Review Article

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Diabetic Dyslipidemia: Current Concepts in Pathophysiology and Management

Internal Medicine Section

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ABSTRACT

Diabetes Mellitus (DM) has assumed pandemic proportions worldwide. The increase in prevalence of this non-communicable disease has been quite alarming. South East Asia is home to approximately 71.4 million of the diabetics, out of which 61.3 million diabetics are in India in 2011 as per the data of International Diabetic Federation. The leading causes of morbidity and mortality for such patients have been attributed to the rising incidences of Cardiovascular Diseases (CVD) as a complication of type 2 diabetes. A major proportion of CVDs are attributed to the occurrence of atherogenic dyslipidemia. The pathophysiologic mechanisms and treatment regimens for dyslipidemia have been evolving and several newer mechanisms are being proposed. The purpose of the review is to throw light on the new concepts regarding pathophysiology and management guidelines of diabetic dyslipidemia. A literature review was performed in pubMed and google using the key words: type 2 DM, dyslipidemia, pathophysiology, treatment. A total of 30 articles over last 10 years were scanned for review. The newer mechanisms of dyslipidemia included: activation of transcription factors, decreased Lipoprotein Lipase (LPL), decreased clearance. The role of remnant particles, adiponectin an anti-inflammatory molecule has also been proposed. The current treatment regimens are based on Low Density Lipoproteins (LDL) and high density lipoproteins (HDL) and the recommendations are different for the various associations. Statins are considered the standard lipid lowering agents in diabetics and have shown mortality benefits in these patients. However, many new drugs like Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors, saroglitazar are emerging as possible alternates for statins in the treatment of dyslipidemia, though their overall cardiovascular benefit is yet to be studied.

Keywords: Adiponectin, Atherogenic dyslipidemia, Lipoproteins, Statins

INTRODUCTION

Epidemiology

Diabetes is becoming a disease of global concern because of its high escalating numbers. The number of diabetics is expected to increase from 382 million in 2013 to 592 million by 2035 [1]. Such a great rise in the number of patients represent a heavy disease burden at the individual and population level as well as for the total health care system.

The leading cause of morbidity and mortality for patients with type 2 diabetes is CVD. According to American Heart Association, at least 68% of the people with diabetes aged 65 or older die of heart disease and 16% die of stroke [2]. Furthermore, adults with diabetes are two to four times more likely to have CVD than adults without diabetes. Thus, it is considered as coronary artery disease equivalent [2].

The overall cardiometabolic risk is driven by a complex interplay between several non-modifiable (age, gender, genetics), modifiable (hypertension, hyperlipidemia, hyperglycemia) factors and the components of the metabolic syndrome commonly associated with type 2 diabetes [3]. Amongst all these factors, an entity called atherogenic dyslipidemia comprising of qualitative and quantitative changes in the lipoproteins like LDL, HDL and other Triglyceride Rich Lipoproteins (TRLs) play an important role [4]. This review aims to summarize recent advances in pathophysiology and management guidelines of diabetic dyslipidemia.

Pathophysiology

Different mechanisms are responsible for the development of dyslipidemia in patients with diabetes type 1 and type 2.

In type 1 diabetes, the levels of fasting plasma lipids and HDL is often normal or more favourable than age and gender matched normal patients [5]. This may in part relate to decreases in hepatic cholesterol synthesis in patients with type 1 diabetes. Despite this higher levels of LDL cholesterol and triglycerides still relate to CVD [6].

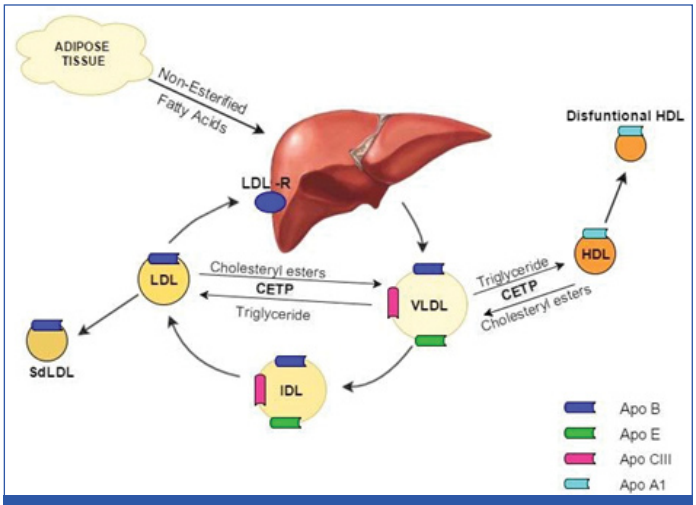
In type 2 diabetes, the typical pattern is that of the dyslipidemia of the metabolic syndrome with hypertriglyceridemia and reductions in HDL cholesterol. Other lipoprotein alterations include increases in LDL particle number, small dense LDL, and apolipoprotein (apoB) [7].

Insulin resistance/deficiency in type 2 diabetics in association with other factors like adipocytokines, hyperglycemia lead to qualitative, quantitative and kinetic changes in normal lipid metabolism [Table/Fig-1] including :

(1) Increased VLDL.

(2) Increased LDL.

(3) Decreased HDL [7].



[Table/Fig-1]: Normal lipid metabolism.

1. Increased very low density lipoprotein:- It has been demonstrated that insulin plays a role in almost all the steps of Very Low Density Lipoprotein (VLDL) production and secretion.

A) Overproduction:- Recently it has been reported that overproduction of large VLDL1 particles resulting from increased production of both VLDL1-triglyceride and VLDL1 apoB is a key factor determining the concentration of serum triglycerides in subjects with type 2 diabetes [8].

Disturbance in triglyceride synthesis:- Triglyceride (TG) are derived from many processes like synthesis from (a) Free Fatty Acid (FFA) re-esterification, (b) De Novo Lipogenesis (DNL) and (c) Uptake of remnant particles [9].

The FFA availability is increased in insulin resistance states due to unabated lipolysis in adipose tissues as a result of the reduced inhibition of hormone sensitive lipase [6].

Accelerated DNL promoted by insulin resistance and hyperglycemia are being increasingly recognized as important contributors [10].

Increased apo B100:- Insulin resistant states in diabetics presumably activate endoplasmic reticulum based Microsomal Transfer Protein (MTP). The later then leads to assembling of TG with apoB100 preventing the degradation of apoB 100 [11].

(B) Increased secretion:- Increased secretion of VLDL probably results from increased expression of apo-CIII mediated through unopposed activity of Forkhead Box Protein 01 (FoxO1) in the liver in insulin resistant states [12].

(C) Decreased catabolism:- Reduced LPL activity stems from insulin deficiency and/or insulin resistance (activator of LPL) states present in diabetics. This leads to decreased catabolism of VLDL [13].

In addition to this quantitative change in VLDL, there is qualitative change seen as well in the form of increased synthesis of more atherogenic form of VLDL i.e. large VLDL1 particle size [14].

2. Increased small dense LDL:- In patients of type 2 diabetes, increased VLDL1 results in formation of small dense low density lipoproteins by a well explained mechanism:

Cholesteryl Ester Transfer Protein (CETP) mediated triglyceride movement from VLDL1 to LDL.

Lipoprotein mediated lipolysis of the triglyceride rich LDL into small dense LDL [15].

3. Reduced HDL:- Diabetics have increased catabolism of the small dense HDL (formed from VLDL1 via CETP) particles resulting in decreased concentration of HDL [16].

4. Postprandial Hyperlipidemia:- Postprandial hyperlipidemia is highly prevalent in diabetic patients [17]. This is mediated by several mechanisms:-

(A) Decreased LPL (lipoprotein lipase) activity:- This leads to increase in the residence time of triglycerides in circulation [18].

(B) Decreased clearance of TRL remnants:- Hepatic clearance of Triglyceride Rich Lipoprotein (TRL) remnants, is mediated by the Heparan Sulfate Proteoglycan (HSPG) syndecan-1 which is rapidly metabolised in diabetics due to increased induction of heparan Sulfate 6-O-Endo-Sulfatase 2 (SULF2) [19].

Newer insights into the pathophysiology

Role of Adiponectin:- Recently there has been interest in role of reduced levels of adipokines such as adiponectin as seen in insulin resistance states in the pathogenesis of dyslipidemia in diabetics. They have been thought to increase FFA availability for VLDL production [20].

Association with NAFLD:- Hepatic lipid homeostasis is regulated by the balance between the import and export of lipids, and an imbalance between these processes leads to increased VLDL secretion or lipid accumulation in hepatocytes as seen in Non-Alcoholic Fatty Liver Disease (NAFLD), a common finding in subjects with type 2 diabetes [21].

Causative role of remnant particles:- Remnant particles formed as a result of hydrolysis of triglyceride rich lipoproteins are rich in cholesteryl ester and thus cannot cross endothelium efficiently. Raised levels of these remnant particles as seen in diabetics may increase cardiovascular risk [22].

Low HDL; an innocent by stander:- Contrary to the common perception that cardiovascular risk results from low HDL, recent studies have suggested that HDL might just to be a marker rather than the proposed causual mechanism [23].

Management of Diabetic Dyslipidemia

Lipid Goals:- Various guidelines have proposed different goals for LDL and HDL in diabetics [Table/Fig-2].

1. National Cholesterol Education Program and Adult Treatment Panel III:- These guidelines have put forth target LDL and HDL levels based on a patient's risk of having a cardiovascular event in forthcoming 10 years [24].

National Cholesterol Education Program and Adult Treatment Panel III	American Association of Clinical Endocrinologists
• DM and ASCVD LDL-C <70 mg/dL Non-HDL-C <100 mg/dL • DM only LDL-C <100mg/dL Non-HDL-C <130mg/dL	• Extreme Risk LDL-C <55mg/dL • Very High Risk LDL-C <70mg/dL Apo-B <80 mg/dL • High Risk LDL-C <100mg/dL Apo-B <90mg/dL • Moderate Risk LDL-C <100mg/dL Apo-B <90mg/dL • Low Risk LDL-C <130mg/dL

[Table/Fig-2]: Showing recommendations on LDL-c goals.
DM: Diabetes Mellitus ASCVD: Atherosclerotic Cardiovascular Disease LDL: Low Density Lipoproteins HDL: High Density Lipoproteins

2. American Association of Clinical Endocrinologists (AACE):- According to the new 2017 guidelines, individuals with type 2 diabetes (T2DM) should be considered as low risk (having no risk factors), medium risk (having <2 risk factors with 10 years risk <10%), high risk (having >2 risk factors with 10 years risk 10-20%, T2DM or Chronic Kidney Disease (CKD) with no risk factors), very high risk (acute coronary syndrome, carotid or peripheral vascular disease, 10 years risk >20%; diabetes or CKD with one or more risk factors; heterozygous familial hypercholesterolemia (HeFH) or extreme risk (with unstable angina, established CVD in patients with other comorbidities like T2DM, CKD stages 3/4, HeFH) and each category has different LDL cholesterol goals and are depicted in [Table/Fig-2] [25].

Treatment

(A) Non-pharmacological therapies:

1. Diet:- Dietary changes consist of reduced caloric intake that should include at least five servings per day of fruits and vegetables, at least six servings per day of grains with one-third as whole grains, fish and lean meat. Patients should limit intake of saturated fats, trans fats and cholesterol [26]. The diet should also include 2 gm/days of plant and 10–25 gm/days of soluble fiber [26].

2. Exercise:- Moderate intensity exercise lasting for 30 minutes, four to six times per week is the recommended exercise program by American Association of Clinical Endocrinologists (AACE) [26].

(B) Pharmacological

I) Cholesterol lowering Agents:-

1. Statins:- NCEP-ATP III, AACE, ADA and ACC/AHA guidelines all recommend statins as first-line therapy for dyslipidemia in diabetics [24,26-28]. High-intensity and moderate-intensity statin treatment is emphasized [Table/Fig-3].

- High-intensity statin therapy includes atorvastatin 80 mg once daily (40 mg may be used if 80 mg is not tolerated) and rosuvastatin 20–40 mg once daily [29].
- Moderate-intensity statin therapy includes atorvastatin 10–20 mg once daily, fluvastatin 40 mg twice daily, lovastatin 40 mg once daily, pravastatin 40–80 mg once daily, rosuvastatin 5–10 mg once daily, simvastatin 20–40 mg once daily and pitavastatin 2–4 mg once daily [29].

Name of the Associations	High Intensity Statin Therapy	Moderate intensity Statin Therapy
American Diabetes Association Standards of Medical Care In Diabetes	• DM and ASCVD any age • DM, age 40-75 and 1 risk factor • DM, age <40 or >75 and risk factor	• DM, age <40 or >75 and 1 risk factor • DM, age >40 and no risk factors
American College of Cardiology/American Heart Association Blood Cholesterol Guidelines for ASCVD Prevention	• DM and LDL >190 mg/dL • DM, age 40-75 year, LDL 70-189 mg/dL and 10 year ASCVD risk >7.5%	• DM, age 40-75, LDL70-189 mg/dL 10 year ASCVD risk <7.5%

[Table/Fig-3]: Showing guidelines for statin therapy by different associations.

Both ACC/AHA assess 10 year and lifetime risk of having a cardiovascular event based on age, sex, race, total cholesterol, HDL-c, blood presuure, diabetes status and smoking status [27].

2. Fibrates: They are peroxisome proliferator-activated receptor (PPAR)-α agonists, so they reduce triglycerides and modestly increase HDL cholesterol and lead a small decrease in cardiovascular mortality [30].

3. Ezetimibe:- This 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 [31].

4. Purified omega-3 fatty acids:- They lower triglycerides but they have little effect on HDL or LDL cholesterol. A recent trial of omega-3 fatty acids in patients with metabolic syndrome or type 2 diabetes disappointingly found no effect on CHD risk [32].

II) Antidiabetic Agents:- In addition to their glucose-lowering properties, antidiabetic agents that directly improve insulin resistance may have effects on lipid levels, especially TG levels [Table/Fig-4].

III) Antihypertensive Agents:- Some antihypertensive agents are known to be lipid neutral (angiotensin-converting enzyme inhibitors, calcium-channel blockers, and angiotensin II receptor blockers) or lipid friendly (α-blockers). In patients with type 2 diabetes and dyslipidemia, a lipid-neutral/friendly antihypertensive would be expected to be associated with greater clinical benefits than a lipid-hostile antihypertensive such as a β-blocker or thiazide diuretic [42].

IV) Bile Acid Sequestrant:- Colesevelam, the bile acid sequestrant has been used in practice to reduce LDL levels as well as improve blood glucose levels in Type 2 diabetes patients [43].

Future of Dyslipidemia Management:- Many new drugs have emerged for the treatment of dyslipidemia. However, their role in improving lipid profile in association of diabetes is yet to be studied.

S.No	Antidiabetic Agents	Effects on Lipids
1.	Metformin [33]	LDL ↓ HDL ↔↑ Total Cholesterol ↓↔ Triglycerides ↓↔
2.	Gliclazide [33]	Total Cholesterol ↓ Triglycerides ↓
3.	Glimepiride [33]	HDL ↔↑
4.	Pioglitazone [33]	HDL ↑ Total Cholesterol ↑ Triglycerides ↓
5.	Sitagliptin [34]	HDL ↔↑
6.	Vildagliptin [35]	HDL ↔↑
7.	Linagliptin [36]	No effect
8.	Teneligliptin [37]	LDL ↓ HDL ↑ Total Cholesterol ↓ Triglycerides ↓
9.	Canagliflozin [38]	LDL ↑ HDL ↑ Total Cholesterol ↑ Triglycerides ↑
10.	Empagliflozin [34]	LDL ↔↑ HDL ↔↑ Total Cholesterol ↔↑
11.	Exenatide [39]	LDL ↔↑ HDL ↔↑ Total Cholesterol ↓↔ Triglycerides ↓
12.	Liraglutide [40]	Triglycerides ↓
13.	Dulaglutide [41]	LDL ↓ Total Cholesterol ↓ Triglycerides ↓

[Table/Fig-4]: Showing the effects of glucose lowering drugs on lipid profile.
↓: decrease, ↑: increase ↔: no effect

I) PCSK9 inhibitors:- Recently, PCSK9 inhibitors like evolocumab and alirocumab have shown very good reductions in LDL levels in patients with high cardiovascular risk including type 2 diabetes. They should be considered in patients with clinical CVD who are unable to reach LDL-C/non- HDL-C goals with maximally tolerated statin therapy [44]. However, at present they are priced too high for use in routine clinical practice.

II) Saroglitazar:- It is a PPAR -α/γ agonist and has been shown to significantly reduce plasma triglyceride, total cholesterol, non-HDL cholesterol, and VLDL cholesterol, and HbA1c and fasting glucose levels [45].

III) Other drugs:- Some new LDL lowering drugs like thyroid mimetics, antisense oligonucleotides or Microsomal Transfer Protein Inhibitors (MTPI), triglyceride lowering drugs like peroxosimal proliferator activating receptors agonists, diacylglycerol acyl transferase-1 inhibitors, HDL lowering drugs mimetic peptides, modulators of inflammation (e.g. phospholipase inhibitors) and gene therapy in rare diseases (e.g. lipoprotein lipase deficiency) are in their initial stages.

CONCLUSION

Various hypotheses have been put forward to explain the typical diabetic dyslipidemia, summary of evidences point out that the overproduction of VLDL1 particles initiates a sequence of events that results in the atherogenic lipid triad consisting of elevated plasma concentrations of fasting and post-prandial TRLs, small dense LDL and low HDL cholesterol. However, the potential links between anti-inflammatory biomarkers like adiponectin and accumulation of hepatic fat remains is to be explored further. Though, various recommendations have been put forward, the therapeutic interventions for dyslipidemia are only complementary to the basic recommendations of adequate control of blood glucose, blood pressure and various other lifestyle modifications. Though,

various treatment guidelines and all the available drugs for treatment of diabetic dyslipidemia have been discussed here, physicians are advised to individualize the treatment as per the characteristics and needs of specific patients using these guidelines.

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