Dyslipidemia in type 2 diabetes mellitus (T_2dm): Pathophysiology, pattern and management

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Abstract
Type 2 diabetes mellitus (T_2DM) is related with severe cardiovascular morbidity and mortality throughout the worldwide. Dyslipidemia, high blood glucose level, and coronary artery diseases are well linked with each other in T_2DM and it has been demonstrated that higher prevalence of cardiovascular disease (CVD) in T_2DM is due to chronic uncontrolled hyperglycemia. Dyslipidemia, which affects almost 50% of patients with T_2DM, is a cardiovascular risk factor and characteristic features of dyslipidemic diabetes are elevated plasma triglyceride level, decline in high density lipoprotein cholesterol (HDL-c) level, and raised level of small dense low density lipoprotein (LDL) particles. An adequate availability of many lipid-lowering agents and nutritional supplements provides novel and effective treatments in control of lipid levels in diabetes patients. Several hypolipidemics, such as statins, fibric acid derivatives, niacin, and bile acid sequestrants, are available to target normalization of the entire lipid profile in T_2DM patients. This review highlights the prevalence, underlying pathogenesis, patterns and various management approaches of dyslipidemia in patients with T_2DM.

Keywords: Type 2 diabetes mellitus, Dyslipidemia, Cardiovascular disease, statins, Triglycerides.

Introduction
"Sweet is Sweet but until it is not too Sweet". As the diabetes a major healthcare concern and challenges the global population, diabetic organizations worldwide call for unanimous resonance of Diabetes Voice to tackle diabetes with healthy living. With an emerging of new pathophysiology linked with diabetes, patients are receiving access to the newer therapeutic category agents.[1] Diabetes is a common endocrine metabolic disorder which can leads to complications in various parts of our body and might results in premature death. The increase in the pervasiveness of this disease is quite distressing. According to the latest 2016 data from the WHO, 422 million adults are suffering with diabetes mellitus (DM).[2] Dyslipidemia is a major risk factor for macrovascular complications in patients with Type-2 DM (T_2DM) and affects 10% - 73% of the population. Dyslipidemia is prominent in DM which causes death of about 80% of the patients due to cardiovascular disease (CVD).[3] Although, both diabetes and dyslipidemia represent different genetic disorders, there is a chance of concurrence in same individual.[4]

DM is a group of metabolic disease characterized by hyperglycemia, glucosuria, hyperlipidemia, negative nitrogen balance and sometimes ketonemia.[5] Dyslipidemia is defined as elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides (TG); low high-density lipoprotein (HDL) cholesterol; or a combination of these abnormalities.[6] Diabetic dyslipidemia is manifested as raised LDL, decreased HDL, and elevated TG. Elevated TG level is a significant risk factor for coronary heart diseases.[7]

DM if left untreated can leads to several life threatened macrovascular and microvascular complications. The microvascular complications are retinopathy, nephropathy, and neuropathy, while the macrovascular complications of diabetes include angina, myocardial infarction, transient ischemic attack, and stroke.[8] The objective of this paper is to provide a comprehensive datum to summarize the various pathophysiology, patterns and management involved in diabetic dyslipidemia.

Pathophysiology
Several mechanisms are involved in the development of dyslipidemia in T_2DM. Hepatic glucose and metabolism of lipids are varied in metabolic disorders like T_2DM. The normal lipid metabolism is shown in Fig. 1. There exist typical patterns of dyslipidemia in T_2DM, which reveal an elevated TG and LDL and decreased level of HDL. Insulin resistance or deficiency in T_2DM can lead to altered normal lipid metabolism, which in turn leads to raised production of TG, VLDL, LDL and diminished production of HDL.[4]

Raised VLDL Levels
The mechanism for increased VLDL levels are: overproduction, increased secretion & reduced catabolism.[9-11]

Overproduction
Raised production of VLDL-TG and VLDL Apolipoprotein B (Apo B) resulting in increased formation of VLDL. Normally, insulin inhibits the expression of Microsomal Transfer Protein (MTP) and thus blocks the lipidation of Apo B and reduces the secretion of Apo B. But in T_2DM, insulin resistance leads to the activation of MTP.

Increased Secretion
Insulin fails to arrest lipolysis in adipose tissue and Forkhead Box Protein 01 (Fox 01) in liver due to resistance in T_2DM. This results in the activation of MTP and Apolipoprotein CIII (Apo CIII). These mechanisms cause the increased secretion of Apo B in the form of VLDL particles.

Reduced Catabolism

Defective catabolism of VLDL shows the suppressed activity of LPL. Since insulin is the activator of LPL, the activity will be declined in T_2DM.

Increased small dense LDL (sdLDL)

Increased level of VLDL in plasma results in the formation of sdLDL. The sdLDL is produced through the following steps: [12]

1. CETP eases the movement of TG from VLDL to LDL (TG-rich LDL).
2. Hepatic lipase enzyme acts on this TG-rich LDL.
3. Raised lipolysis of TG-rich LDL leads to the generation of sdLDL.

Decreased HDL

Hepatic lipase enzyme hydrolyses TG and phospholipids and produce small dense HDL particles. In T_2DM, the activity of hepatic lipase increases. It leads to accelerated HDL metabolism resulting in diminished levels of HDL.[13]

Pattern of Dyslipidemia in T_2DM Patients

The best time to go through the prevalence and pattern of dyslipidaemia with DM is at the time of the diagnosis of diabetes as subsequent management with pharmacological drugs or non-pharmacological measures can modify the both pattern as well as the prevalence of dyslipidaemia.[14] The recent literature surveys demonstrate that various studies have been performed to identify the difference in the pattern of dyslipidemia in T_2DM patients in different population. Studies conducted in Indian population were listed in Table 1[7, 15-18] and studies conducted in different parts of the world were mentioned in Table 2.[14,19-22]

Management of Dyslipidemia

The management of dyslipidemia diabetes needs a comprehensive strategy to regulate the levels of lipid and to discuss over associated metabolic complicated disorders and modifiable risk factors like hypertension, diabetes, obesity, and cigarette smoking. There are mainly 2 principal approaches for dyslipidemia, lifestyle intervention and lipid modifying drug therapy.[23]

Non Pharmacological Treatment:[23]

Diet

Dietary approaches extend from one extreme to another regarding fats, sugar, and protein content. Caloric intake should be reduced and it include five servings per day of fruits and vegetables and six servings per day of grains together with one- third of whole grains, fish and lean meat. Reduce the intake of saturated fats, trans fats, and cholesterol.

Exercise

Intensity of the exercise should be for 30 minutes. It is beneficial in patients with diabetic dyslipidemia as it prevents development and progression of atherosclerosis and improvements are seen in all parameters of dyslipidemia including HDL, TG and LDL with regular physical activity.

Table 1: Study in Indian population

Parameters	Punjab	Madhya Pradesh	Odisha	Mangalore	Southern India
Year	2016	2015	2017	2015	2012
Recruitment period	Mar 2015-Aug 2015	Mar 2013-Oct 2014	May 2015-Jan 2016	Dec 2014	March 2010 to April 2012
Study design	Cross-sectional study	Cross –sectional study	Cross- sectional study	Cross -sectional study	Cross sectional study
Age	45-60	>30 yrs	≥40	>18	>18
Subjects	Men & women-285	M:29 F:21	M:362 F:41	M:50 F:50	M:533 F:287
Lipid levels	TG-↑ LDL-↑ HDL-↓	TG-↑ LDL-↑ HDL-↓	TG-↓ LDL-↑ HDL-↓	TG-↑ LDL-↑ HDL-↓	TG-↑ LDL-↑ HDL-↓

Table 2: Studies conducted at different countries

Parameters	Nepal	Pakistan	Sri-Lanka	South Africa	Ethiopia
Year	2017	2016	2016	2017	2015
Recruitment period	July –Dec 2014	2014-2015	January 2012-July 2013	July – August 2012	Mar – Nov 2014.
Study design	Cross –sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Age	NA	>40 or<40	<45 or>45	>18	Not mentioned
Subjects	M:84 F:64	M:120 F:80	M:289 F:114	M:86 F:114	M:172 F: 123
Lipid levels	↑TG ↓HDL ↑LDL	↑TG ↑LDL ↓HDL	↓TG ↑LDL ↓HDL	↑TG ↑LDL ↓HDL	↑TG ↑LDL ↓HDL

Table 3: Guidelines for statin therapy by different associations

Names 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 factors.	-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 4: Effects of glucose lowering drugs on lipid profile

Sl. No	Antidiabetic Agents	Effects of antidiabetic agent on lipids profile
1	Metformin[28]	↓LDL ↔↑HDL ↓Total Cholesterol (TC) ↔↓TG
2	Pioglitazone[29]	↓LDL ↑HDL ↑TC ↓TG
3	Rosiglitazone[29]	↑LDL ↑ HDL ↓TG
4	Saroglitazar[30]	↓LDL ↓TC ↓VLDL
5	Sitagliptin[31]	↔↑HDL
6	Linagliptin[32]	No effect
7	Teneligliptin[33]	↓LDL ↑HDL ↓TC ↓TG
8	Canagliflozin[34]	↑LDL ↑HDL ↑TC ↑TG
9	Empagliflozin[31]	↔↑LDL ↔↑ HDL ↔↑TC
10	Exenatide[35]	↔↑LDL ↔↑HDL ↓↔TC ↓TG
11	Dulaglutide[36]	↓LDL ↓TC ↓TG

↓: decrease, ↑: increase, ↔: no effect

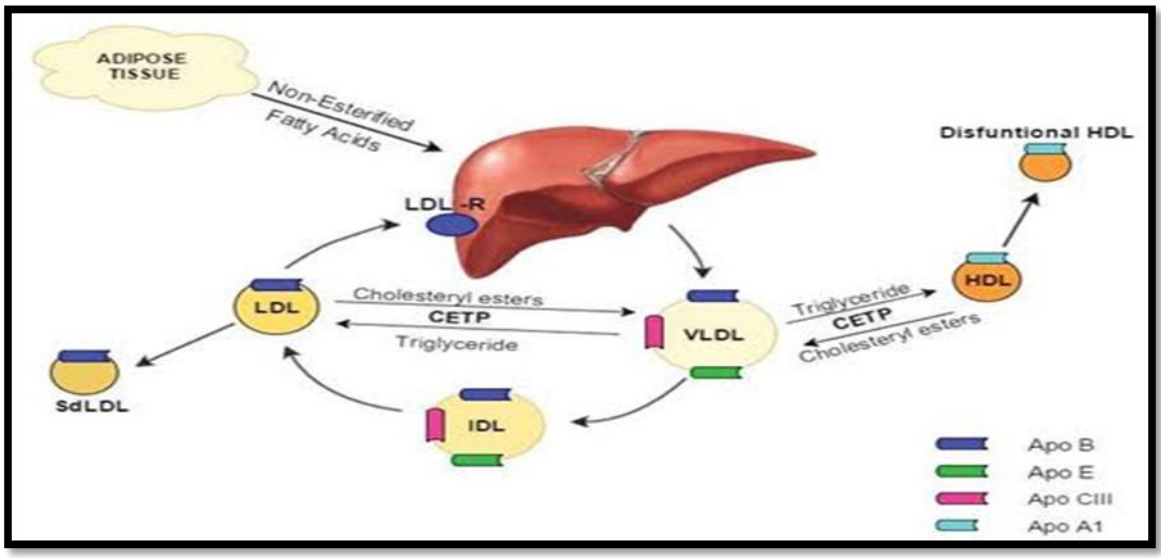

Fig. 1: Normal lipid metabolism

Pharmacological Treatment

Cholesterol Lowering Agents

Statins

The initial therapy which is used in the treatment of diabetic dyslipidemia is that statin therapy. AACE, ADA and ACC/AHA guidelines for statin therapy is given in Table 3.[23-25] For patients with LDL level between 100 and 129 mg/dl, the treatment strategy that could be considered should include statin. High intensity statin therapy includes atorvastatin 80 mg/day and rosuvastatin 20-40 mg/day.[25] 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.[26]

Fibrates

Fibrates are peroxisome proliferator activated receptor (PPAR)-α agonists, they reduces TG level and are capable of slightly increasing the level of HDL cholesterol and are

evidenced with decreased cardiovascular mortality. LDL lowering can also be achieved by these agents at very high dose fibric acid derivatives.[27]

Ezetimibe

This is a selective cholesterol absorption inhibitor as well as a lipid-lowering agent when used as monotherapy and it 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.[28]

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. The effect of antidiabetic drugs on lipid profile is depicted in Table 4.[1,29-36]

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 T_2DM patients.[37]

Conclusion

In the current study, various mechanisms and hypotheses are proposed to explain the pathophysiology of diabetic dyslipidemia. All these data suggests that, overproduction of VLDL is the core of all other events occurs in diabetic dyslipidemia. The common pattern of diabetic dyslipidemia is hypertriglyceridemia, high levels of LDL cholesterol and low level of HDL cholesterol. Different methods are preferred for the control and treatment of diabetic dyslipidemia and are described in nutshell. Individualization of therapy is important for better outcomes.

Conflict of Interest: None.

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