CHAPTER 10

DYSLIPIDEMIA

Davut SAKIZ[1]

INTRODUCTION

Since lipids are insoluble in water, they are transported in serum by complexing with hydrophilic proteins. The complex formed by these proteins and lipids is called lipoprotein. Lipoproteins transport lipids for use in structural functions, synthesis functions, and energy production functions. The main structural function of lipids is to participate in the structure of cell and organelle membranes. Bile acid synthesis and steroid hormone hormone synthesis can be given as examples of basic synthesis functions. Lipids can be used to produce energy as well as essential substances for energy storage.

Lipoproteins contain apolipoproteins, esterified cholesterol, triglycerides, non-esterified cholesterol, phospholipids, ligands and enzyme activators/inhibitors. The excess of some lipoproteins may initiate subendotelial retention and atherosclerosis [1]. Dyslipidemia fundamentally refers to an increase in atherogenic lipoproteins and a relative decrease in non-atherogenic lipoproteins.

PHYSICAL AND CHEMICAL PROPERTIES OF LIPOPROTEINS

The density of chilomicrons is <0.95 g/mL. Chilomicrons are the largest lipoproteins. Chylomicron size ranges from 80-100 nm. It consists of approximately 90-95% triglycerides, 2-4% cholesterol esters, 2-6% phospholipids, and 1% cholesterol. The major apolipoprotein on its surface is ApoB-48. Chylomicron also contain all apoproteins except ApoIII among apoAI-V.

The density of VLDL is 0.95-1.006 g/ml. Its dimensions are between 3-80 nm. It consists of approximately 50-65% triglycerides, 8-14% cholesterol esters, 12-16% phospholipids and 4-7% cholesterol. The major apoprotein on its surface is ApoB-100. It also contains ApoA-I, ApoC-II-III, ApoE, ApoA-V.

The density of IDL is 1.006-1.019 g/mL. Its dimensions are between 25-30 nm. It consists of approximately 25-40% triglycerides, 20-35% cholesterol esters, 16-24% phospholipids and 7-11% cholesterol. The major apoprotein on its surface is ApoB-100. It also contains ApoC-II-III, ApoE.

[1] M.D., Mardin Training and Research Hospital, davut.dr@hotmail.com

The density of LDL is 1.019-1.063 g/mL. Their size is between 20-25 nm. It consists of triglycerides approximately 4-6%, cholesterol esters 34-45%, phospholipids 22-26% and cholesterol 6-15%. The major apoprotein on its surface is ApoB-100.

The density of HDL is 1.063-1.210 g/mL. Its dimensions are between 25-30 nm. It consists of triglycerides about 7%, cholesterol esters 10-20%, phospholipids 55% and cholesterol 5%. The major apoprotein on its surface is ApoA-I. It also contains ApoA-II, ApoC-III, and ApoE.

The density of Lp(a) is 1.006-1.125 g/mL. Its dimensions are between 25-30 nm. It consists of triglycerides approximately 4-8%, cholesterol esters 35-46%, phospholipids 17-24% and cholesterol 6-9%. The major apoprotein on its surface is Apo(a). It also contains ApoB-100.

Lipoproteins that can pass through the endothelium may be involved in the atherosclerotic process. Lipoproteins with a molecular size below 80 nm and containing Apo-B on their surface can pass through the endothelial wall. So, lipoproteins other than chylomicron and HDL have atherogenic effects. [2].

DYSLIPIDEMIC CONDITIONS

Hypercholesterolemia, hypertriglyceridemia, familial combined (mixed) hyperlipidemia, familial hypercholesterolemia, elevated Lp(a), familial chylomicronemia syndrome (FCS) are the main types of dyslipidemia. familial hypoalphalipoproteinemia, familial dysbetalipoproteinemia, hypoalphalipoproteinemia, beta-sitosterolemia, lysosomal acid lipase deficiency and lipodystrophy are the other and rare genetic conditions of dyslipidemia [3].

The definition of hypercholesterolemia varies according to the cardiovascular risk status of the patients. This will be discussed in the following sections. The condition where triglyceride is above 150 mg/dl is called hypertriglyceridemia. Conditions where trigylicerid is above 500 mg/dl are called severe hypertriglyceridemia. LDL-C level is >190 mg/dl in heterozygous familial hypercholesterolemia (>160 mg/dl in children). Its prevalence is expressed as 1 in 250. Homozygous familial hypercholesterolemia is considered when LDL-C> 500 mg/dl. Prevalence of homozygous familial hypercholesterolemia is 1/1 million. [4].

CAUSES OF SECONDARY DYSLIPIDEMIA

Poor lifestyle causes of secondary dyslipidemia include excessive alcohol consumption, sedentary life, diet rich in saturated fat, foods containing high carbohydrates, and malnutrition. Secondary dyslipidemia may also occur due to hypo-

thyroidism, pregnancy, uncontrolled diabetes, kidney failure, proteinuria, obesity, prediabetes, nephrotic syndrome, metabolic syndrome, cholestatic liver diseases, lipodystrophy, chronic inflammatory diseases and paraproteinemias.

From drugs, glucocorticoids, cyclosporine, mTOR kinase inhibitors, retinoids, protease inhibitors, interferons, selective receptor modulators, paclitaxel, anabolic steroids, cyclophosphamide, oral estrogens, asparaginase, progestins, antipsychotic drugs, bile acid sequestrants, thiazide are among the causes of dyslipidemia. [2].

ASSESSING DYSLIPIDEMIA AND ASCVD RISK

A detailed anamnesis must be taken. System query should be done. Smoking, diet, blood sugar disorders, obesity, hypertension, presence of cardiovascular disease, metabolic syndrome, presence of inflammatory disease, liver disease, proteinuria, pancreatitis history and medications used should be questioned.

Presence of cardiovascular disease, hypertension, diabetes and dyslipidemia in family history should be evaluated. A complete physical examination should be done. Special attention should be paid to height, weight and BMI. Also, waist and hip circumference, peripheral pulses, cardiac murmurs, ankle-brachial index, tendon xanthomas, lipemia retinalis, xanthelesma, corneal arcus, eruptive xsanthoma [5].

In biochemical evaluation, lipid profile, uric acid level, thyroid function tests, hsCRP, HbA1c, fasting blood glucose, post-prandial glucose should be screened. ECG and, if necessary, stress tests should be performed. Coronary artery calcium scoring is suggested especially by Canada Cardiovascular Society (CCS). Also, carotid intima media thickness may be considered [6].

Hypothyroidism, pregnancy, uncontrolled diabetes, kidney failure, proteinuria, obesity, prediabetes, nephrotic syndrome, metabolic syndrome, cholestatic liver diseases, lipodystrophy, chronic inflammatory diseases and paraproteinemia, which are causes of secondary dyslipidemia, should be investigated and necessary treatment should be performed [7].

RISK SCORING AND CLASSIFICATION

After evaluating the patients, it is necessary to classify the cardiovascular risks of the patients using the cardiovascular risk scores according to their findings. Among the frequently used cardiovascular risk scorings are Framingham risk score, systematic coronary risk estimation (SCORE), Globorisk, pooled cohorts, CUORE, reynolds risk score, QRISK2, and prospective cardiovascular munster study (PROCAM).

The European Society of Cardiology (ESC) uses and recommends the SCORE risk classification [4]. In the SCORE classification, patients are classified according to their 10-year risk of fatal cardiovascular events. In this classification, the risk of fatal cardiovascular events is evaluated according to gender, smoking, age, systolic blood pressure and total cholesterol levels. Canada Cardiovascular Society (CCS) and American Association of Clinical Endocrinologists (AACE) primarily recommends Framingham risk score system. In the Framingham risk score classification, patients are classified accoreding to their 10-year risk of fatal and non-fatal cardiovascular events. In this classification, the risk of fatal and non-fatal cardiovascular events is evaluated according to gender, smoking, age, total cholesterol, HDL and systolic blood pressure.

According to ESC recommendations, patients are evaluated in low risk, medium risk, high risk and very high risk classes. The low-risk group includes patients with a SCORE score of <1% at risk. There are patients in the intermediate risk group with a SCORE risk score between 1-5%. In addition, young patients with DM duration <10 years without other risk factors are also in the intermediate risk group (T1DM <35 years; T2DM <50 years). High-risk group criteria include having a single significantly high risk factor, familial hypercholesterolemia without other significant risk factors, no target damage but with additional risk factors or existing DM for more than 10 years, stage 3 chronic kidney disease, and SCORE risk of 1-5%. Patients with a definitive documented atherosclerotic event, diabetes mellitus with target organ damage, diabetes mellitus with at least three risk factors, diabetes mellitus for more than 20 years, chronic kidney disease stage 4-5, SCORE risk >10%, ASCVD or other familial hypercholesterolemia, which is a risk factor, is very high risk criteria.

CCS recommends medical treatment to patients in two groups as "statin indicated prevention conditions" and "primery conditions". "statin indicated conditions" patients are those with clinical atherosclerosis, abdomina aortic aneurysm, diabetes mellitus, chronic kidney disease and advanced hyperlipidemia. Clinic atherosclerosis group includes patients with myocardial infarction, acute coronary syndromes, stable angina, documented coronary disease by angiography, stroke, transient ischemic attack, documented carotid disease, peripheral artery disease, claudiacation and/or ankle brachial index <0.9. Patients with diabetes mellitus over 40 years of age, those with DM for more than 15 years, those over 30 years of age and those with microvascular complications are in the statin indicated group. Those with proteinuria over three grams per day and those with stage chronic kidney disease are in the "statin indicated conditions" group. The advanced hyperlipidemia group includes patients with LDL-C>190 mg/dl and patients with familial hypercholesterolemia.

"The "Primary prevention conditions" group is also evaluated in two groups: intermediate risk and high risk. In the intermediate risk group, patients with a Framingham risk score between 10-19% and LDL-C>135 mg/dl or non-HDL-C>166 mg/dl or ApoB>1.2 g/L are included. Men over the age of 50 and women over the age of sixty who have one of the criteria of low HDL-C, impaired fasting glucose, high waist circumference, smoker, and hypertension are also in the intermediate risk group. The high-risk group consists of patients who are in the highest risk group according to the Framingham risk score or another cardiovascular risk scoreCCS does not recommend pharmacotherapy to the low risk group. Patients with a Framingham risk score <10% are included in this group.

According to the evaluation of AACE, the risk categories are limited to low, moderate, high, very high and extreme high [2]. Patients without risk factors are considered low risk. Patients with only one risk factor and patients with a risk score >10% are considered moderate risk. Patients with two or more risk factors, DM patients with a risk score of 10-20%, and patients with stage 3 chronic kidney disease are considered high risk. Patients with known cardiovascular disease, DM and an additional risk factor, advanced chronic kidney disease with proteinuria, and heterozygous familial hyperlipidemia are considered very high risk. Those with progressive atherosclerotic cardiovascular disease, DM or chronic kidney disease with atherosclerotic disease, and premature cardiovascular disease are considered as extreme high risk.

TREATMENT STRATEGIES ACCORDING TO CARDIOVASCULAR RISK AND CHOLESTEROL LEVEL

According to ESC guideline recommendations, medical treatment is recommended in addition to lifestyle recommendations after LDL-C exceeds 190 mg/dl in low-risk patients. Only lifestyle changes are recommended below the LDL-C level of 116 mg/dl in low-risk patients. If levels between 116-190 mg/dl cannot be controlled with lifestyle interventions, pharmacological treatment is recommended.

In moderate risk patients, after LDL-C exceeds 190 mg/dl, medical treatment is recommended in addition to lifestyle recommendations. Only lifestyle changes are recommended below the LDL-C level of 100 mg/dl. If blood cholesterol levels between 100-190 mg/dl cannot be controlled by lifestyle interventions, pharmacological treatment is recommended.

In high-risk patients, medical therapy is recommended in addition to lifestyle interventions after LDL-C exceeds 100 mg/dl. Only lifestyle changes are recommended for LDL-C below 70 mg/dl. If levels between 70-100 mg/dl cannot be controlled with lifestyle interventions, pharmacological treatment is recommended.

In very high risk patients, when the LDL-C level exceeds 70 mg/dl, medical treatment is recommended in addition to lifestyle recommendations. Only lifestyle changes are recommended for patients with LDL-C below 55 mg/dl. If LDL-C levels between 55-70 mg/dl cannot be controlled by lifestyle interventions, pharmacological treatment is recommended.

In secondary prevention patients, when LDL-C exceeds 55 mg/dl, medical therapy is recommended in addition to lifestyle interventions. If the LDL-C level of 55 mg/dl cannot be controlled by lifestyle interventions, pharmacological treatment is recommended.

TREATMENT GOALS ACCORDING TO RISK CATEGORIES

ESC recommends lowering LDL-C levels below 116 mg/dl in low-risk patients, below 100 mg/dl in moderate-risk patients, below 70 mg/dl in high-risk patients, and below 55 mg/dl in very high-risk patients. Non-HDL-C targets are <85, 100, and 130 mg/dL for very high, high, and moderate risk individuals, respectively. ApoB targets are <65, 80, and 100 mg/dL for very high, high, and moderate risk individuals, respectively. Lowering the LDL cholesterol level is the first target. Reducing non-HDL-C and ApoB levels is the secondary target. No target for triglyceride levels but <150 mg/dL indicates lower risk. Higher levels indicate the need to evaluate risk factors. ESC also recommends lowering HbA1c levels below 7% in DM patients.

On the other hand, AACE, recommends LDL-C <130 mg/dl, non-HDL-C <160 mg/dl and triglyceride <150 mg/dl in low-risk patients. There is no recommendation for ApoB in low-risk patients in the AACE guideline. LDL-C <100 mg/dl, non-HDL-C<130 mg/dl, ApoB<90 mg/dl and triglyceride<150 mg/dl levels are recommended in moderate risk patients. LDL-C <100 mg/dl, non-HDL-C <130 mg/dl, ApoB <90 mg/dl and triglyceride <150 mg/dl levels are recommended in high-risk patients. In very high risk patients, LDL-C <70 mg/dl, non-HDL-C<100 mg/dl, ApoB<80 mg/dl and triglyceride<150 mg/dl levels are recommended. In extreme risk patients, LDL-C <55 mg/dl, non-HDL-C<80 mg/dl, ApoB<70 mg/dl and triglyceride<150 mg/dl levels are recommended.

ALGORITHMIC APPROACH IN PHARMACOTHERAPY

First of all, the need for treatment should be decided according to the risk group and cholesterol level (described above). Treatment goals should then be determined. For this reason, ESC recommends statin therapy at the highest tolerable dose, while AACE states that moderate intensity insulin can be used in low

and intermediate risk patients. It is recommended by the guidelines to plan ezetimibe treatment in patients who could not achieve the goals with high-dose and high-potency statins. In cases where adequate lipid reduction cannot be achieved according to cardiovascular risk levels, treatments such as bempedoic acid and niacin may be considered.

Proprotein convertase subtilisin kexin 9 inhibitors (PCSK9I) are recommended in patients with secondary prevention and familial hypercholesterolemia with another risk factor. It can also be suggested to be used in primary prevention patients who are in the very high risk group.

The CCS recommends the use of PCSK9I in high-risk patients if LDL-C>85 mg/dl, ApoB>80 mg/dl, non-HDL-C>115 mg/dl with intensive statin and ezetimibe therapy. In addition, it is recommended to use PCSK9 inhibitors (evolocumab, alirocumab) to lower LDL-C in patients with familial hypercholesterolaemia whose LDL-C level remains above the target despite maximally tolerated statin therapy. Phase III efficacy studies show a consistent reduction in LDL-C levels and a reassuring and consistent reduction in CV events. Because of the very high lifetime risk faced by patients with familial hypercholesterolemia or ASCVD, clinicians must balance the expected benefits of potent LDL-C lowering with PCSK9 inhibitors against the lack of conclusive outcome data.

Statin therapy is recommended as the drug of first choice to reduce the risk in individuals with high atherosclerotic cardiovascular risk with triglyceride>200 mg/dl. In high-risk patients with triglyceride levels between 135-499 mg/dL despite statin therapy, omega-3 polyunsaturated fatty acid (icosapent ethyl 2x2 g/day) should be considered in combination with a statin. Fenofibrate or bezafibrate in combination with statins may be considered in high-risk patients with TG levels of 200 mg/dL and LDL-C target. Due to the possible side effects of gemfibrozil, it is recommended not to be considered in combination treatments. Since the risk of pancreatitis is high with triglycerides >500 mg/dl, fibric acid derivative treatment should be considered primarily. In cases where these treatments are insufficient, niacin treatment can be planned considering the side effects. In patients with high triglycerides, it is recommended that triglycerides be checked before and after starting a bile acid sequestrant. Because bile acid sequestrants can increase triglyceride levels. Bile acid sequestrants are contraindicated when triglycerides are above 500 mg/dL [8].

Before and during pregnancy lipid lowering drugs are contraindicated. Also, lipid-lowering drugs are not used during breastfeeding. In mandatory situations, bile acid sequestrants (BAS) and/or LDL apheresis may be considered.

OVERVIEW OF DYSLIPIDEMIA MEDICATIONS

Statins (hydroxymethylglutaryl CoA reductase inhibitors) have potent LDL-lowering and moderate triglyceride-lowering effects. Efficacy has been demonstrated in cardiovascular outcome studies . They can increase the risk of glucose intolerance and DM. They are safe drugs with the possibility of myalgia and rhabdomyolysis. Since they are metabolized via c-P450, they can interact with other drugs metabolized by these enzymes.

Cholesterol absorption inhibitör ezetimide is a potent LDL-lowering agent. Ezetimibe has no effect on triglycerides. It has been shown to have a protective effect in cardiovascular outcome studies. Mild diarrhea is a common side effect.

PCSK9Is (alirocumab and evolocumab) are very potent statin-lowering agents. Cardiavascular outcome trials have been shown the protective effect of PCSK9Is. Significant reductions in major advers cardiovascular events were seen in the FOURIER and ODISSEY studies. There was no decrease in deaths from all causes. This was associated with a short follow-up period of 2.8 years and insufficient time to assess mortality reduction. PCSK9I has no or very slight effect on triglyceride.

BAS have low-moderate efficacity. cholestyramine, colestipol, colesevelam are the main BAS. They are not recommended in hypertriglyceridemic patients because they increase triglyceride levels. They reduce the risk of glucose intolerance and diabetes. Gastrointestinal side effects are common. They can inhibit the absorption of thyroid hormones, A-D-E-K vitamins, as well as other medications.

ATP-citrate lycase inhibitör bempedoic acid lowers LDL-C and non-HDL cholesterol. No significant effect on triglyceride. It has been found to slightly reduce the risk of glucose intolerance and diabetes. There are data showing that bempedoic acid increases the likelihood of tendon rupture and increases uric acid levels. After CLEAR wisdom and CLEAR harmony studies, there is February 2020 FDA, April 2020 EMA approval, April 2021 NICE recommendation [9].

Omega-2 fatty acid eicosapentaenoic acid stands out with its triglyceride-lowering effect. The beneficial effect of eicosapentaenoic acid in cardiovascular outcome studies has been demonstrated at a dose of 4 grams [10]. This effect was not observed at lower doses. The triglyceride-lowering effect of docosahexaenoic acid is limited. Cardiovascular protection effect of docosahexaenoic acid has not been demonstrated.

Fibric acid derivatives fenofibrate, fenofibric acid and gemfibrozil are used because of their triglyceride and non-HDL-C lowering effects. It has no significant effects on LDL-C. A slight creatinine elevation may be seen with fenofibrate.

There is a possibility of cholelithiasis and hepatitis. Fenofibrats beneficial effects have been shown in diabetic retinopathy. May increase the efficacy of anticoagulants. It should be noted that gemfibrozil may cause muscle toxicity when used with a statin.

Niacin is an agent with both triglyceride and LDL-C lowering effects. However, there is insufficient evidence that it provides cardiovascular protection. Niacin is known to impair glucose tolerance. May cause hepatotoxicity, abdominal pain, dyspepsia and jaundice. In addition, flushing, itching, uric acid elevation and gout may also develop. Muscle toxicity may occur when used with statins. To prevent statin intolerance, the decision should be made on the basis of pre-existing symptoms and the risk-benefit ratio. Lower doses should be considered in patients at risk.

STATIN INTOLERANCE

In statin intolerance, bilateral muscle symptoms (eg, pain, weakness, cramps, stiffness) develop with initiation of statin use. Relief occurs with discontinuation of treatment, and relapse occurs with resumption. statin intolerance has been reported to occur between 5-20% in clinical studies. Rhabdomyolysis (Creatinin Kinase > 10 ULN) occurs at a rare rate of ~1/10,000 patient-years. Risk factors for statin intolerance are age > 75, being woman, low BMI, being East Asian, history of muscle symptoms, impaired kidney and/or liver function, diabetes, HIV, certain medications (e.g. fibrates, erythromycin, fluconazole), low vitamin D , hypothyroidism is acute infection. Patients should be informed about statin intolerance. Discontinue the statin if symptoms are considered significant. If the myopathy is not severe, lower dose, less frequent dosing may be attempted after patient reassessment (1-3/week) when symptoms resolve. A different statin may be tried. Vitamin D deficiency should be normalized. Adding CoQ10 may considered by pshysicians. Non-statin treatments can be added when necessary. Although statins have been speculated to have adverse effects on the liver, kidneys, cognitive functions and eyes, there is no effective evidence on these issues. The true intolerance rate of statin is quite low. Patient complaints are usually due to the nocebo effect.

CONCLUSION

Determining the cardiovascular risk is the basis of the dyslipidemia drug treatment plan. It is the common recommendation of the guidelines to make a treatment plan according to the risk level and lipid levels. However, compliance with

both healthy lifestyle and medications is challenging for patients and physicians. It should be kept in mind that adverse effects of dyslipidemic drugs are not as frequent as they are concerned. A holistic and continuous approach with a patient-centered approach is essential.

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