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DYSLIPIDEMIA IN PATIENTS WITH DIABETES: ETIOLOGY AND MANAGEMENT

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Author MD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author PB managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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Review Article

ABSTRACT

Diabetic dyslipidemia is a cluster of lipoprotein abnormalities characterized by increase in triglyceride level, decrease in high-density lipoprotein-cholesterol levels and increase in small dense low-density lipoprotein (LDL) particles. It is most common to have dyslipidemia in type 2 diabetic patients and it affects 70% of the patients. Diabetis is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) which is one most common reasons of death in many countries. In this review we have discussed several pharmacological and non paharmacological treatment modalities including several trials which had positive effects on cardiovascular events in patients who has diabetes. ASCVD is is reduced in patients by lowering the LDL-C levels by 30 to 45 % usinf statin therapy. Other therapies like Ezetimibe, pcsk9, has shown posititve effects on loweing LDL-C levels and ASCVD event reduction.

Keywords: Dyslipidemia; lipoprotein; cholesterol; cardiovascular events, triglycerides.

1. INTRODUCTION

Lipoproteins which contain cholesterol and triglycerides, they are of high risk for cardiovascular disease, and also coronary artery disease, peripheral arterial disease and ischemic cerebrovascular disease. Lipoproteins are divided into the ones that contain apolipoprotein (apoB) and the ones that do not contain apolipoprotein, and these usually overlap with high density lipoproteins. The lipoproteins that contain apolipoprotein B are called apoB-lipoproteins. When there is dietary fat in the food, intestine synthesizes and secrets triglyceride rich chylomicrons, which are lipolytically processed to remnant particles. Liver works on synthesizing and secreting different class of triglyceride rich apoB lipoproteins which are called VLDLs (exceptionally low density lipoproteins) [1]. These are also processed lipolytically down to remnant particles and then to LDLs (Low density lipoproteins). These LDLs and remnants are mostly removed by liver from the blood through several pathways. Lot of data from the past indicated that development of atherosclerosis is promoted by apoB lipoproteins and therefore they are best targets for therapeutic development to lower the blood concentrations and eventually lower the risk of cardiovascular disease. The risk of cardiovascular disease is inversely related to plasma HDL-C levels. This in turn supports the concept that HDL cholesterol is usually protective against atherosclerosis are very weak, making HDL an uncertain target for therapeutic intervention.

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2. LOW-DENSITY LIPOPROTEINS

LDL containing cholesterol is a major focus of therapeutic intervention for many decades so far, and it was observed that LDL was a casual risk factor in both randomized trials of LDL-c reducing drugs and also in studies of human genetics of LDL-C and their relation to CVD. The drugs that are proved helpful in lowering LDL-C, three classes if these drugs have shown positive impact on reducing outcomes related to ASCVD. From the research Lipid research clinical programs that was conducted in 1984 the bile acid sequestrant cholestyramine has shown positive results in reducing CHD events in 1980s. After the first approval of statin in 1988, various randomized trials have been conducted to see the effects of statins on reducing cardiovascular events, and the results proved to be positive [1]. After that stain therapy with high intensity, that reduces LDL-c to a greater extent has been discovered to lower the CV events [2]. Recently the cholesterol absorption inhibitor ezetimibe was proven to lower the CV events when added to a statin compared to statin alone [3].

3. HIGH DENSITY LIPOPROTEINS

CV events are inversely associated with plasma levels of HDL cholesterol (HDL-C) [4,5,6]. There is also strong inverse relation between TG levels and HDL-C as the casual nature of this epidemiological association has been uncertain with TGs. But the hypothesis of HD; states that HDL-C is related to ASCVD casually and that intervention to increase the levels of HDL-C will lower the risk of ASCVD. Preclinical studies of infusing HDL and apoA-I overexpression which shows the inhibition or atherosclerosis has strengthened this hypothesis [6,7,8]. Since the generation of HDL hypothesis, several research analysis has advanced our understanding of HDL metabolism. Liver and intestine synthesis HDL through the secretion of apolipoprotein A-I (apoA-I), which will recruit lipids through ABCA1 transporter to generate the nascent type pre beta HDL particle. Enzyme lecithin cholesterol, acyl transferase (LCAT) esterifies free cholesterol to cholesteryl ester (CE) form , there by forming mature HDL. scavenger receptor B-1 (SR-BI) takes up HDL CE either selectively through scavenger receptor B-1 (SR-BI) in the liver or in exchange for triglycerides it is transferred to apoB-lipoproteins.TG is hydrolyzed by hepatic lipase and endothelial lipase and phospholipids in HDL promoting its catabolism.

4. TRIGLYCERIDE-RICH LIPOPROTEINS

Occurrence of CV is associated strongly with levels of triglycerides both fasting and non-fasting. For TG lowering agents some randomized controlled trails were conducted and yielded unclear answers unlike LDL. Under these trails, patients with high TG levels were never considered into trails, and some other group of researchers analyzed it in the high TG groups suggested potential benefit. On the other hand, the development of cardiovascular disease has established results saying TG rich lipoproteins are the reason for CVD.

Even after controlling LDL-C and HDL-C TG levels associated with common variants cause CHD. In TG rich lipoprotein metabolism the specific variants and genes involved are more convincing. With the decrease in TG levels the common gain of function variant in LPL and loss of function is seen in the gene APOC3, which encodes the protein apoC-III known to inhibit LPL and hepatic uptake of TRL, is associated with reduced TG levels and reduced CHD. In an exome sequencing experiment in persons with early CHD compared with older healthy controls, after the "top hit" of the LDLR gene, the next most significant gene showing an imbalance of mutations in cases versus controls was APOA5, which encodes the protein apoA-V, an activator of LPL and known modulator of triglyceride metabolism. Thus, the genetic studies strongly support a causal role for at least some TG-rich lipoproteins influenced by the "LPL node" in the development of ASCVD. The importance of this observation is that novel therapeutic interventions targeted to the TG-rich lipoprotein axis could reduce cardiovascular risk in a manner orthogonal to reduction in LDL levels [9,10,11].

4.1 Lipid Lowering Agents

4.1.1 Statins

In patients who have type2 diabetes , and with CVD or patients who are over 40 year and have CVD, therapy with statins is commonly more recommended treatment to lower the LDL-C levels [12,13]. The risk of CVD is high in many patients even though statin therapy is used for LDL-C lowering [12]. The positive effects of statin treatments are mediated through lowering of LDL-C levels, also the HDL-C levels and other lipoproteins also may play role [14]. Treatments with statin are capable of lowering non HDL-c more than apoB as it requires more intensive treatment compared to non HDL-C [15].

The most common side effects from the use of statin therapy is problems in gastrointestinal systems, muscle aches, and hepatoxicity and myotoxicity are the most significant adverse reactions related to the dose levels of statin [16]. In patients with severe renal impairment proper precautions needs to be taken.

Table 1. Low-density lipoprotein-cholesterol lowering medications

Drug class	Mechanism of action	Clinical efficacy	Adverse reactions
Statins	Inhibition of HMG coenzyme A Reductase	Effective highly	Myalgia, myositis, rhabdomyolysis, elevation in liver enzymes, diabetes
Ezetimibe	By binding to Niemann pick CI like protein , intestinal cholesterol absorption is decreased.	Effective Moderately; It is Safe to add it to statin therapy	Worse the function of liver, rhabdomyolysis, myopathy when statins are added. Infection in the upper respiratory tract, diarrhea.
PCSK9 inhibitors	Inhibition of Proprotein Convertase Subtilisin/Kexin Type 9	Very highly effective when combined with statin therapy	Reaction at the place of injection including itching, swelling, erythema and pain
Bile acid sequestrants	Reabsorption is prevented and also bile acids in the small intestine	Effective moderately, safe when added to stain therapy, not desired when triglycerides are greater than 300 mg/dL	abdominal pain, bloating, Constipation and drug malabsorption

IN achieving LDL-C goals high dose of statin therapy has proven best effective results with effects positive on lipoprotein subfractions in patients with type 2 diabetes, which may translate into clinical benefits in terms of anti-atherogenic potential and helps in reduction of cardiovascular events [16].

4.2 Other Therapies to Lower Lipid Levels

Niacin is an older drug used to treat dyslipidemia for more than five decades [17,18]. In raising HDL-C levels it is amazingly effective but in high doses it can worse the hyperglycemia. Some other side effects of using niacin are flushing, nausea, upset in gastrointestinal track, itching and hypertension. A combination therapy of using niacin with statin is suggested for lipid lowering in patients with diabetic dyslipidemia to achieve optimal lipid levels. These combination therapies are not evaluated for long terms effects on cardiovascular events reduction, or safety when compared to monotherapy. When niacin is used with statin the risk of myopathy is higher [19]. Another combination of niacin and laropiprant which is a prostaglandin D2 receptor antagonist and anti-flushing agent has helped reduce flushing caused by niacin in patients with type 2 diabetes [20]. Another set of studies were done on patients who has hypercholesterolemia or mixed dyslipidemia, and the treatment with niacin laropiprant and simvastatin has significant improvements on lipid parameters vs niacin laropiprant alone, but an increase in flushing and other side effects related to niacin stain alone [21,22].

For patients who cannot tolerate statin therapy, they can use another cholesterol absorption inhibitor Ezetimibe as an effective lipid lowering agent as monotherapy [23]. To increase the impact of Ezetimibe in LDL-C lowering it can be used in combination with statin therapy. Ezetimibe combined with atorvastatin can show the same benefits as of high dose of atorvastatin in lowering LD-C levels. This also proved better tolerability in some patients and so can be used for therapy in patients with type 2 diabetes, who did not show proper response for statin treatments [24,25].

Fibrates are helpful in lowering TG and non HDL-C levels and in increasing HDL-C, but there are some controversies in the trails that were conducted in patients with type 2 diabetes [26]. In a study that was conducted in 9795 patients with type 2 diabetes, fenofibrate has shown no effects on coronary event rate relative to placebo [26]. But the results did not show or prove that therapy with statin and fenofibrate is safe. Another study names Action to control cardiovascular risk in diabetes study has provided further insight on whether the combination of fibrate and statin is safe enough to provide CVD benefits apart from statin therapy alone. In this study a total number of 5518 patients with type 2 diabetes were taken into consideration, and there is no difference seen between statin therapy alone results and the therapy that combine statin and fibrate regarding nonfatal myocardial infraction, death from cardiovascular disease [27]. Some of the common adverse reactions of fibrates are disturbances in gastrointestinal, headaches, rashes, pancreatitis, myotoxicity, and myalgia. In patients with severe renal dysfunction and who has gallbladder disease and severe hepatic dysfunction adjuvant fibrate therapy is not recommended [28].

5. PROPROTEIN CONVERTASE SUBTILISIN/ KEXIN TYPE 9 INHIBITORS

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK 9) inhibitors Alirocumab and Evolocumab are very potent drugs in lowering LDL-C levels significantly when used alone or in combination with statins. PCSK9 by binding LDL receptors can be targeted for intrahepatic lysosomal degradation. This leads to increase of LDL receptors for which it causes a reduction in LDL-C levels [29]. These are given every 2 to four weeks as subcutaneous injections.

PCSK9 inhibitors are indicated in patients with ASCVD who are on stain therapy at maximum tolerable levels with or without ezetimibe but has LDL-C >= 70 mg/dl or non HDL-C >= 100 mg/dl. They are also indicated in patients who has LDL levels >= 190 mg/dl with underlying homozygous familial hypercholesterolemia or heterozygous familial hypercholesterolemia [29].

In 2015 a long term trial named ODYSSEY has enrolled 2341 adults that are at high probability risk of CVE due to history of established coronary artery disease or had presence of heterozygous familial hypercholesterolemia, or coronary risk equivalent states. These adults had LDL-C levels greater than or equal to 70 mg/dl despite being on maximum tolerated dose of statin and were randomized to receive alirocumab 150 mg or placebo. Alirocumab therapy decreased LDL-C from 122.8 mg/dl to 52 mg/dl in 48 months [30].

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In the trials of ODYSSEY, use if alirocumab was studied in patients who have had ACS. This trial was conducted on 18924 patients in a randomized way at different centers, double blindly, and all of these patients had an episode of ACS in the last 1 to 12 months. The LDL -C levels are at 70 mg/dl in these patients. Levels of apolipoprotein B levels are at levels 80 mg/dL and non HDL-C levels are at levels of 100 mg/dl. These patients are already under treatment of receiving statin therapy at a dose of high intensity and are now given alirocumab 75mg subcutaneously. After two and half years of treatment there is 15 percent reduction in the primary end point, which is death of heart disease, ischemic stroke fatal or non-fatal, myocardial infraction [31]. Patients who have diabetes are 29% of the total cohort size and appear to have gained benefit which is not detailed.

Another set of trials OSLER-1 and OSLER-2 evaluated Evolocumab which is a PCSK9 inhibitor. This study was done on a cohort size of 4465 patients, and they were randomly assigned in a 2:1 ratio to get Evolocumab with standard therapy. Evolocumab has lowered LDL-C levels to 48 mg/dL from 120mg/ dL. This accounts to a reduction of 61% of LDL-C compared to results of standard therapy alone [32]. Atheroma regression is induced by PCSK9 inhibitors and atheroma volume is decreased. In Glagov randomized clinical trials which was conducted on 968 patients, and they are randomly given evolocumab 420mg subcutaneous injections placebo or monthly. Evolocumab has lowered atheroma volume by 0.95 percent and decreased total atheroma volume by 5.8 mm [33].

In atrial named FOURIER which was conducted on 27564 patients who has ASCVD and LDL levels greater than 70 mg/dL, and they were on tolerable statin levels and are given evolocumab subcutaneous injection or placebo. At 48 weeks the reduction in LDL-C at an average is 59 percent in the patients group. There is a risk reduction in the primary end point which is about 15 percent [34]. There is no new signs of diabetes was seen. In another series of

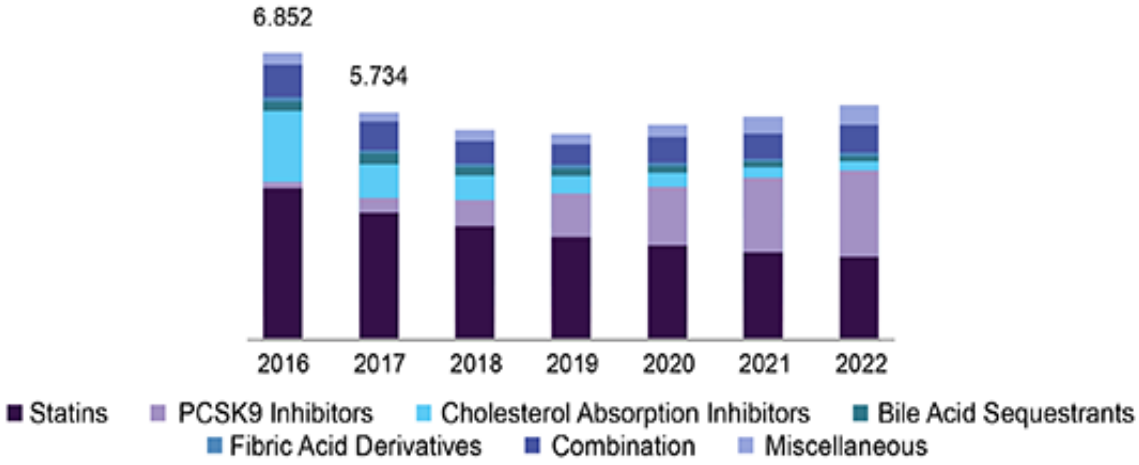

Fig. 1. Drugs usage for hyperlipidemia [36]

treatments done in 11031 patients the risk reduction in end point was 17 percent. This study was conducted in patients who has CVD and the PCSK9 role in the prevention of CVD in these patients is still unknown [35].

The cost of PCSK9 inhibitors is expensive with a cost of 14000 dollars [37], and it is hundred times more than statin therapy and it is highly unbearable for developed along with developing countries. These drugs can be tolerated well but develop a reaction at the site of injection.

6. BAS

The end products of cholesterol catabolism are bile acids. Commonly used Bile acids are cholestyramine, and colesevelam. These bind to bile acid in the intestinal lumen and enterohepatic circulation is decreased which lead to increased production of bile acid in the liver that causes a reduction in cholesterol level.

It is shown that long term effects of cholestyramine in men have shown a decrease in cholesterol and LDL cholesterol by 13.4 and 20.2 percent, and coronary heart disease is reduced by 19 percent in comparison with placebo [38]. SO they are useful next to statins in reduction of LDL-C levels. They are contra indicated if levels of TG are greater than 400 mg/dL, and so risk of pancreatitis is increased.

Several studies have shown improvement in glycemic o=control with colesevelam in T2DM and so they have shown positive effect on reduction of LDL-C and HbA1C levels. The data in support of reduction of CVE do not have any support [39].

7. OMEGA-3 FATTY ACIDS

To lower the triglyceride levels omega 3 fatty acids are used as an add on therapy. The formulation of omega 3 fatty acid contains EPA - eicosatetraenoic acid and docosahexaenoic acid.

Lipid intervention trial by Japan EPA showed the results that patients who have impaired glucose metabolism and hypercholesterolemia has reduced coronary artery disease by 22% when compared to normoglycemic patients [40,41]. But in the trial ORIGIN, the benefits shown by omega 3 fatty acid in reducing cardiovascular events did not show the same benefit as placebo in patients who has diabetes, impaired fasting glucose [41].

Another study on cohort size of 8179 patients to lower cardiovascular risks with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT), double-blind, randomized multicenter, placebo has shown positive effect on CVD risk reduction in patients with diabetes. In this study patients were already treated using statins and had a fasting TG level of 130 to 490 mg/dL and LDL-C level between 40to 100 mg/dL. They are randomly given a daily dose of 4mg icosapent ethyl or placebo.

The endpoint as primary was cardiovascular death, myocardial infraction, nonfatal stroke or unstable angina with a median follow up of four and half years. The reduction seen in primary end point was 25 percent with icosapent ethyl vs placebo. Around 55 percent of the patients has diabetes and they showed better benefit compared to non-diabetic. Mortality rate was reduced by 13 percent but increase in hospitalizations for atrial fibrillation. Before any recommendations are seen for diabetes, we need to see the publication in the diabetic sub group.

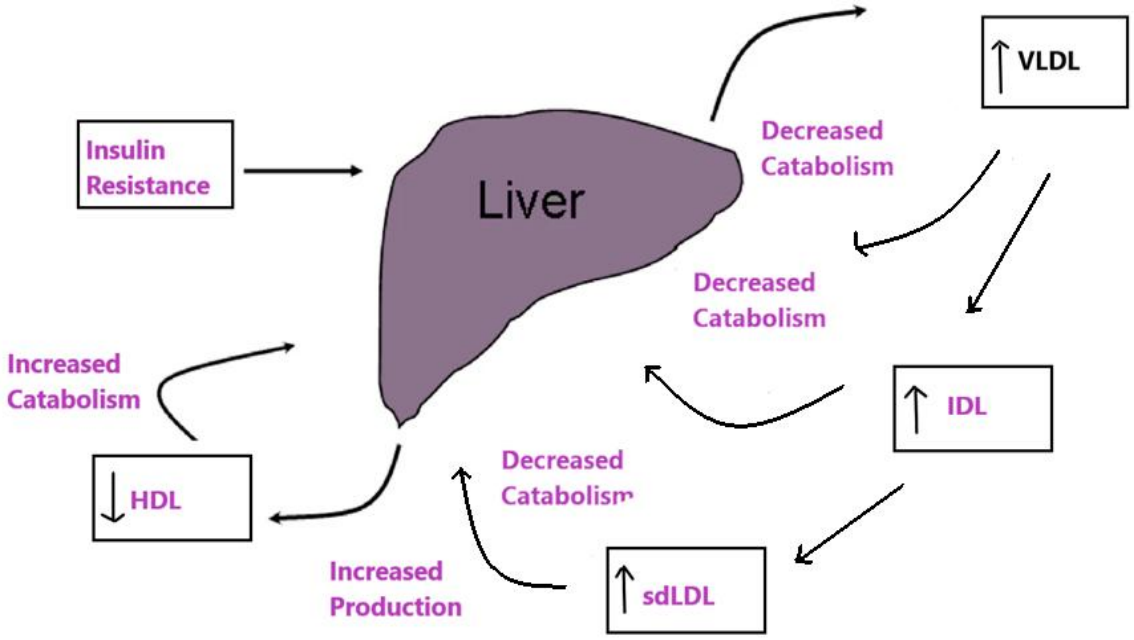

Fig. 2. lipoprotein metabolism changes associated with dyslipidemia and diabetes type 2

Interestingly in the primary prevention cohort including diabetics there appears to be no significant benefit: Hazards Ratio of 0.88 (0.7-1.10).

Along with the glucose lowering properties antidiabetic agents also improve insulin resistance and have effects on lipid levels, particularly TG levels. Even though there is no effect on HDL-C levels, these agents might alter the lipoprotein ratio in HDL toward more anti atherogenic HDL particles. As an example we can take metformin and it is shown to increase HDL-C levels and lower LDL-C, TG levels and TC. Another example pioglitazone is shown to lower TG levels and increase HDL-C levels. Another agent rosiglitazone has shown to increase the LDL-C, HDL-C, and TC levels, and it was seen that TG levels are not affected by thiazolidinedione. Another study was conducted on evaluating effect of use of pioglitazone or rosiglitazone for four months, along with statin therapy in 127 patients who has type 2 diabetes, and the results showed that even though similar finding were found regarding HbA1c and weight gain pioglitazone, but not rosiglitazone, was associated with significant improvements in the lipid profile.

Surprisingly both of the thiazolidinediones has shown to increase LDL particle size and decrease LDL oxidation and the conditions that impair atherosclerosis [42]. It is also reported that HDL-C can be improved by pioglitazone and also TG parameters when used along with metformin or sulfonylurea therapy in patients with diabetes type 2. It is proved to be more effective when combined with statin therapy in improving lipid and apolipoprotein than with sulfonylurea [43]. Using sulfonylurea alone has not proved any improvements in lipid profile but adding acarbose to sulfonylurea therapy has not only improved glycemic control but also provides improvement sin lipid parameters particularly TG levels [44,45,46].

8. CONCLUSION

Type 2 diabetes is associated with elevated TG serum levels, low HDL-C levels and high LDL particles. Disturbance in metabolism of lipids which is linked to insulin resistance is the primary event in type2 diabetes development. Most of the adults who has type 2 diabetes do not have optimal lipid profiles. To lower the risk of CVD in patients with type 2 diabetes dyslipidemia, it is important to act on lipid lowering therapy. First option is to lower LDL-C levels and then the atherogenic pattern of dyslipidemia associated with type 2 diabetes may require an advanced treatment approach that ultimately aims for full normalization of the lipid profile to decrease cardiovascular risk. Even with the help of aggressive lipid lowering therapies patients did not come into normal lipid levels which could lower the CVD risk. Use of treatments like bile acid sequestrant, statin therapy, helps control the type 2 diabetes in patients with dyslipidemia which can help lower it.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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