL-C > 40 mg/dL in men and > 50 mg/dL in women desirable (Table 2).

TREATMENT MODALITIES

The options available are glycemic control, lifestyle measures and specific lipid-modifying drugs (Table 4).

Flowchart 1: Stepwise approach to treatment of dyslipidemia in diabetes

No ← Serum TG ≥ 500 → Yes		
GOAL 1	Achieve LDL-C goal - TLC# - Statins, Fibrates, Ezetimibe	TG lowering - Very low fat diet - Weight management and physical activity - Fibrates or nicotinic acid - When TG < 500 mg/dl, target LDL goal
	↓	
GOAL 2	Achieve Non-HDL-C goal	
	- Intensify TLC - Intensity therapy with LDL lowering drug - Add nicotinic acid or fibrate to lower VLDL	
	↓	
GOAL 3	Achieve HDL-C goal - Glycemic control - Intensify TLC - Add Nicotinic acid or fibrates	

#Therapeutic Lifestyle Changes

Strict glycemic control

Tight control of blood sugars can significantly reduces TG levels. HDL-C, being inversely related to TG, tends to rise with attainment of good glycemic control. LDL-C however is not altered by glycemic control.

Therapeutic Lifestyle changes

- Regular physical activity and weight reduction can reduce TG and raise HDL-C. LDL-C, however is not significantly altered by exercise.
- Moderation of alcohol can also help to reduce TG levels
- Smoking cessation is critical to reduce overall CV risk.
- Medical nutrition therapy
  - Total carbohydrate to be reduced to 50-60% of calories
  - Total fat to be reduced to < 30% of total calories.
  - Saturated fat must reduced to < 7% of calories
  - MUFA and PUFA up to 10-15% of calories
  - Protein intake to be increased 10-20%% of calories.

- Increased dietary fiber (soluble/viscous) to 10-25 g/day e.g.-Soy protein, Fenugreek
- Cholesterol < 200 mg/day

The Role of Statins in CHD risk reduction

Practically every clinical manifestation of atherosclerosis has been shown to be reduced by statin therapy, including fatal and nonfatal myocardial infarction, sudden cardiac death, episodes of unstable angina, revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), stroke, symptoms of peripheral arterial disease, and total mortality. Importantly, statin therapy has not been associated with an increase in non-cardiovascular events. These data demonstrate that statins improve the quality of life (by reducing nonfatal events) and also prolong survival (by reducing total mortality).

The 2013 ACC/AHA guidelines recommended treatment initiation with stains and initial dose based on individuals' cardio-vascular risk, rather than LDL-C levels alone. The guidelines identified 4 Statin Benefit Groups (Table 5). In 2016, a comparison of the ACC/AHA guidelines with the 2014 National Lipid Association (NLA) recommendations provided guidance for treatment with moderate and high intensity statin therapy (Table 5, Table 6).

Approach to treatment of dyslipidemia

The scientific statement from the AHA and ADA recommends that the primary goal is to lower LDL-C followed by non-HDL-C lowering and HDL-C elevation (Flowchart 1).

CONCLUSIONS

Despite the steady decrease in mortality from CVD, the incremental CVD risks associated with T2DM persist. As a result, considerable work remains to be done to enhance our understanding of how to more effectively prevent CVD in patients with T2DM. The treatment goals for diabetic with or without CHD is stricter compared to those without diabetes. The primary goal is to lower LDL-C followed by non-HDL-C lowering and HDL-C elevation. Due to their proven benefits, statins remain the most commonly used drugs followed by fibrates.

REFERENCES

1. RM Parikh, Joshi SR, et al. Prevalence and pattern of diabetic dyslipidemia in Indian type 2 diabetic patients. Diabetes & Metabolic Syndrome. *Clinical Research & Reviews* 2010; 4:10–12.
2. Misra A, Luthra K, et al. Dyslipidemia in Asian Indians: Determinants and Significance. *J Assoc Physicians India* 2004; 52:137-42.
3. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143-421.
4. Fox CS, Golden SH, et al. Update on Prevention of Cardiovascular Disease in Adults with Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015; 38:1777–803.
5. Stone NJ, Robinson JG, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129 (25 Suppl 2): S1-45.
6. Jacobson TA, Ito MK, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol* 2015; 9:129-69.
7. Adhyaru BB, Jacobson TA. New Cholesterol Guidelines for the Management of Atherosclerotic Cardiovascular Disease Risk: A Comparison of the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines with the 2014 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia. *Endocrinol Metab Clin North Am* 2016; 45:17-37.
8. Handelsman Y, Bloomgarden ZT, et al. American association of clinical endocrinologists and American college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract* 2015; 21(Suppl 1): 1-87
9. Garber AJ, Abrahamson MJ, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. *Endocr Pract* 2016; 22:84-113.
10. American Diabetes Association Standards of Medical Care in Diabetes 2016. *Diabetes Care* 2016; 39(Suppl. 1): S1–S112
11. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282:2340-2346.